

# Priority Medicines for Europe and the World 2013 Update

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**Universiteit Utrecht**



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# Acronyms

AD	Alzheimer disease
AIDS	Acquired immunodeficiency syndrome
ALD	Alcoholic liver disease
AMR	Antimicrobial resistance
AMTSL	Active management of the third stage of labour
ART	Antiretroviral therapy
ARVs	Antiretrovirals
AUD	Alcohol use disorders
CDSS	Computerized decision support system
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DALY	Disability Adjusted Life Year
DNDi	Drugs for Neglected Diseases initiative
DG	Directorate General
EEA	European Economic Area
EC	European Commission
EDCTP	European and Developing Countries Clinical Trials Partnership
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic health records
EMA	European Medicines Agency
EPR	External price referencing
EU	European Union
EU27	27 Member States of the European Union (as of 2013)
ETEC	Enterotoxigenic <i>Escherichia coli</i>
FDA	(U.S.) Food and Drug Administration
FP	Framework Programme
FIND	Foundation for Innovative New Diagnostics
GBD	Global burden of disease
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
IAPO	International Alliance of Patients' Organizations
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IFPMA	International Association of Pharmaceutical Manufacturers' Associations
IHD	Ischaemic heart disease
IMD	Incrementally Modified Drug
IMI	Innovative Medicines Initiative
JPI	Joint Planning Initiative
MDD	Major depressive disorder
MDG	Millennium Development Goal
MDR	Multi-drug resistant
MMR	Maternal mortality ratio
MMV	Medicines for Malaria Venture
MRSA	Meticillin-resistant <i>Staphylococcus aureus</i>
NCE	New Chemical Entity
NICE	National Institute of Health and Care Excellence
NIH	(U.S.) National Institutes of Health
NME	New molecular entity
NRT	Nicotine replacement therapy
OA	Osteoarthritis
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
PDP	Product development partnership
PIP	Paediatric Investigation Plan
PPH	Postpartum haemorrhage
PPP	Public-private partnerships
PPV	Pneumococcal polysaccharide vaccine
R&D	Research and development
RCT	Randomized clinical trial
RDT	Rapid diagnostic test
RR	Risk ratio
RSV	Respiratory syncytial virus
SMEs	Small- and medium-sized enterprises
SPC	Summary of Product Characteristics
TI Pharma	Top Institute Pharma
TB	Tuberculosis
UNICEF	United Nations Children's Fund
WHA	World Health Assembly
WHO	World Health Organization
XDR	Extensively drug-resistant
YLD	Years Lived with Disability
YLL	Years of Life Lost (due to premature mortality)

## Preface

In 2003, the Netherlands Government contracted with the WHO to produce a report on Priority Medicines for Europe and the World. The original Priority Medicines Report written by Warren Kaplan and Richard Laing was presented on 18 November 2004 in The Hague in the Netherlands. Following the production of the Report, the Netherlands established a public-private partnership, Top Institute (TI) Pharma, to implement the recommendations, while the European Commission (EC) considered the report for competitive calls for proposals under the Framework Programmes for Research and Technological Development.

Much has changed since 2004. In its conclusions of the 3053rd meeting of the Employment, Social Policy, Health and Consumer Affairs Council (December 2010), the Council of the European Union invited the European Commission and the Member States to *“take the initiative of updating the 2004 priority medicines report, in cooperation with WHO experts, (...) continue to encourage the strengthening of coordination and prioritisation in the allocation of resources for pharmaceutical research to increase the probability of valuable innovations that meet unmet health needs, where appropriate through the development of partnerships, and (...) to foster dialogue with stakeholders on access to medicines in Europe, and in developing countries.”* As a result, the EC (DG Enterprise and Industry) contracted with the WHO to update the 2004 Report, and established a Working Group on Prioritisation under the Process on Corporate Responsibility in the Field of Pharmaceuticals to guide the revision process. This time, while the original authors have been closely involved, experts from the WHO Collaborating Centres in Utrecht, Boston and Vienna as well as experts from other institutions have contributed to the production of the background papers and chapters. To complement the financial support from the European Commission, the Netherlands Ministry of Health, Welfare and Sports provided support to the Utrecht WHO Collaborating Centre to produce Chapters 7 and 8. The Government of Belgium provided support for two meetings on the role of patients and citizens on priority setting. The work was carried out in the period July 2012 to May 2013.

The background papers have been circulated and extensively reviewed by interested stakeholders in industry, EU Member States, WHO departments and external experts. All chapters which are based on the background papers have been externally reviewed. These documents will be available on the WHO web site.

A draft version of the report was widely circulated for review and comments. This final version of the updated 2013 Report includes changes based on the comments and additional information received during the review process. The electronic version of this report, the individual chapters, background papers and annexes are available on the WHO web site at...[http://www.who.int/medicines/areas/priority\\_medicines/en/](http://www.who.int/medicines/areas/priority_medicines/en/) .



## Executive summary

The 2013 Report *Priority Medicines for Europe and the World* provides a public-health-based medicines development agenda, based on a systematic methodology for this priority setting. It is an update to the original 2004 Report *Priority Medicines for Europe and the World* and takes into account changes in global health and pharmaceutical innovation since 2004 in order to better address current and future patient needs.

This latest updated report analyses pharmaceutical innovation from a global public health perspective for Europe and the world, based on the principles of equity and efficiency. For this analysis, four inter-related criteria have been applied to determine priority disease areas of research:

- Criterion 1: The estimated European and global burdens of disease;
- Criterion 2: The common risk factors amenable to pharmacological intervention that have an impact on many high-burden diseases;
- Criterion 3: The prediction of disease burden trends, based on epidemiological and demographic changes in Europe and the world;
- Criterion 4: The principle of “social solidarity” applied to diseases for which there are currently no market incentives to develop treatments.

Pharmaceutical “gaps” have been established for the diseases and risk factors identified. A gap exists for a disease or condition when: pharmaceutical treatments for that condition will soon become ineffective (e.g. due to resistance); the delivery mechanism or formulation is not appropriate for the target patient group; or when an effective medicine either does not exist or is not sufficiently effective (e.g. lack of basic scientific knowledge or lack of financial incentive due to market failure).

Within the context of identifying the pharmaceutical gaps which have an impact on the health of people in Europe, particular emphasis has been placed on identifying those research needs which are also relevant for the rest of the world. This “commonality of interest” is an important bridging aspect of the project between Europe and the world for both the 2004 Report and the updated 2013 Report.

In identifying priorities for pharmaceutical research for 2014 to 2020, data from the World Health Organization (WHO) Global Burden of Disease Database in Geneva and the Institute of Health Metrics in the United States were used to identify the most relevant diseases with the highest burden of disease, as well as the most relevant risk factors in Europe and the world. Information on predicted public health threats was obtained from the WHO, the EU and other official sources.

Pharmaceutical gaps were identified based on in-depth studies of the identified diseases and risk factors. This involved the use of data on the effectiveness of existing

treatments from multiple sources, including the Cochrane and other databases, the National Institute for Health and Care Excellence (NICE), WHO reports and industry sources. In addition, cross-cutting issues and enablers and barriers to innovation are addressed in Chapters 7 and 8.

Although substantial progress has been made since the original 2004 Priority Medicines Report in the development of diagnostics and medicines for some disease areas, a number of the pharmaceutical gaps persist and new gaps have been identified. In order to close these gaps, suggestions are made for updated research agendas and a supportive policy environment. Key findings of the updated 2013 Report are:

- **The population of Europe and the world is ageing**, with more people — especially women — living beyond the age of 80. Since 2004, for the first time in Europe, there are now more people over the age of 65 than under 15 years. With this ageing there is a marked increase in diseases of the elderly such as osteoarthritis, low back pain, hearing loss and Alzheimer disease.
- **Many chronic noncommunicable diseases (NCDs)** contribute substantially to the disease burden (disability and mortality) in both Europe and the world. While prevention remains important, more research into the development of new medicines and the improvement of existing medicines will benefit all.
- **Ischaemic heart disease and stroke** are the largest contributors to the European burden of disease and among the leading contributors to the global burden of disease. Effective medicines exist to treat CVD, which reduce the incidence of recurrent heart attacks or strokes. However, these medicines are not adequately utilized for secondary prevention. Research is needed on how to optimize secondary prevention treatment through the use of existing medicines.
- **Depression** is also a large and increasing contributor to the current and future global burden of disease. Priority research areas remain the treatment of depression among adolescents and the elderly, reducing side-effects and identifying the best treatment strategy for different populations and age groups.
- **Stroke, osteoarthritis, Alzheimer disease, hearing loss, low back pain, chronic obstructive pulmonary disease (COPD) and alcoholic liver disease** are seven high-burden conditions, in Europe particularly, for which the currently available treatment is inadequate in reversing or halting the progression of disease. Hearing loss and low back pain were not identified as priorities in 2004 but have now been added, based on new data on the burden of disease. A major challenge for all of these diseases is the **absence of specific biomarkers** which could be used to identify potential pharmaceutical products, diagnose and monitor the progression of disease, or assess the effect of treatment. Continued support is therefore needed for basic research for these conditions.
- **Antibacterial resistance and pandemic influenza** remain major threats to global public health which require a coordinated international effort. Research priorities are the development of new rapid diagnostic tests, new business models for research and development (R&D) for new medicines and vaccines, and prevention of infections through vaccination, infection control and other environmental measures.

- **Malaria and tuberculosis (TB)** represent major threats, especially in low- and middle-income countries; TB is also an important disease in some European countries. For both diseases, rapid diagnostic tests have been developed and funding is needed for additional investment in R&D for diagnostics, medicines and vaccines. Antimicrobial resistance will remain a threat until primary prevention with vaccines occurs.
- **Diarrhoea, pneumonia, neonatal conditions and maternal mortality** are major contributors to the global burden of disease. Some existing therapies are often not available in low- and middle-income countries due to health system limitations such as health care management and affordability and other barriers. Meanwhile, the lack of point-of-care diagnostics creates problems in case management. Research is needed to improve diagnosis and treatment, including reducing the cost of existing treatments and diagnostic devices.
- For **neglected tropical diseases and rare diseases**, new mechanisms to promote the translation of basic research into clinically important products remain a priority. While progress has occurred since 2004 in the treatment of Buruli ulcer, other diseases such as leishmaniasis, trypanosomiasis and dengue still require substantial research.
- **Tobacco use, alcohol abuse and obesity** are risk factors that underlie many of the most common serious NCDs affecting both Europe and the world. While prevention efforts must take precedence, research is needed on pharmaceutical methods to address these risk factors and the pathologies exacerbated by these risk factors (e.g. COPD, various cancers, alcoholic liver disease, osteoarthritis and diabetes).
- Pharmaceutical innovation should also encompass special groups of patients such as the **elderly, women and children**, who have particular needs in relation to dosage forms and products. Research is needed on the use of electronic health records (EHRs) to deliver the much-needed information on safety and effectiveness of medicine use in these populations. Development of appropriate formulations for children and the elderly needs to be supported. Progress has been made in some oral forms but more is needed.
- **Stratified medicine**, in which specific patient groups are identified who would benefit most from particular therapies, will need to be carefully researched over the next decade.
- The systems for **market authorization** and for **pricing and reimbursement decision-making** have different roles for the EU and for the Member States and involve various institutions, but the systems are closely interlinked. In combination, these systems have to function in such a way that they balance the need for new “safe,” “effective” and “affordable” medicines. Innovation in these related areas is needed. Instead of a single market authorization or pricing and reimbursement decisions, multiple decisions over time may be required to respond to new knowledge that is being produced (e.g. using the real-life data in EHRs). Each of these decisions will have an impact on all the parties involved, and can involve both regulatory authorities and Health Technology Assessment (HTA) bodies that provide input to pricing and reimbursement decision-making. In addition, there are many cross-links for research agendas. For example, new methods for evidence

- generation, benefit risk assessment and regulatory dialogue will be needed to support policy tools such as adaptive licensing as well as value-based pricing.
- Developments in the field of **real-life data utilizing EHRs** have created innovative methods to compare and evaluate the performance of new medicines after market approval. Optimal use of EHRs would build on European strengths and could shorten the time needed to bring a product to market, while ensuring safety through active post-marketing surveillance. EHRs could also deliver the much-needed information on the effectiveness and safety of medicines in special patient groups at lower cost than other data collection methods.
  - A major change since 2004 has been the growth, both in Europe and worldwide, of **Public-Private Partnerships** undertaking early, translational and product development research. Notable successes have been achieved by the Innovative Medicines Initiative with enabling research activities but for Product Development Partnerships a tension exists between short-term funding commitments and the long-term development periods that their products require. This tension will need to be addressed if these partnerships are to fulfil their potential.
  - The optimal role of **patients and citizens** in contributing to priority setting and to regulatory and pricing decisions needs to be further developed. Their exact role and the best mechanisms for their involvement remain to be defined.

Much has been achieved in Europe since 2004 but many research needs and opportunities remain. In this updated report several existing and some new gaps in pharmaceutical development have been identified. These will need public funding in order to further improve the health of the people of Europe and the world.

# 1. Introduction

[See Background Paper 1 \(BP1\\_introduction.pdf\)](#)

## 1.1 Context

### 1.1.1 Introduction

This is the second report to be issued on *Priority Medicines for Europe and the World*. It is designed as an update to the original report, which was published in 2004.<sup>1</sup> The original report was initiated during the second half of 2003, when the Government of the Netherlands established the Priority Medicines for Europe and the World Project with the World Health Organization (WHO). The aim was to establish a public-health-based medicines research and development (R&D) agenda and, where necessary, to help bridge the gap between public health needs and the development priorities of the pharmaceutical industry.

In response, the WHO prepared a R&D agenda and methodology based on public health needs and drew up a list of priority medicines<sup>a</sup> to be proposed for research funding by the European Union (EU) as part of its Seventh Framework Programme (FP7) for 2007 to 2013. In addition to identifying priority medicines needed for EU citizens, the aim was to identify those research needs which are also relevant beyond Europe for countries in economic transition and for developing countries. This “commonality of interest” is an important bridging aspect between the health needs of Europe and the world.

The objective of the 2004 Priority Medicines Report, as described in the initial proposal, was:

*to prepare a public-health-based medicines development agenda, for support by the EU in the short- (2005-2006) and medium-term (2007-2010) future, and to develop a systematic methodology in this regard.*

The 2004 Report was generally well received by most of the major stakeholders, including patients’ organizations, industry, governments and regulators.<sup>2</sup> However, there was also some criticism. EURORDIS, the European alliance of rare disease

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<sup>a</sup> Priority medicines may be defined as those medicines which are needed to meet the priority health care needs of the population (“essential medicines”) but which have not yet been developed. For the purposes of this Report, a “priority” medicine for a priority disease is by definition also an improvement on, a replacement for, or a better formulation than already-marketed products.

patients' organizations, had reservations about some aspects of the Report's treatment of rare diseases.<sup>3</sup> The International Alliance of Patients' Organizations (IAPO) in Europe, although generally supportive, would have preferred the Report's content to be have been written in a way that would be more accessible to patients, whom they consider to be critical in moving biomedical innovation forward.<sup>4</sup>

### **1.1.2 What has happened since the 2004 Priority Medicines report was published**

The 2004 Report made several recommendations for future action, including suggestions for the development of new medicines for tuberculosis (TB) and neglected tropical diseases; a call for concerted efforts to deal with antimicrobial resistance (AMR) and a call for increased emphasis on public-private partnerships. Each of these recommendations was addressed in counterpart activities post-2004.

#### ***Top Institute Pharma***

The pharmaceutical gaps identified in the first Priority Medicines Report now constitute the core research portfolio of the Netherlands-based Top Institute (TI) Pharma.<sup>5</sup> TI Pharma's mission is to establish, support and manage public-private collaborations between academia and the international and national pharmaceutical industry, in part to create cross-disciplinary research within the framework of the 2004 Report; to improve the efficiency of the entire medicines development process; and to educate and train biomedical scientists (<http://www.tipharma.com/>).

As of 2012, 60 research consortia had been formed, combining 31 universities, their affiliated medical centres and knowledge institutes and 48 industrial partners, including global pharmaceutical companies and small- and medium-sized enterprises (SMEs). Therapeutic areas, based on the findings of the 2004 Report, consist of immune diseases, cardiovascular diseases, infectious diseases and diseases of the brain.

#### ***Public-Private Partnerships: Innovative Medicines Initiative***

The Innovative Medicines Initiative (IMI) was launched in 2008 as a large-scale public-private partnership between the European Union, represented by the Commission (EC) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). With a total budget of €2 billion, the IMI aims to boost the development of new medicines across Europe through the use of public-private partnerships. The IMI constitutes a novel model for implementing the concept of "open innovation". This has enabled large-scale pooling of industrial research assets by implementing new collaborative endeavours between large pharmaceutical companies and other key actors in health care, including academic institutions, SMEs, patients, and regulatory authorities.<sup>6, 7, 8, 9</sup> The Interim Report on the functioning of the IMI was uniformly positive.<sup>10</sup> The authors formulated a series of recommendations for action and, significantly, stipulated which actor(s) should take responsibility for them.

### *Initiatives to combat antimicrobial resistance (AMR)*

The original Report identified AMR as a priority condition requiring coordinated efforts ([see Chapter 6.1](#)). The problem of AMR has been known for many years and has been recognized by the WHO, the EC and the European Parliament. The Swedish Government during their Presidency of the EU was very active on this issue and convened a major meeting. Through resolutions passed by the World Health Assembly (WHA), WHO Member States have highlighted not only the public health threat of resistant organisms, but also the harm caused by misuse of antimicrobials by patients, prescribers and medicine dispensers. Activities following publication of the 2004 Report are encapsulated in the following WHA Resolutions:

- WHA58.27 – Improving the containment of antimicrobial resistance, 25 May 2005 (see Appendix 1.1).
- WHA60.16 – Progress in the rational use of medicines, 23 May 2007 (see Appendix 1.2).
- WHA62.15 – Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, 22 May 2009 (see Appendix 1.3).

Antimicrobial resistance is the subject of research funded under the FP7 and the IMI, and is also the subject of a Joint Programming Initiative (JPI), which aims to coordinate research activities among EU Member States. In early 2010 the JPI on Antimicrobial Resistance was proposed by Sweden and Italy.<sup>11,12</sup>

In late 2011, the EC issued a five-year “Action Plan against the rising threats from Antimicrobial Resistance”, an increasing problem which has been singled out by the EC as a major public health concern.<sup>12</sup> In 2012 a resolution of the European Parliament on “Rising Threats of Antimicrobial Resistance”<sup>13</sup> and the conclusions of the Council of European Union on the “Impact of antimicrobial resistance in the human health sector and in the veterinary sector – a “One Health” perspective”<sup>14</sup> have underlined the importance which the EU attaches to this subject. One of these research priorities is implemented through the IMI 6th Call on AMR, which forms part of the ‘Action plan against the rising threats from Antimicrobial Resistance’<sup>15</sup> adopted by the EC.

### **1.1.3 Priority-setting experiences (2004 to 2012)**

Today, even in the most developed countries, the demand for health care outweighs the level of resources allocated to finance health. Meanwhile, efforts by national policy makers to set priorities for their health care system, or for the introduction of new technologies, are often conducted on the basis of varying degrees of evidence about the safety, effectiveness and appropriateness of particular interventions. Because there are still no widely accepted models for legitimate and fair priority setting in health care, priority setting remains a real challenge for policy makers in health systems throughout the world. Many different approaches to priority setting have been developed and there has been considerable literature on this since the 2004 Report. This is reviewed briefly in Chapter 3 and in its associated Background Paper. In short, the majority of priority-setting exercises since 2004 have applied a broad definition of

health research as an activity that is not limited to generating new knowledge, but also has a wider vision of implementation in order to help reduce the current disease burden.

### **1.2 2013 Update to Priority Medicines for Europe and the World**

The original Priority Medicines Report was presented on 18 November 2004 at The Hague in the Netherlands. Since then, new research agendas have been developed and the EU has expanded to encompass 27 Member States – with implications for a possible shift in priority diseases. In 2011, a Working Group of the European Commission reported that insufficient dissemination and implementation of the 2004 Report were weaknesses that should be carefully addressed during the 2013 Council Presidencies and recommended that an update of the 2004 Report<sup>16</sup> be undertaken by the WHO (see Background Paper 1) for further information and analysis.

### **1.3 Burden of disease, the epidemiological transition and the commonality of interest**

The Priority Medicines Project focuses on the unmet health needs of different populations. Within Europe, the EU27 all have rapidly ageing populations (see Background Paper 5). Elsewhere, in regions throughout the world, countries are undergoing their own epidemiologic and demographic transitions. As a result, health systems in many parts of the world are faced with ageing populations and an increase in chronic noncommunicable diseases (NCDs) associated with economic development and changes in lifestyle.

Various methods of measuring disease burden have been developed. In this report the concept of Disability Adjusted Life Years (DALYs) is used as an integrated single measure of mortality and disability due to a particular disease or condition. One DALY represents one lost year of healthy life and the burden of disease is a measurement of the gap between current health status and an ideal situation in which everyone lives into old age free of disease and disability (see Background Papers 4 and 5). Mortality is also used here as a measure of burden of disease as this is easy to understand. However, this measure is not able to reflect the burden of pain and suffering experienced by patients with chronic diseases such as osteoarthritis.

We live in an interconnected world with increasingly shared health problems and a “commonality of interests”. The vast majority of chronic NCDs and conditions affecting populations in the EU27, such as cancers, cardiovascular disease, osteoarthritis and Alzheimer disease, are also occurring in the developing world or will be in the not-too-distant future. At the same time, large portions of the world's poorest populations still have to contend with the onslaught of AIDS combined with other infectious diseases such as malaria, trypanosomiasis (sleeping sickness) and tuberculosis (TB) in what amounts to a double burden of disease, that is a burden of

both communicable and non-communicable disease. Perhaps even to a greater extent than in 2004, the health needs of Europe and much of the rest of the world are converging and the so-called commonality of interest identified in the 2004 Report continues to be relevant. A shift in priorities may now be needed, due to population changes such as ageing, or behavioural changes in smoking and dietary habits as well as alcohol consumption. Better understanding of these changes can be used to inform priority setting.

### 1.4 Priority medicines and pharmaceutical gaps: a public health perspective

Priority medicines are designed to fill pharmaceutical “gaps” (i.e. where treatments either do not exist or are inadequate, or where existing treatments are likely to become ineffective in the future, such as those for AMR). For a given disease or condition, priority medicines can be defined as:

1. Essential medicines which should be developed to treat conditions for which few or no effective treatments exist or where the available medicines are of limited efficacy or effectiveness. These are medicines that would fill pharmaceutical gaps and would be useful both in Europe and worldwide in countries where the targeted diseases occur.
2. Essential medicines that have not yet been developed but are needed for diseases and conditions that will become important public health concerns both in Europe and the rest of the world.
3. Medicines needed for special patient groups, including patients with rare (“orphan”) and neglected tropical diseases, the elderly, children and women.

The 2013 Priority Medicines Project continues to identify pharmaceutical gaps and to identify areas for improved delivery mechanisms or better formulations of existing preventive and therapeutic medicines (e.g. formulations for children, fixed-dose combinations (FDCs) or heat-stable formulations).

Although the 2013 Report addresses some high-burden diseases that are largely preventable, such as lung cancer, chronic obstructive pulmonary disease (COPD), alcohol-related diseases, and type 2 diabetes, it should be underlined that, with rare exceptions, any new treatment is unlikely to be a “magic bullet” and that health promotion and disease prevention (not considered in the present Report) must remain very high priorities.

It is encouraging to note that since 2004 major pharmaceutical gaps identified in the original Priority Medicines Report have been addressed. The first of these is the continuing marketing approval of imatinib in more than 110 countries for the treatment of all phases of chronic myelogenous leukaemia and also for the treatment of adult patients with KIT (CD117)-positive gastrointestinal stromal tumors (GIST), which cannot be surgically removed and/or have metastasized. Another example of a gap being addressed is the use of antibiotics to treat the disabling condition of Buruli ulcer,

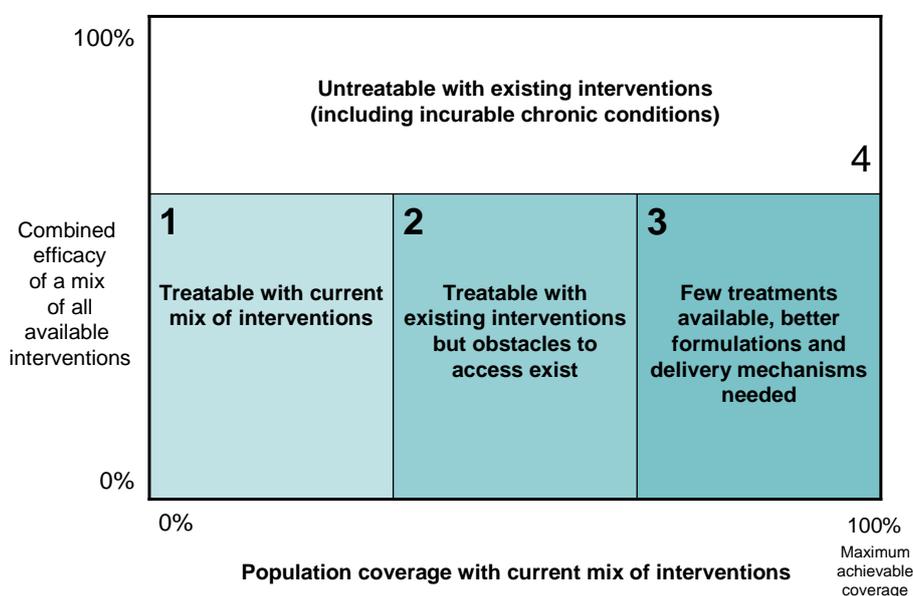
which was being treated primarily with wide surgical excision. Recent studies have confirmed the efficacy of antibiotics in treatment<sup>17, 18</sup> ([see also Chapter 6.9](#)).

## 1.5 Conceptual framework

The 2004 Priority Medicines Report developed a conceptual framework for the Project, which continues to be relevant and is used in this updated report ([see Chapter 3](#)).

Figure 1.5.1 (see 2004 Report: Appendix 3.6) offers a public health perspective of the scale of unmet treatment needs or when existing therapies are inadequate. This model identifies that for some diseases effective treatments exist and are widely used (Area 1). For other diseases, effective treatments exist but obstacles to access are present (Area 2). These obstacles may be due to factors such as cost or weaknesses in the health system. The third category includes conditions for which some treatments exist but the delivery mechanism or formulation may be inappropriate for the target patient group (Area 3). The fourth category encompasses those conditions for which no effective treatment is available (Area 4). The Priority Medicines Project focuses on Areas 3 and 4 and not very much on Areas 1 and 2.

**Figure 1.5.1: Identifying pharmaceutical gaps (unmet therapeutic needs): a public health perspective**



Source: Adapted from the *Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options*, WHO, 1996

### 1.6 Structure of the 2013 Report

Work on this updated report was organized in several stages. The early stages (June-December 2012) involved a review of the original methodology and collection of new, post-2004 data on disease burden and mortality. This new information is, in part, based on the 2010 Global Burden of Disease Study (GBD 2010), with its series of major publications in late 2012.<sup>19</sup> These early stages led to the production of a Preliminary List of diseases and conditions for more detailed studies.

Later stages (September 2012 to May 2013) involved the production of detailed Background documents (Chapter 6), used to develop a Final List of priority diseases and conditions and their pharmaceutical gaps (Chapter 9). Any gaps that had been closed since 2004 were noted. Further updates were related to cross-cutting themes in Chapter 7: relating to the elderly, women, children and stratified medicine and enablers and barriers to innovation in Chapter 8.

Throughout the Project, an international project Advisory Group, including European Economic Area Member States (Belgium, Italy, the Netherlands, Norway, Portugal and the United Kingdom), members of the pharmaceutical industry, academics, non-governmental organizations (NGOs), many patients' groups, representatives of trade organizations, EC staff and WHO staff, met to review progress. In addition, meetings were held in Brussels with EC staff from the Directorates General (DG) for Research and Innovation, Enterprise and Industry and Health and Consumers.

Draft versions of the background documents were distributed for review and comment by external experts. An Interim Report was submitted to the EC on 28th March 2013 for review, comment and use in the priority-setting activities related to Horizon 2020 and the next IMI programme (see Background Paper 2).

### 1.7 Who is the target audience for this report?

It is essential that public health needs and incentives for biomedical innovation are aligned in order to spur the development of new medicines for high-burden diseases and conditions for which there are unmet therapeutic needs. This report is targeted to key decision makers with the expertise needed to bring about this alignment.

The primary audience includes: EU Member States, which are responsible for funding research and paying for medicines, the EU decision-makers, the Council of the European Union, the European Parliament and the European Commission (notably, but not exclusively, the DGs for Research and Innovation, Enterprise and Industry, Health and Consumer Protection and Development). Senior management and scientific directors of research in the European pharmaceutical industry are another crucial audience. Policy makers and politicians at national and regional levels may also find this report and the background papers useful for their decision making. Within WHO, headquarters departments such as Public Health and Innovation and disease control

departments, as well as regional and country offices may find useful information for their work. Meanwhile, researchers who are deciding on future directions for their research efforts may find the methods and conclusions useful for their decisions. In addition, patients' groups and payers (social health insurance organizations and reimbursement authorities) have a common interest in identifying which research should be prioritized and encouraged.

### 1.8 Contents of the 2013 Report

This updated series of chapters has been produced in parallel with a series of updated background papers available on a CD-ROM and on the web. Some additional sections have been added to the background papers since 2004. The original 2004 Report remains available for reference on CD-ROM and on the web (<http://archives.who.int/prioritymeds/report/index.htm>).

**Chapter 2** describes how innovation occurs in the pharmaceutical sector. It highlights continuing concerns about the decline in innovation and competitiveness in Europe, particularly in the context of the global and EU economic slowdown, a situation that did not exist in 2003 to 2004.

**Chapter 3** briefly presents new information on approaches to setting priorities and outlines the approaches selected for use in this report.

**Chapter 4** is an update on the methods used in the study. These were used to generate the preliminary results (Preliminary List) which are described in **Chapter 5**.

**Chapter 6** includes 24 sections which outline the current situation with regard to the diseases or risk factors that comprise the Preliminary List and identifies possible pharmaceutical gaps from the available evidence. Where relevant, the sections also include information on diagnostics and vaccines. These 24 sections (each one a background document) are particularly important as they summarize the evidence base for the recommendations in **Chapter 9** and provide a detailed source of reference material for both policy makers and others wishing to learn more about a particular condition or risk factor.

**Chapter 7** deals with updates to cross-cutting themes. This chapter includes sections focusing on children, women and the elderly as population groups with particular health needs, together with sections on stratified medicine.

**Chapter 8** takes a fresh look at issues related to promoting innovation. Specifically, one section addresses new ways of creating incentives for pharmaceutical innovation, and another looks at the development of public-private partnerships for new medicines. Two other sections discuss regulatory policies and pricing policies, while the two final sections deal with health information systems in the context of priority medicines and the role of patients in the pharmaceutical innovation process.

**Chapter 9** provides the list of priority diseases and conditions for which pharmaceutical gaps exist and gives recommendations for different stakeholders, based on the updated information in this report. This chapter includes limited references, as comprehensive documentation is provided in the background documents.

### 1.9 Areas not addressed by this study

This study does not address in any detail health system issues such as access or quality of care. The importance of non-pharmaceutical prevention related to tobacco use, alcohol-related diseases and obesity are not dealt with. Nor does the report address gaps related to logistical or sociological barriers. The study makes limited reference to issues related to intellectual property, as this is the subject of much recent work and continuing debate (see Background Papers 1 and 2).

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# 2. Background to the 2013 Priority Medicines Project

[See Background Paper 2 \(BP2 background.pdf\)](#)

## 2.1 Introduction

Since well before the publication of the 2004 Priority Medicines Report, the goal of biomedical technology companies has been to conduct research and commercialize products in a stable, predictable operating environment that encourages and rewards innovation. However, various pressures currently being placed on pharmaceutical companies can have a negative impact on innovation. It appears that these pressures have been increasing since 2004. The financial investment required for pharmaceutical development has increased, threatening to make the development of new medicines increasingly unaffordable for companies, payers and patients.<sup>1</sup>

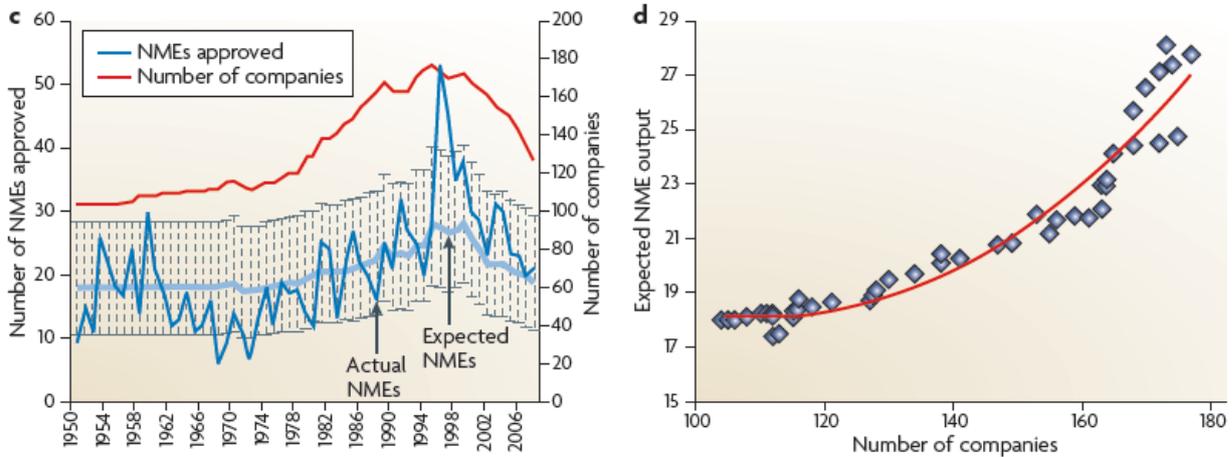
## 2.2 Pharmaceutical innovation: current challenges

Although the data can be subject to different interpretations, some studies suggest that innovation in the pharmaceutical industry occurs in waves of activity, as evidenced by several successive "generations" of medical (and other) technologies over the past two hundred years<sup>2,3,4</sup> (see Background Paper 2).

However, as of 2013 there had not yet been a corresponding increase in output in terms of new medicines being approved, as the rate of introduction of new molecular entities (NMEs) has remained about the same over the past 30 years.<sup>5</sup> Meanwhile, attrition rates have risen sharply, especially in late-phase clinical trials.<sup>6</sup>

Figure 2.2.1 (panel c) suggests that the rate of discovery of NMEs simply reflects the capacity of the pharmaceutical industry, although the data only go up to 2006. The output of industry NMEs tracks the expected value based on the established research and development model. The expected NME output and the number of companies are closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output simply by changes in the number of companies (Figure 2.2.1, panel d).

Figure 2.2.1: Dynamics of pharmaceutical innovation



Source: Munos B. *Lessons from 60 years of pharmaceutical innovation.*

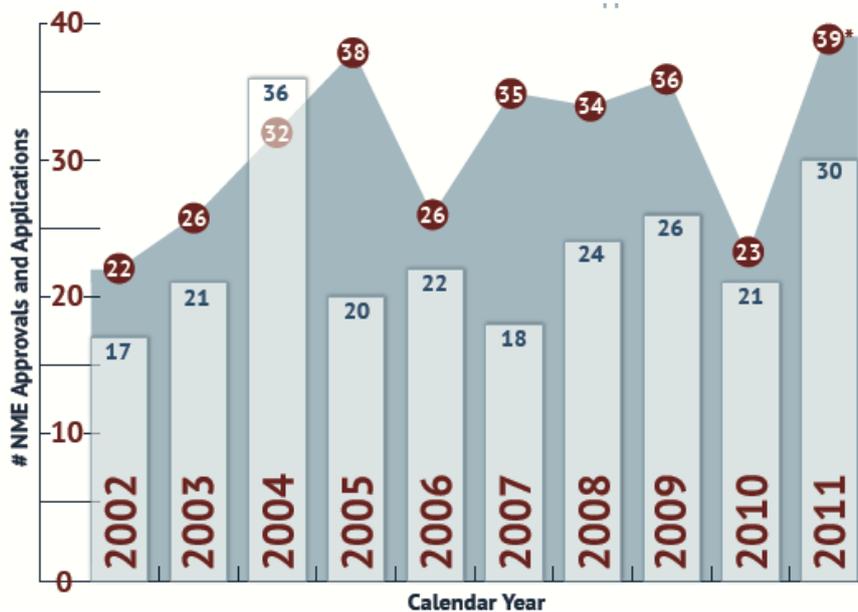
*Reviews Drug Discovery* 8, 2009, 959-968, doi: 10.1038/nrd2961

Panel c: Output of NMEs over time

Panel d: Correlation of the expected output of NMEs and the number of companies providing the NMEs.

However, more recent analysis shows that in 2011, the United States Federal Drug Administration (FDA) approved 30 NMEs, excluding new biologicals (see Background Paper 2). The 30 NMEs approved in 2011 represent the second highest total in the period 2002 to 2011, after the 32 NMEs approved in 2004 (see Figure 2.2.2). In 2012 the FDA approved 39 NMEs.<sup>7</sup>

Figure 2.2.2: Time series of the output of NME applications (circles) and approvals (bars) for the U.S. Food and Drug Administration (FDA)



Source: The Novel New Drugs of 2011. U.S. Food and Drug Administration, 2012.

### 2.3 The European pharmaceutical industry in context

Since 2004, and even before that date, the global pharmaceutical industry has seen a consolidation of companies and the creation of huge multinational corporations. This merging of companies across the Atlantic means that it is sometimes difficult to characterize a company as "European." North America is the world's leading market for pharmaceutical products and most new products today are launched in the United States because of the size of its market and the absence of price controls.

Meanwhile, in 2011 Europe remained the second largest global market for pharmaceutical sales. The presence of a highly-skilled workforce and robust framework for the protection of intellectual property rights (IPRs) were key factors in the decision by industry to invest €27.5 billion in R&D in Europe in 2011.<sup>1</sup> The pharmaceutical industry is one of the few sectors to contribute positively to the EU's trade balance. Its trade surplus of €48.3 billion in 2011 was the highest among the high-tech industries.<sup>1</sup>

Annual global expenditure on medicines will reach nearly US\$ 1.2 trillion by 2016 (EU5 countries<sup>b</sup>, Japan, the United States, and emerging markets), up from over US\$ 900 billion in 2011.<sup>8</sup> In the developed markets, including Europe, Japan and the United States, spending is expected to decline to 57% of the global total – down from 76% in 2006. This is due to growth in emerging markets as well as the expiry of patents for a number of significant brand-name medicines, slower increases in spending on branded products, and increased cost-containment measures by payers.<sup>8</sup>

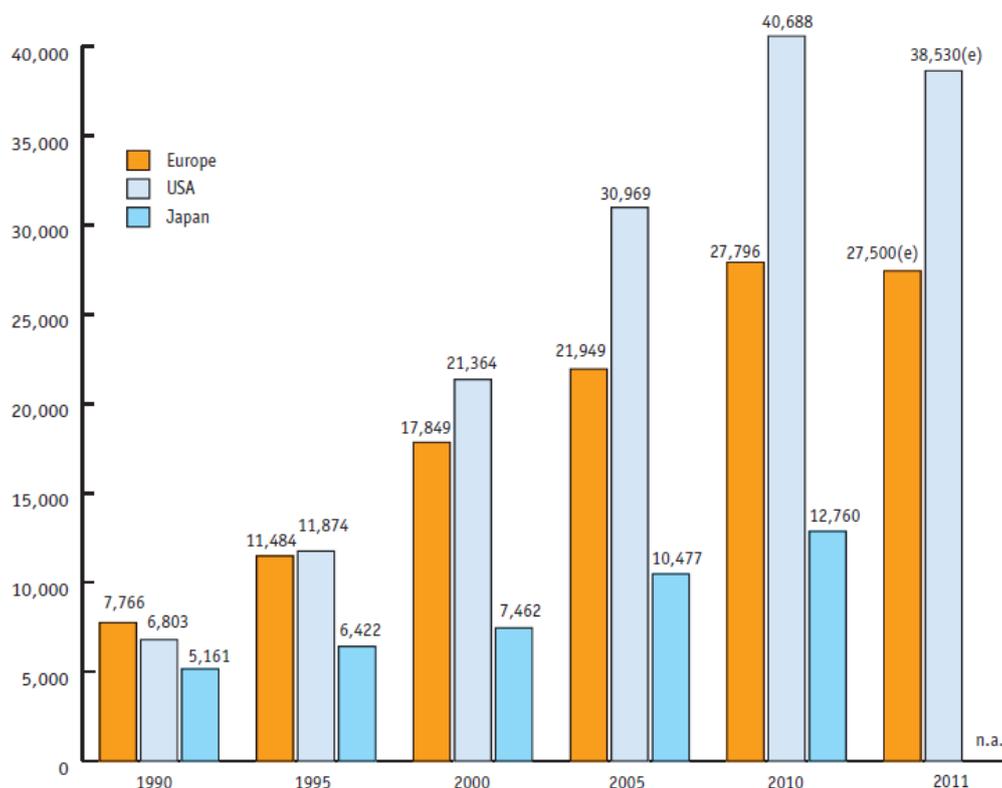
Of these sales, however, only 7% are driven by products launched within the last five years, indicating the continued reliance of industry on more established products. From a business viewpoint, the ever-increasing cost of medicines development is an incentive for companies to invest in products likely to provide the highest rate of return on R&D investment. This leads to a somewhat conservative business model (i.e. the development of medicines against proven targets) using approaches that have already been clinically and financially successful<sup>9</sup> (see Background Paper 2).

The level of investment in pharmaceutical R&D in Europe, Japan and the United States varies significantly, with the highest concentration of biopharmaceutical R&D expenditure in the United States. The latest 2011 data reported by EFPIA companies show pharmaceutical R&D expenditures leveling off in the United States and Europe (Figure 2.3.1). In 2011, a total of 49 innovative medicines were approved by the European Medicines Agency (EMA) for a range of different diseases (not including national authorizations). They include: 37 new medicines (not including medicines for rare ("orphan") diseases), 11 new medicines for orphan diseases and one advanced-therapy medicine for the EU market.<sup>1</sup>

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<sup>b</sup> The EU5 countries are France, Germany, Italy, Spain and the United Kingdom.

**Figure 2.3.1: Pharmaceutical R&D expenditure in Europe, USA and Japan  
(Millions of national currency units\*), 1990-2011**



\*Note: Europe: € million; USA: \$ million; Japan: ¥ million × 100, (e) : estimate  
Source : European Federation of Pharmaceutical Industries and Associations:  
EFPIA Annual Review of 2011 and Outlook for 2012

The United States accounts for an estimated 38.1% of global pharmaceutical production, just ahead of Europe and well ahead of Japan (See Background Paper 2, Figure 2.4). Together, these three regions account for the bulk (approximately 82%) of global pharmaceutical production by value. In 2009, the Asian region was by far the fastest growing market, with an estimated growth of 15.9%, while the growth of the North American and European markets was estimated at 5.5% and 4.8% respectively in value (See Background Paper 2, Figure 2.5).

Today medicines regulators are progressively increasing the requirements for product authorization in an effort to promote safety and efficacy. At the same time, reimbursement authorities appear to be more and more interested in controlling pharmaceutical costs. The ability of the major pharmaceutical industries to innovate is under growing pressure from loss of revenue owing to patent expirations, increasingly cost-constrained health systems and more demanding regulatory requirements.<sup>10</sup> As a result, it is becoming increasingly difficult to provide appropriate incentives for the development of products for important public health needs, such as medicines for rare diseases, individualized therapy, or diseases that occur mainly in low-income countries.

### 2.4 EU Policy Space: Pammolli, G-10 Report

In addition to the general perception that the pharmaceutical R&D model has not been producing enough innovative molecules, in Europe in the late-1990s a specific perception emerged that the European pharmaceutical industry was losing ground to the United States. This was reinforced by the publication in 2000 of a report entitled *Global Competitiveness in Pharmaceuticals: A European Perspective*, the so-called Pammolli Report, named after one of its authors (see 2004 Report Appendix 2.1).<sup>11</sup> The perception was further strengthened by the 2002 Report of the European Commission High Level Group on Innovation and Provision of Medicines (the “G-10 Medicines Group”). (See 2004 Report Appendix 2.2). Similar patterns of losing competitive advantage were also confirmed for the biotechnology industry in a 2007 report.<sup>12</sup>

In 2011, a further analysis by Pammolli and colleagues confirmed that, although investment in pharmaceutical R&D has increased substantially over recent decades, there was still a lack of a corresponding increase in output in terms of the approval of new medicines, an indication of continuing challenges in therapeutic innovation.<sup>13</sup> However, the authors also investigated potential variations in productivity with regard to the regional location of companies and found no evidence of any “productivity gap” between the United States and Europe.

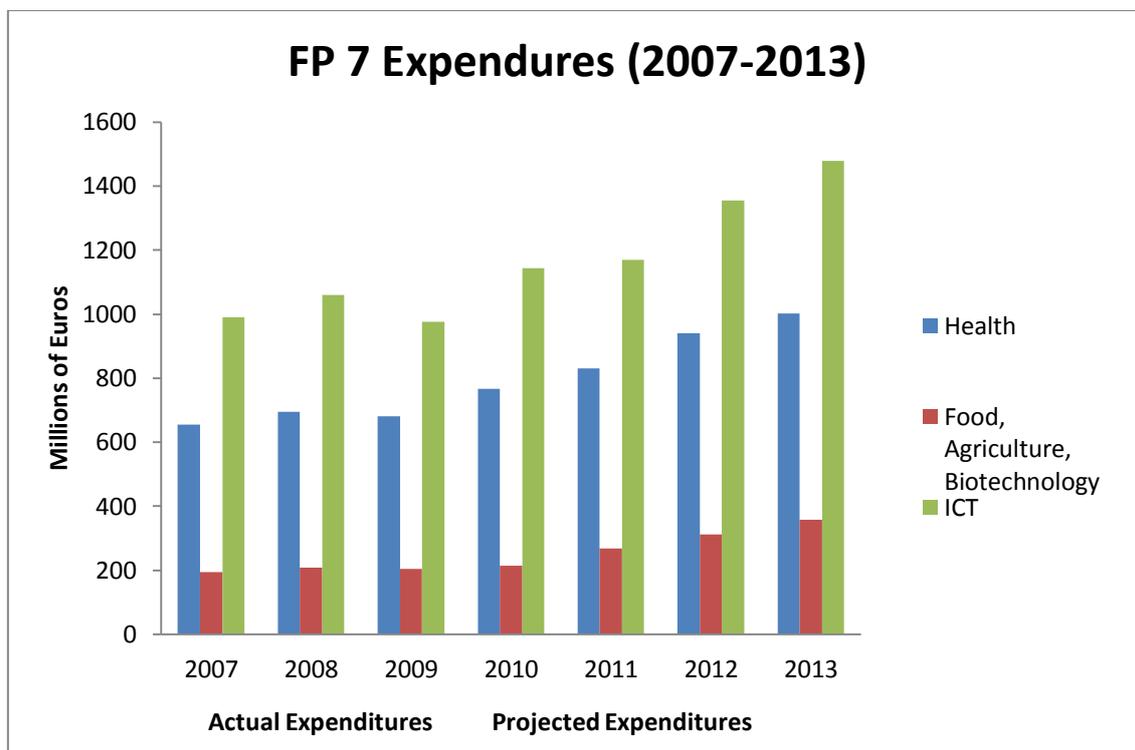
### 2.5 The Framework Programmes

Since 1984, the European Commission (Directorate General (DG) Research and Innovation) has undertaken a series of multi-year Framework Programmes (FPs), funding programmes created in order to support and encourage research in the European Research Area (ERA). The specific objectives and actions vary between funding periods. The original Priority Medicines Report was designed to provide analysis for the FP6 (2002 to 2006: about €17.8 billion total budget of which €2.5 billion for the Thematic Area “Life Sciences, genomics and biotechnology for health”) and the planned FP7 (2007 to 2013).

#### 2.5.1 The Seventh Framework Programme

The FP7 was adopted for the period 1 January 2007 to 31 December 2013.<sup>14</sup> Figure 2.5.1 shows for 2007 to 2011 the *actual* FP7 expenditures in the referenced subject matter and the *planned* expenditure for 2012 to 2013.<sup>15</sup> The total budget for health-related activities over the duration of FP7 is €6 billion.<sup>16</sup>

Figure 2.5.1: Actual Expenditures FP7 (2007-2011) and Projected Expenditures (2012-2013)



Source : European Commission, Research and Innovation, FP7, Budgets, available at [http://ec.europa.eu/research/fp7/index\\_en.cfm?pg=budget](http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget)

## 2.6 Innovative Medicines Initiative (IMI)

Launched in 2008 with a total budget of €2 billion up to 2013, the Innovative Medicines Initiative (IMI) <sup>17</sup> is an industry-European Union public-private partnership, involving the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Its aim is to facilitate the development of new medicines by supporting a more efficient discovery and development process.

Since 2008, the IMI has awarded grants totalling €580 million to the most promising research projects in areas including brain disorders, metabolic diseases, inflammatory diseases, cancer, infectious diseases and, most recently, antimicrobial resistance (AMR) ([see Chapter 6.1](#)). The IMI is currently engaged in an 8th Call for Proposals.

## 2.7 Horizon 2020

The most recent version of the FPs (2014 to 2020) is “Horizon 2020”, which at the time of publication is subject to negotiation between the Council of the European Union and

the European Parliament. This will combine all research and innovation funding currently provided through the FPs and other sources for a range of research areas not limited to biomedical topics.

### 2.8 United States Policy Space: the National Institutes of Health (NIH)

The National Institutes of Health (NIH) Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programmes that require participation by at least two NIH Institutes or Centers (ICs) or would otherwise benefit from strategic planning and coordination (see Background Paper 2, Appendix 2.5).

The requirements for the Common Fund encourage collaboration across the ICs while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short-term, exceptionally high-impact, trans-NIH programmes known collectively as the NIH Roadmap for Medical Research (see Appendix 2.5).<sup>18</sup>

Roadmap Programmes span all areas of health and disease research and IC boundaries. These are programmes that might not otherwise be supported by the NIH ICs, because of their scope or because they are inherently risky. Roadmap Programmes are expected to have exceptionally high potential to transform the manner in which biomedical research is conducted. They are also expected to be short-term (5–10 year) programmes. The annual Common Fund budget was US\$ 498 million in 2008. To date, the Common Fund has been used exclusively to support the Roadmap Programme.

Initiatives funded through the Roadmap/Common Fund fit into one or more of these major themes and address specific roadblocks or gaps to:

- Foster high-risk/high-reward research
- Enable the development of transformative tools and methodologies
- Fill fundamental knowledge gaps
- Change academic culture to foster collaboration.

Many of the programmes have achieved significant research advances. There are over 20 programmes currently in operation (<http://commonfund.nih.gov/initiativeslist.aspx>), ranging from nanomedicine (<http://commonfund.nih.gov/nanomedicine>) to global health (<http://commonfund.nih.gov/globalhealth>). (See <http://commonfund.nih.gov/grants/fundedresearch.aspx> for a list of current (2012) funding opportunities and funded projects).

#### 2.8.1 Criticism and defence of the NIH Roadmap Programme

The presentation of the 2006 NIH Roadmap, at a time of government cut-backs in general, led one critic to assert that the NIH should rely more on pharmaceutical

companies to fund large clinical trials. The relatively more limited NIH funds could then be reallocated to basic science grants (known as “R01 grants” in the United States).<sup>19,20,21</sup>

In response, representatives of 50 leading academic medical centres focusing on clinical research argued that the pharmaceutical industry had to focus on profit-generating opportunities in order to meet its commitment to investors. Therefore, the pharmaceutical industry was not best qualified to deal with “... *sustaining the issues specific to academic science*”<sup>22</sup>

## 2.9 Regulatory strategic plans by the European Medicines Agency: EMA Road Maps

In 2005, the European Medicines Agency (EMA) developed a new strategy for its work up to 2010.<sup>23</sup> Since then, various initiatives have been undertaken and progress made with the implementation of the EMA 2010 Road Map (described in two Status Reports published in May 2006 and October 2007.<sup>24,25</sup> In December 2010, the EMA published a further document (Road Map 2015) setting out a strategic vision for the operation of the Agency from 2011 to 2015<sup>26</sup> (see Background Paper 2, Appendix 2.4). See also Implementing the European Medicines Agency’s Road map to 2015: The Agency’s contribution to Science, Medicines, Health EMA/MB/550544/2011.<sup>27</sup>

The Road Map 2015 report identifies the following drivers for the future activities of the EMA:

- Need to ensure efficient operation of the Agency’s core business
- Addressing ongoing public health needs including demographic changes, emerging public health threats, AMR and rapid development of new technologies
- Evaluating new and emerging science which may address unmet medical needs
- Ensuring that the model for regulating medicines remains current and effective
- Protection of public safety
- Addressing the need for more openness and transparency and
- Addressing the impact of globalization.

More specifically, to address current and anticipated public-health needs over the next five years, the EMA intends to focus on activities relating to addressing gaps in medicines development, responding to new and emerging science and putting in place the necessary preparedness mechanisms to respond to emerging health threats.

In the context of this updated report, three main ‘gaps’ in drug development have been identified by the EMA; neglected and rare diseases, specific activities relating to ageing populations and the need to address the pipeline gap for new antibiotics. Each of these EMA priorities has a counterpart in the present report.

The focus of efforts to address the challenges of new and emerging science will include efforts to enhance liaison between approaches to drug and diagnostic development,

facilitation of biomarkers and the science supporting the development of more personalized medicines.

With regard to its responsiveness to public-health threats, the EMA intends to build on experience with influenza pandemic preparedness to assist the EC in the development of a strategy with European partners to ensure a coordinated European response. The EMA also intends to intensify work on a European and international perspective to minimize the risk of AMR arising from the use of both human and veterinary medicines within the framework of Community and international activities, including the Transatlantic Taskforce on AMR established based on the conclusions of the 2009 EU-US summit ([see Chapter 6.1](#)).

### 2.10 Regulatory strategic plans by the U.S. Federal Drug Administration (FDA)

In March 2004, the United States Food and Drug Administration (FDA), the American counterpart of the EMA, produced a document entitled “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products” which argued that “... *applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences.*”<sup>28</sup> In its 2006 Critical Path Report, the FDA presented its diagnosis of the scientific challenges as a medical product *pipeline* problem, which meant that innovative medicines were not reaching patients. The report then laid out a path forward, beginning with extensive outreach and consultation with public and private stakeholders.<sup>29</sup>

The FDA has since developed a “Critical Path Opportunities List” including several aspects relevant to this Report: biomarker development; streamlining clinical trials; developing new antibiotics to combat emerging infections and bioterrorism; and the development of new therapies for children and adolescents.<sup>30</sup> Most recently, the FDA produced a strategic plan, entitled “Strategic Priorities 2011–2015: Responding to the Public Health Challenges of the 21st Century”<sup>31</sup> (see Background Paper 2, Appendix 2.6a).

### 2.11 Global initiatives

In March 2010 the European Commission issued a communication on “The EU Role in Global Health”<sup>32</sup> The communication states that the EU should apply the common values and principles of *solidarity towards equitable and universal coverage of quality health services* in all external and internal policies and actions. This would be achieved through democratic and inclusive governance, an emphasis on universal coverage and coherence between relevant EU policies related to global health. With regard to research, the communication stresses that research should benefit all people and that the EU Research Framework Programmes should continue to give priority to actions which address global health challenges.

On 26 May 2012, the WHO World Health Assembly (WHA) adopted a resolution calling for an inter-governmental meeting (held in November 2012) to examine in depth the proposals made in April in the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (see Background Paper 3) established in 2010 under Resolution WHA63.23. Such proposals included: open approaches to R&D; pooled funds; direct grants to companies in developing countries; prizes for milestones and end-products; and patent pools. One of the recommendations of the Working Group was to start multilateral negotiations for the possible adoption of a binding convention on health R&D.<sup>33</sup>

In November 2012, a three-day closed door meeting resulted in agreement by WHO Member States to endorse a strategic work plan that includes proposals on the coordination, financing and monitoring of R&D expenditures.<sup>34</sup>

### 2.12 Conclusions

Since 2004, the global and EU policy space has changed in a significant way. At the European level, FP7 and Horizon 2020 have created what is hopefully a broader, integrated vision of biomedicines policy and innovation going forward. Additionally, there is seen to be a growing involvement of regulatory agencies such as FDA and EMA in this area through explicit priorities in their strategic agendas for the future. Also, at the global level co-ordination and discussions have evolved much since the previous Report.

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## 2. Background to the 2013 Priority Medicines Project

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## 3. Approaches to priority setting

[See Background Paper 3 \(BP3 Approaches.pdf\)](#)

### 3.1 Introduction

This chapter reviews the various approaches which have been used to set priorities for health research — both at the international and national level — and explains the rationale for the choice of methods used in this Project (see 2004 Report, Background Paper 3 and present Report, Background Paper 3). The key message underlined in the 2004 Report and reiterated here is that all methods of priority setting have limitations and that different methods need to be used, depending on the particular circumstances. A combination of methods has therefore been used in this Report.

Priority setting is a challenge at all levels (global, national and local) and for all contexts in health systems. Both consumers and funders are demanding greater accountability for how limited health resources are used to meet health system goals. As a result, public and private sector research funders have to make difficult decisions about which fields and specific studies to support.

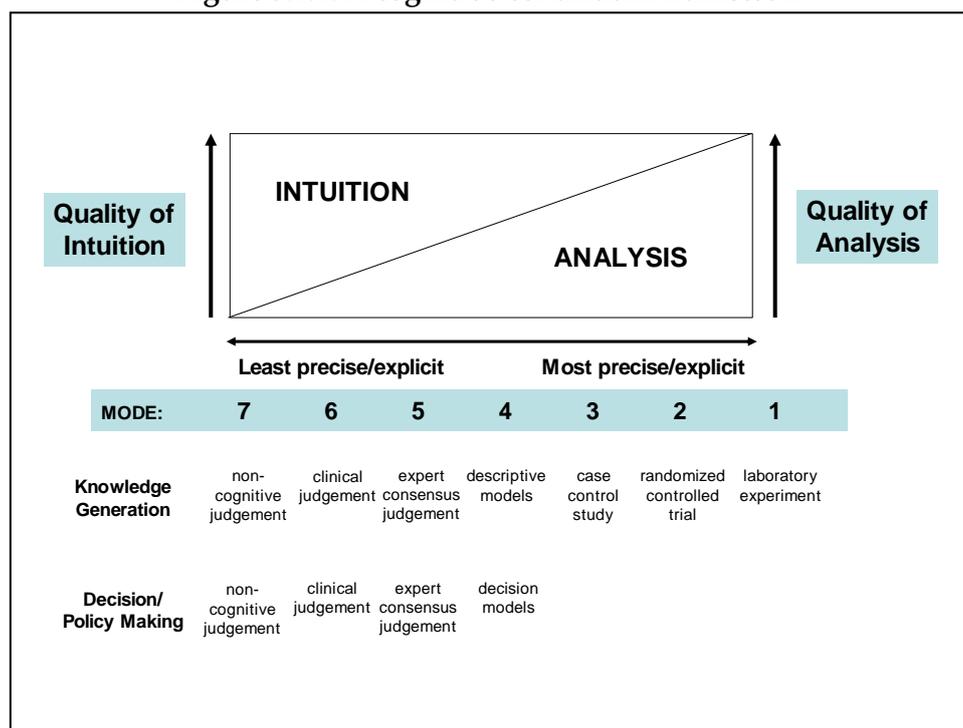
However, there is virtually no consensus regarding which, or whose, values should guide decisions about allocation of research funding and how these values should inform priority setting. In short, there is no “best practice” (see Viergever et al. 2010. A checklist for health research priority setting <sup>1</sup> and Appendix 3.1).

There are two broad approaches to setting priorities for health research: the use of technical analyses, which rely on quantifiable epidemiologic, clinical, financial or other data; and the use of interpretive assessments, which rely on consensus views of informed participants. Technical approaches depend on the availability of data, and priorities tend to be based on measurable units such as diseases (burden of disease) or interventions (with respect to their costs and use). The difficulty with quantitative methodology is that it hides value judgments that might reflect those of stakeholders not involved in the methodology, such as users and payers of health care services. Interpretive or consensus stakeholder approaches relying on the subjective judgments of participants are, in theory, capable of dealing with value judgments and multifaceted assumptions, and they have been used for research priority setting in large, governmental agencies like the United States National Institutes of Health (NIH),<sup>2</sup> the Science and Technology Council of Australia,<sup>3</sup> or even large pharmaceutical companies.

## 3.2 Conceptual framework for the Priority Medicines Project

The conceptual framework for this updated 2013 Report has not changed. The Project used different methods from the spectrum of possible approaches: evidence-based approach (burden of disease and mortality data); future projections approach; risk factor approach; and social solidarity approach. A framework for this kind of analysis has been developed by the University of Colorado in the United States (see Figure 3.2.1).

Figure 3.2.1: A cognitive continuum framework



Source: Dowie J. In *Health Care Priority Setting*. Oliver A. ed. Nuffield Trust, UK

## 3.3 Approaches to priority setting

### 3.3.1 Overview of the literature post-2004

There have been several literature reviews in this fairly active area since 2008.<sup>1,4, 5, 6, 7, 8</sup> Reports have evaluated priority setting against an ethical framework. The factors that impact priority setting have been studied as well, such as amount and type of stakeholder engagement, cultural factors supporting explicit priority setting, decision maker/group composition (size and clarity of process, local ownership and awareness and representation), and management of local politics. These are summarized in Background Paper 3. A key conclusion of this review for the present updated report is

that there is still very little information on how **funding** decisions are developed for biomedical research.

#### 3.3.2 Defining a priority medicine: the role of regulatory authorities

The regulatory authorities of the EU, Canada and the United States determine whether a medicine should be a “priority” for regulatory purposes. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have established categories of medicines, based on whether or not they demonstrate improvement over existing medicines. Such a designation facilitates the registration process.<sup>9</sup> Although not intended for use in prioritizing research, in practice this designation is intended to reward successful research (see Background Paper 3).

##### *European Union*

In November 2005, one year after the publication of the 2004 Priority Medicines Report, accelerated assessment was introduced by revised EU pharmaceutical legislation. Companies can request accelerated assessment provided they are able to demonstrate that their product responds to unmet medical needs or constitutes a significant improvement over the available methods of prevention, diagnosis or treatment of a condition.<sup>10</sup> An accelerated assessment is conducted in a maximum of 150 days although if major objections to this are uncovered during the assessment, the timing is reverted to the normal timetable for the centralized procedure, which allows a maximum assessment period of 210 days. In 2007, the medicinal product, eculizumab, from Alexion Europe SAS, was the first medicinal product for which an accelerated assessment procedure was concluded successfully.

Two other pathways to address 'unmet medical needs' are the conditional approval and the exceptional approval pathway.<sup>11,12</sup> In case of conditional approval, marketing authorization is granted based on a smaller package of clinical data, with follow-up obligations to submit additional clinical efficacy and safety evidence of the product. For some products, such as certain orphan medicinal products for extremely rare diseases, it will usually never be possible to assemble a full dossier. These products may be approved under an 'exceptional approval' scheme, without further post-approval obligations.

##### *The United States*

The classification system of the FDA assigns all new drug approvals to categories representing distinct levels of innovation, and this classification is of particular relevance here as it highlights the different meanings of the term *innovation*. The FDA reviews new drug applications (NDAs) and awards *priority* status based on chemical type and therapeutic potential. With regard to the latter, a drug qualifies for *priority review* if it offers a potentially significant improvement over marketed products. With regard to the former, a *new molecular entity (NME)* is a drug whose active ingredient has never before been approved by the FDA for the USA market. An incrementally

*modified drug (IMD)* is one that relies on an active ingredient present in a drug already approved for the USA market (or a closely related chemical derivative of such an ingredient), and has been modified by the manufacturer. Drugs are classified as *other* if they rely on an active ingredient that is already available in an identical marketed product. A *standard drug* is a product that does not qualify for priority review and it can be a NME, IMD or other. Most United States observers would view priority NMEs as the most innovative type of new drug.

The FDA has also granted priority status to some IMDs, indicating that they provide therapeutic advances even though they are derivatives. Priority IMDs are also moderately innovative. The FDA, however, rates many NMEs as standard and, although based on new compounds, these drugs usually have the same mechanism of action and outcomes as other drugs on the market. Standard NMEs may have different safety and efficacy profiles from other marketed drugs in the same class. Thus, standard NMEs may enhance clinical outcomes even if they do not demonstrate significant improvement over other medicines already available.<sup>13</sup>

The FDA's *fast track* process is designed to facilitate the development, and expedite the marketing review, of drugs that both target "serious" diseases and fill an "unmet medical need". Determining whether a disease is "serious" is generally based on whether the drug will have an impact on factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Filling an "unmet medical need" is defined as providing a therapy where none exists or providing a therapy which may be potentially superior to existing therapy. If there are existing therapies, a fast track drug must show some advantage over available treatment, such as: showing superior effectiveness; avoiding serious-side effects of an available treatment; improving the diagnosis of a serious disease where early diagnosis results in an improved outcome; or decreasing the clinically significant toxicity of an accepted treatment. Most products that are eligible for "fast track" designation are likely to be considered appropriate to receive a priority review. A drug that receives "fast track" (and probably also priority review) designation is eligible in effect for more frequent contact with the FDA as well as eligibility for a third component of prioritization, "accelerated approval" i.e., marketing approval on an effect on a surrogate, or substitute endpoint reasonably likely to predict clinical benefit. All of these procedural measures indicate a willingness of the FDA to `prioritize` applications to accelerate regulatory review prior to market authorization.

Another FDA initiative, *priority review vouchers* are, in essence, a prize incentive for companies to invest in new drugs and vaccines for neglected tropical diseases. A provision of the Food and Drug Administration Amendments Act (HR 3580) awards a priority review voucher to any company that obtains approval for a treatment for a neglected tropical disease. The voucher, which is transferable and can be sold, also entitles the bearer to a priority review for another product.

#### 3.4 Public sector priority setting for research and development

The United States National Institutes of Health (NIH), the largest public funder of biomedical research in the world, has identified five criteria that play a critical role in decisions about funding biomedical research: (1) public health needs; (2) scientific merit of specific study proposals; (3) potential for advances in a particular area; (4) distribution across diverse research areas (since it is impossible to predict exactly where advances will occur); and (5) national training and infrastructure needs. The first of these criteria, public health needs, is determined on the basis of five considerations: the number of people with a specific disease; the number of deaths attributable to a specific disease; the degree of disability caused by a specific disease; to what extent a specific disease shortens the average human lifespan; the financial and social costs of a specific disease; and threats posed to others by contagious disease. According to the NIH in 1997, these five considerations for determining “public health needs” were of equal importance in allocating research resources.<sup>14</sup>

At the time of the 2004 Report, only four institutes of the NIH - the National Cancer Institute (NCI), the National Institute of Child Health & Human Development (NICHD), the National Institute on Aging (NIA) and the National Institute of Environmental Health Studies (NIEHS) - had the facility to retrieve bibliometric data to track the publications and assess the potential public health impact of their grantees. Of these, three institutes (NIEHS, NICHD and NIA) have collaborated to develop a database to improve the priority-setting process.<sup>15</sup> The Office of Portfolio Analysis (OPA) was only recently established in 2011 by the NIH as a whole to “enable NIH research administrators and decision makers to evaluate and prioritize current, as well as emerging, areas of research that will advance knowledge and improve human health.”<sup>16</sup>

With regard to the practical output of awarding NIH grants, there is still inadequate linkage between NIH awards and literature/citation data. Some preliminary bibliometric analysis suggests that the effect of a publication’s “impact factor” is more predictive of the fate of R01 grants than the number of subsequent citations of the investigators. At a Portfolio Analysis Workshop in July 2012, a survey of over 500 participants showed that 47% thought that measuring the impact of NIH grants would be the most important task in the work of the OPA.<sup>16</sup>

Since the late 1980s, there have been many attempts by various international organizations and less formal groups to develop methods for prioritizing health research (see also 2004 Report Chapter 3, Annex 3.1). During the 1990s, a series of commissions undertook studies aimed at priority setting for health or for health research, but none of these specifically focused on pharmaceutical research. The studies are summarized below in roughly chronological order:

**The Commission on Health Research for Development (1990)** was an independent international initiative formed in 1987 with the aim of improving the health of people in developing countries through a focus on research (see 2004 Report, Chapter 3 Appendix 3.1).

**The Essential National Health Research (ENHR)** approach was developed to define: who sets priorities and how to get participants involved; the potential functions, roles and responsibilities of various stakeholders; information and criteria for setting priorities; strategies for implementation; and indicators for evaluation. It was designed to not only specify broad research areas but also give a detailed listing of priority possibilities/options as well as to involve a broad range of stakeholders and significant engagement with experts. Significantly, discussion and decisions on funding are supposed to be based on tapping the skills and knowledge of scientists from a wide range of disciplines.<sup>17</sup>

**The World Development Report (1993)** was produced by the World Bank in conjunction with the WHO and used a key measure of the burden of disease and disability called the Disability Adjusted Life Year (DALY), which has also been used in this Project (see Background Paper 4).<sup>18</sup>

**The Ad Hoc Committee on Health Research (1996)** was established in 1994 by the WHO. It identified a systematic “five-step” process which is the basis of the conceptual model used in this project.<sup>19</sup> Briefly, these five steps include: 1. Calculate the burden of the conditions or risk factor (look at the *magnitude*); 2. Identify the reason why the disease burden persists (look at *determinants*); 3. Judge the adequacy of the current knowledge base (assay *knowledge*); 4. Assess whether new R&D would improve population health and at what cost (understand *cost and effectiveness*); 5. Assess the adequacy of the current level of effort.

**The Global Forum for Health Research (2000)** created a framework (Combined Approach Matrix) which brings together in a systematic manner all information (current knowledge) related to a particular disease or risk factor<sup>20</sup> (see 2004 Report Chapter 3, Appendix 3.6).

**WHO-IFPMA Round Table (2000-2001)** was a joint task force, comprising representatives of the WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), convened to establish a working list of infectious diseases and to review disease burden as a way of directing research priorities. The task force also used additional criteria such as mortality, societal costs, likelihood of treatment, and future trends. (See 2004 Report Chapter 3, Appendix 3.7).

**The UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR)** prioritized research by using an adapted version of the Global Forum’s framework for priority setting, expanded to include information on the comparative advantages of the TDR.<sup>21</sup> (See 2004 Report Chapter 3, Appendix 3.4).

#### 3.5 Approaches to priority setting post-2004

**Priority Setting Methodologies in Health Research (2008)** was the theme of a workshop held at the WHO in Geneva, Switzerland in April 2008. The overall objective was to develop practical proposals for user-friendly methodologies for priority setting in health research, for application in developing countries. Specifically, the workshop (1) reviewed the main priority-setting methodologies utilized to date; (2) reviewed and assessed case studies of priority setting in various countries and for various topic areas; and (3) developed a framework of guiding principles and a practical approach to priority setting by bringing together salient elements of existing methodologies (see Background Paper 3 and Annexes).

**The Child Health and Nutrition Research Initiative (CHNRI) (2007)** approach emphasized principles of legitimacy and fairness and provided a detailed listing of individual research questions scored against pre-defined criteria. Technical experts independently scored each research option against these five criteria. As in other methods, stakeholder input was sought and used to rank the five criteria from the most important to the least important. These rankings were then adjusted to provide relative “weights” that determined the importance of the research option. Everything is recorded, is repeatable, can be reviewed, and can be challenged and revised at any time based on feedback, so this is a very dynamic process. The role of non-experts was limited to selecting and weighing criteria. Once consensus is reached on areas of research there is no further stakeholder involvement.<sup>22,23</sup>

#### 3.6 Private sector prioritization methods

Methods of prioritization in the pharmaceutical industry vary from company to company depending on their history and strategic vision. Decisions about new medicines are generally made within a set of four different contexts: scientific opportunity, market assessment, available and required resources, and medical need. The common steps taken are to:

- Review the marketplace to identify unmet medical needs.
- Benchmark competitor products to understand the competitive landscape.
- Identify the market segments and patient populations a product will target.
- Identify all possible additional indications that might make the compound more valuable.
- Create a dosing and delivery profile to provide optimal dosing and delivery mechanisms.
- Understand the broad market preferences for the key characteristics of the product. The goal of market research at this point would be to find a product profile which payers are willing to pay for and which provides a sufficient return on investment (for example, is the product profile such that physicians would prescribe it at the levels needed to justify further development?).
- Assemble market research to profile key geographic markets to ensure product success.

The strength of this approach is that it clearly identifies products that the "market" is willing to pay for and that will ensure an adequate return on investment. Unfortunately, this approach will ignore diseases which mainly affect the poor in low-income countries.

### 3.7 Prioritizing for the Priority Medicines Project

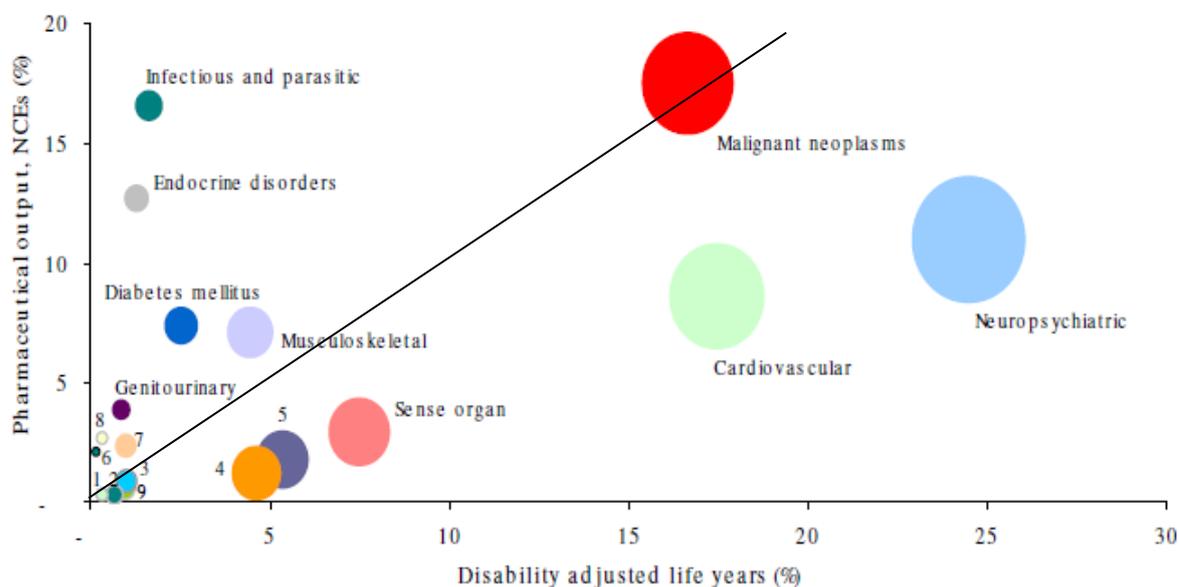
An assumption in the methods used in this report is that the higher the disease burden, the greater the cost to society of the disease, and the greater the need for research. Priorities are then set based on: the relative contribution of each disease to the total burden; and the measure of burden, ranging from epidemiologic measures to combinations of mortality and morbidity (such as the Disability Adjusted Life Year (DALY)). A version of this approach is used in the present method (see Background Paper 4).

A recent study by Catalá-Lopez et al examined whether efforts to develop innovative medicines in Europe are focusing on the most relevant conditions from a global public health perspective.<sup>24</sup> The authors reviewed the information on new medicinal products approved by the EU centralized procedure from 1995 to 2009 and evaluated the association between authorized medicinal products and burden of disease measures, based on DALYs in the EU and worldwide. They considered 520 marketing authorizations for medicinal products and 338 active ingredients. There was a positive, high correlation between DALYs and new medicinal product development ( $r = 0.619$ ,  $p = 0.005$ ) in the EU, and a moderate correlation for low- and middle-income countries ( $r = 0.497$ ,  $p = 0.030$ ) and worldwide ( $r = 0.490$ ,  $p = 0.033$ ).

Figure 3.7.1 shows a plot of the DALY burden of the then EU25 countries versus the proportion of total new chemical entities (NCEs) attributed to that condition (see Catalá-López et al. *Population Health Metrics*, 2010<sup>24</sup>).

The size of the "bubble" is the weighted fraction of each condition to the total DALY burden. The black line is the 1:1 situation where the fraction (%) of NCEs for that condition matches the proportional DALY burden for that condition. In the EU25, infectious and parasitic diseases, blood and endocrine disorders, diabetes mellitus and genitourinary diseases were all relatively over-represented with regard to NCEs in relation to the disease burden they generate (points above the 1:1 line in Figure 3.7.1), while the most under-represented conditions were neuropsychiatric diseases, cardiovascular diseases, respiratory diseases, sense organ conditions and digestive diseases (points below the 1:1 line). At the global level (data from the same source, not presented here), the most under-represented conditions were perinatal conditions, respiratory infections, sense organ conditions, respiratory diseases and digestive diseases.

**Figure 3.7.1: Bubble plot representing disability-adjusted life years (DALYs) for EU-25 and active ingredients (NCEs)**



Source: Catalá-López et al. *Population Health Metrics*, 2010, 8:34

Note: The areas of the bubbles are DALYs' weighted contribution of each disease condition(s) to the total burden of disease. 1: Other neoplasms; 2: Unintentional injuries (poisoning); 3: Congenital anomalies; 4: Digestive diseases; 5: Respiratory diseases; 6: Skin diseases; 7: Respiratory infections; 8: Maternal conditions; 9: Perinatal conditions

### 3.8 Providing a menu of complementary priority setting approaches

As in the 2004 Report, the present report uses several complementary approaches for establishing priorities for biomedical research. Where adequate data are available on burden of disease and on the efficacy or lack of efficacy of treatments, an evidence-based approach has been used (Modes 1-2 in Figure 3.2.1). Where data on burden of disease or efficacy do not exist, projection or trend analysis methods have been used (Modes 4-6 in Figure 3.2.1). For rare diseases and neglected diseases or where market failures occur, principles of social solidarity have been applied (Modes 4-7 in Figure 3.2.1). (See Background Paper 3). Where it is clear that risk factors play a role in the development of multiple disease states (mainly noncommunicable diseases), risk factors (obesity, smoking) have themselves been used as a priority condition (Modes 4-7 in Figure 3.2.1).

In order to bring complementary information to this approach, the framework developed by the Global Forum has also been used to ask additional questions about the current state of diseases of interest. This framework can be seen in the templates developed for determining pharmaceutical gaps in Chapter 6. As these are different though complementary methods the outcomes of each approach cannot be directly

compared. All four approaches are presented to give a comprehensive overview of “pharmaceutical gaps” that can be prioritized for research.

### **3.8.1 Priorities based on evidence-based approach (For example, acute stroke, chronic obstructive pulmonary disease (COPD), Alzheimer disease: Modes 1 and 2 in Figure 3.2.1)**

For this approach, burden of disease analysis has been used to determine a preliminary list of high burden diseases and conditions. The combination of burden of disease and clinical efficacy provides a preliminary list of conditions which have pharmaceutical gaps ([see also Background Paper 5](#)).

### **3.8.2 Priorities based on projections and trends (For example, antimicrobial resistance (AMR), pandemic influenza: Modes 4-7 in Figure 3.2.1)**

Looking ahead, what are the emerging diseases that could affect the EU and the world? The answers to these questions form the second prioritization method and are based primarily on consensus judgements and observational and clinical evidence. Although AMR is not a disease or condition *per se*, its importance as a threat to global public health is expected to continue to grow. The same holds true for pandemic influenza.

### **3.8.3 Priorities based on social solidarity (For example, rare or neglected diseases: Modes 4-7 in Figure 3.2.1)**

The ethical and moral aspects of priority setting have been selected as the third prioritization method along the continuum of Figure 3.1. Ethics and moral values are often invoked to mobilize support for various health initiatives, and theories of social justice (for example, the fair and equitable treatment of people) have been applied to justify medicine and public health as a special “social good” (see 2004 Report, Background Paper 3). Many European countries have a long history of social solidarity. This has been demonstrated by the creation of universal social security systems and of national health systems which are intended to ensure universal access to medical care and pharmaceuticals.

In the EU and elsewhere, governments have enacted legislation to protect the interests of people suffering from rare (“orphan”) diseases. This requires society to spend substantial funds on a limited number of people who suffer from rare diseases. At a global level, based on principles of global solidarity, similar efforts are needed to address neglected diseases, which mainly affect the poor in low-income countries, as well as other poor populations. In response, orphan diseases and neglected diseases have been selected as priority diseases, even though the former affect small numbers of patients and the latter affect patients living outside the EU. Special patient groups (the elderly, women and children) are also considered since these groups often lack effective medicines.

#### 3.8.4 Priorities based on risk factors

(For example, smoking, obesity: Modes 4-7 in Figure 3.2.1)

The most critical disease risk factors that will affect the EU countries and the world going forward were selected as the fourth prioritization method along the continuum of Figure 3.2.1. The answers to these questions are based on data generated by the WHO's *Global Burden of Disease: 2004 Update* and by the analyses of the more recent and distinct *Global Burden of Disease Study 2010* (see Chapter 4 and associated Background documents). Obesity and tobacco use are risk factors for major chronic noncommunicable diseases (NCDs) that influence both length and quality of life. More specifically, obesity and smoking are well-established independent risk factors for cardiovascular diseases. While all of these risk factors can and should be addressed through prevention and health promotion activities, possible opportunities for pharmacotherapeutic approaches exist. As a result, these risk factors were added to the Preliminary List.

### 3.9 Conclusions

In this report, four complementary approaches to prioritization are used in an effort to overcome the inadequacies of any one of these approaches when used exclusively. For those decision makers who would like to use only evidence-based approaches, it should be noted that absence of evidence does not necessarily mean there is no threat or need. For those who would prefer to use a consensus-based expert opinion approach, it should be pointed out that such expert groups have often missed important developments. And while an approach based on the use of projections and trends is critical in efforts to prepare for future threats to global public health, it inevitably involves the use of judgments made on the basis of uncertain information. For those who would use social solidarity as the sole criterion for prioritization, it is important to note that there are many people, both rich and poor, from developed and developing countries, who have benefited substantially from medical advances achieved as a result of approaches based on evidence or projections and trends.

In this report a combination of methods have been used to achieve a balanced and optimal result. By using these four approaches together, the health needs of both Europe and the world have been taken into account in addressing pharmaceutical gaps for diseases of current and future public health importance.

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# 4. Methods used in the Priority Medicines Project

[See Background Paper 4 \(BP4 Methods.pdf\)](#)

## 4.1 Introduction

The methodology described in this chapter is designed to determine pharmaceutical gaps and to create a public-health-based research agenda for the European Union (EU). This Project has combined a number of methods to produce a methodology that can be used for priority setting at country, regional and global levels. The method is intended to be explicit and reproducible (source data are provided on the WHO web site). This chapter provides details of the four complementary approaches used: the evidence-based approach; future projections approach; the risk factor approach; and the social solidarity approach. (See Background Paper 4).

## 4.2 Applying the methodology

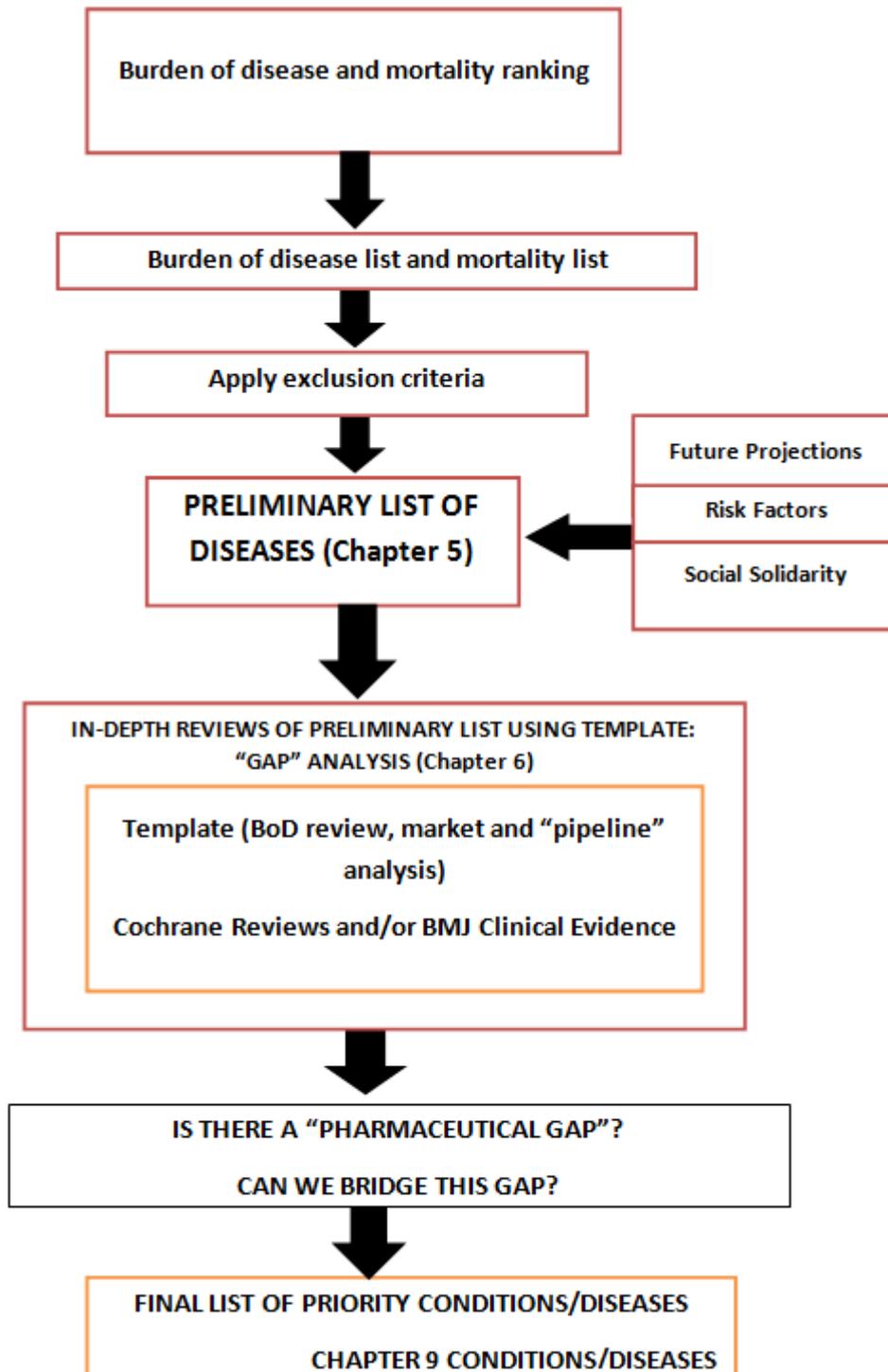
The methodology involves the use of analyses of several different factors: demographics, burden of disease and clinical efficacy.

1. The first step was a review of demographic factors (such as life expectancy and age distribution) for countries in Europe (including the EU27) and the world to set the context for the Report.
2. A ranking exercise was then carried out, using burden of disease information (Disability Adjusted Life Years (DALYs) and mortality), to generate two lists: one list of the major diseases and conditions which account for the majority of the total DALY burden in both the EU 27 and the rest of the world; and the second a counterpart list for the total mortality burden of major diseases and conditions ([see Chapter 5, Tables 5.3 and 5.4](#)). These are called the *burden of disease and mortality lists* in Figure 4.1.
3. Some of the conditions on these lists, such as road traffic accidents, were then excluded, mainly because pharmacotherapies were not amenable to deal with these conditions.
4. Additional criteria derived from the three other approaches (Section 4.7) were then applied to generate additions to the diseases and conditions on these two lists. These included: health-related projections and trends; risk factors; and social solidarity/social justice/equity. The Primary List was then generated by combining

the DALY and mortality lists, removing any duplicate conditions, and adding new ones based on the three additional approaches (Figure 4.1).

5. A series of background papers were then commissioned for each of the conditions identified on the Preliminary List. These are the *in-depth reviews* referred to in Figure 4.1. Each reviewer was asked to format the background paper according to a template described in more detail in section 4.9. They were also asked to review the Cochrane Database of Systematic Reviews to determine whether the pharmaceutical interventions available to treat these Preliminary List diseases were efficacious. Information on diagnostics and vaccines was also included, where appropriate. The purpose of these in-depth reviews was to determine whether a pharmacotherapeutic treatment gap existed in any of the selected conditions. The detailed Background Papers are summarized in Chapter 6.
6. The diseases and conditions on the Preliminary List identified as having pharmaceutical gaps were then added to the Final List, as shown in Figure 4.1. Key aspects of the methodology will be discussed in more detail now.

Figure 4.1: Schematic of the methodology used in the Priority Medicines Report



### 4.3 Sources of data: Demographic

The demographic component of this report is based on important regional and international reports and databases in which the following parameters were analysed: life expectancy at birth; age distribution of the world population; fertility rates; and distribution of people living in urban and rural areas. The primary database used was the World Development Indicators database<sup>1</sup> (see Background Paper 5).

### 4.4 Geographical definitions

In some parts of this report, data on the EU 27 countries (listed below) has been used as well as on subunits of the EU27, depending on when various countries joined the EU.

**EU 27:** As of 2013, the 27 Member States of the European Union are Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Where data on the 27 individual EU countries was not available, data on the WHO European Region was used. This was the case, for example, for the DALY statistics used, which were based on the 2008 estimates from the WHO Global Burden of Disease Database. The WHO European Region comprises over 50 countries, including the EU27, and covers a vast geographic region, from Iceland to Kazakhstan.

While the WHO Global Burden of Disease 2004 bases data for Europe on the WHO European Region, the GBD 2010 study provides differentiated data for three European sub-regions (established on the basis of epidemiological homogeneity and geographic contiguity). A total of 21 regions were created globally, of which three are relevant to the European countries:

1) Central Europe:

Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, the former Yugoslav Republic of Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia.

2) Eastern Europe:

Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine.

3) Western Europe:

Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.

### 4.5 Sources of data: Burden of Disease

#### 4.5.1 Disability Adjusted Life Years (DALYs)

Over the past these decades, the WHO, the World Bank and many other organizations have used and promoted the concept of DALYs as an integrated measure of mortality and disability. The indicator combines mortality and morbidity in a single measure. One DALY can be thought of as one lost year of 'healthy' life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability. In brief, DALYs are a way of aggregating the number of life years lost by sufferers from each disease with the amount of disability suffered while they are still alive. These two amounts are combined in a complex manner to give the overall burden of that disease. Disease burdens are thus measured in DALYs lost due to each disease. This burden of disease approach can be broken down to show the relative contributions of different conditions to the overall burden of disease and it can show the burden of disease that can be attributed to known risk factors.

Although the DALY methodology is not perfect, it is the best single tool available for the intended audience of this report (i.e. strategic planners and decision makers). It provides a single summary measure of ill health, a fundamental tool for policy makers when considering the relative benefits of different policy options (see Background Paper 1.3).

Measuring the burden of disease using DALYs is well-established. It can be broken down to show the relative contributions of different conditions to the overall burden of disease; it can show the burden of disease that can be attributed to known risk factors; and can be combined with cost to assess cost-effectiveness. In calculating DALYs, this Report uses projections for 2008 for the EU27 and the world, obtained from the WHO Global Burden of Disease Database.<sup>2</sup>

In late 2012, a new study on worldwide burden of disease was published: the *Global Burden of Disease Study 2010* (GBD 2010). This study was not an update of the WHO's *The Global Burden of Disease: 2004 Update*, but a new collaborative global burden assessment exercise, which includes a more extensive set of disease sequelae, age groups and regions.<sup>3,4</sup>

The GBD 2010 analyses differ in several ways from those of the WHO Global Burden of Disease 2004 (see Background Paper 4). For example, in the GBD 2010 Study, death rates and numbers have been estimated with 95% uncertainty intervals (95% UIs). In Chapters 5 and 6, the most recent 2010 data has been presented in addition to the 2008 projections.

### 4.5.2 Mortality

Mortality is also used here as a measure of burden of disease as this is easy to understand. However, this measure is not able to reflect the burden of pain and suffering experienced by patients with chronic diseases such as osteoarthritis. The mortality data used here are actual (not estimated) data for 2008 from the WHO Global Burden of Disease Database<sup>1</sup> which estimates global and regional mortality. These data have been disaggregated into broad categories and then into specific disease categories and are made available by country, sex and age group. The GBD 2010 Study also provided mortality data.<sup>4</sup>

### 4.6 Applying exclusion criteria to the Burden of Disease and Mortality List

Once the burden of disease and mortality lists had been generated, the next step was to eliminate conditions and diseases that, based on the reviewers experience and literature review, could not be cured or treated with pharmaceutical interventions designed for the specific condition. These were: intentional and unintentional injuries; road traffic accidents; refractive errors; birth trauma; and childhood cluster diseases.

### 4.7 Considerations to generate additions to the Preliminary List.

Several other domains or factors were analysed in order to identify other diseases and conditions that should be added to the Preliminary List. These were risk factors based on analyses carried out as part of the WHO Global Burden of Disease 2004 study; social solidarity; and future trends and projections (demographic and epidemiological).

#### *Approach based on risk factors*

Substantial proportions of global disease burden are attributable to major risk factors. In both developing and high-income countries, leading risk factors such as smoking, alcohol consumption and obesity account for a large burden of disease. Prevention strategies that target these known risks can provide substantial and underestimated public health gains. For this reason, risk factors were added to the list of conditions and diseases used to generate the Preliminary List (Figure 4.1).

#### *Approach based on projections and trends*

As in the 2004 Report, diseases that will affect the EU countries and the world were reviewed. What existing diseases will grow in importance? The answers to these questions form another prioritization method and are based primarily on consensus judgements and observational and clinical evidence. In addition, resolutions of the WHO World Health Assembly (WHA) and the European Parliament have identified antimicrobial resistance (AMR) as a serious threat to global public health.<sup>5,6</sup>

### *Approach based on social solidarity*

Again as in 2004, another approach used concepts of social justice, social solidarity and equity to place on the Preliminary List certain conditions with pharmaceutical gaps, such as rare (orphan) diseases and neglected tropical diseases. Diseases affecting special patient groups (the elderly, women and children) are also included ([see also Background Papers 7](#)).

### **4.8 Generating the Preliminary List**

Based on the three considerations outlined above, pharmaceutical interventions dealing with obesity and smoking (risk factors), those for AMR and influenza (epidemiologic projections) and those for rare (orphan) diseases and neglected tropical diseases (based on social solidarity concerns) were added to the list together with the disease burden “league tables” to create a Preliminary List of Diseases (see Chapter 5 and the associated Background Papers).

### **4.9 Background reviews**

In-depth or background reviews of each of the Preliminary List entities were based on the Global Forum for Health Research approach.<sup>7</sup> The diseases and conditions identified in the Preliminary List were rigorously reviewed by asking the following questions:

- What is the size and nature of the disease burden?
- What is the control strategy? Is there a pharmaceutical gap?
- Why does the disease burden persist?
- What can be learnt from past/current research into pharmaceutical interventions for this condition?
- What is the current “pipeline” of products that are to be used for this particular condition?
- What are the opportunities for research into new pharmaceutical interventions?
- What are the gaps between current research and potential research issues which could make a difference, are affordable and could be carried out in a) five years or b) in the longer term?
- For which of these gaps are there opportunities for pharmaceutical research?

This is the same set of questions posed in the in-depth reviews in the 2004 Priority Medicines Report. Based on these specific reviews, opportunities to close existing pharmaceutical gaps have been identified for each condition.

### 4.10 Background reviews: clinical efficacy

A prerequisite for the in-depth reviews was to have a measure of the clinical efficacy of the different pharmaceutical interventions currently available. The primary data source used for this was the collection of analyses in the Cochrane Database of Systematic Reviews.<sup>8</sup> The reviewers also used the Clinical Evidence summaries of the *British Medical Journal*<sup>9</sup> which present information in a less quantitative format. The Cochrane systematic reviews, based on relevant studies from the international medical literature, are conducted by the international Cochrane Collaboration, an organization of over 7 000 health professionals, researchers, scientists and consumers from approximately 80 countries. There are 50 international Cochrane Review Groups. These highly structured reviews summarize and synthesize results from the highest quality research studies, usually randomized, placebo-controlled trials. The results are combined statistically.

The work of the Cochrane Groups is considered the gold standard in the search for the best systematic reviews of medical evidence. However, the Cochrane Database has a number of limitations. One of the drawbacks is that these reviews are retrospective. As a result, the most recent interventions or products without market approval may not have sufficient numbers of patients or trials to warrant a systematic review. Moreover, some of the interventions that are reviewed may no longer be used in clinical practice or have been superseded by other, more effective interventions.

Another drawback is that most trials data in the Cochrane Database are randomized placebo-controlled trials and do not include other data such as that from observational studies ([see also Chapter 8.4](#)). Where possible, decisions should be based on comparison of new interventions with current practice, not with placebos. What is important from a public health viewpoint is not whether a new intervention works better than “nothing”, but whether it works better than the current best available treatment.

Another limitation of the Cochrane Database is the limited data on adverse events – information which may be useful in determining R&D priorities. The randomized clinical trials in the database are designed to assess efficacy and only occasionally report side-effects. Analyses of the available data on adverse events from the Cochrane Database were not used in determining priorities because only a small number of trials were involved. The difficulty faced in obtaining this data underlines the need to improve the regulatory process using Phase IV research (post-marketing surveillance) to collect data on both adverse events and exposure to pharmaceuticals in large numbers of patients.

#### *Measures of clinical efficacy*

Clinical efficacy is a measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in a clinical trial. The Cochrane Reviews should be viewed in terms of clinical efficacy and not clinical effectiveness; the latter defined as the

## 4. Methods used in the Priority Medicines Project

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accuracy or success of a diagnostic or therapeutic technique when carried out in a “real-world” clinical environment. That is, clinical effectiveness is the extent to which a treatment achieves its intended purpose. In the present Report these terms are not used interchangeably and the reader should be aware of this distinction.

The Cochrane system uses different statistical measures for summarizing the results of a large number of placebo-controlled clinical trials. In order to display all of the data in a consistent way, the results from the original Cochrane tables of results have been reviewed to extract the Relative Risk (RR) and Odds Ratios (ORs) and other measures. This involved the use of revising the existing pooled mean estimates of the Relative Risk and Odds Ratios from the existing Cochrane analyses comprising the same intervention so that desired (i.e. beneficial) outcomes have ratios greater than one. This is not necessarily the normal manner of presentation as, depending on the outcome measurement, beneficial outcomes may have Relative Risk or Odds Ratios less than one. Nonetheless, where appropriate, these transformations make it possible to display the results graphically in a way in which treatment effects better than placebo fall above the horizontal line.

As an example, Figure 4.2 shows the results obtained from many trials of different treatments for heart attacks (myocardial infarction). The mean Relative Risk and/or Odds Ratios derived from many trials for each intervention are displayed as square boxes in the vertical lines. These vertical lines represent “95% confidence intervals.” This means that if the trials comprising the pooled results were repeated by re-sampling 100 times, in 95 of the 100 times, the true value for the mean Relative Risk and Odds Ratios would fall somewhere along the vertical line.<sup>c</sup>

Where the square box is above the horizontal “1” line but the confidence interval line crosses below the horizontal “1” line this means that the benefits shown by the various clinical trials for the particular intervention might have occurred by chance alone. Therefore, in the statistical sense, the intervention has not been shown to have an unequivocal benefit. Figure 4.2, shows that in many trials the intervention was more clinically efficacious than the placebo as the lower boundary of the confidence interval is above the horizontal “1” line.

In the Background Papers of Chapter 6, a number of these charts are used to show where pharmaceutical gaps have been identified by using this methodology. Although these particular Cochrane-generated figures may mix different treatments and outcomes, it is striking how, for some conditions, nearly all the pooled trial results consistently demonstrate efficacy, while others, consistently fail to demonstrate efficacy.

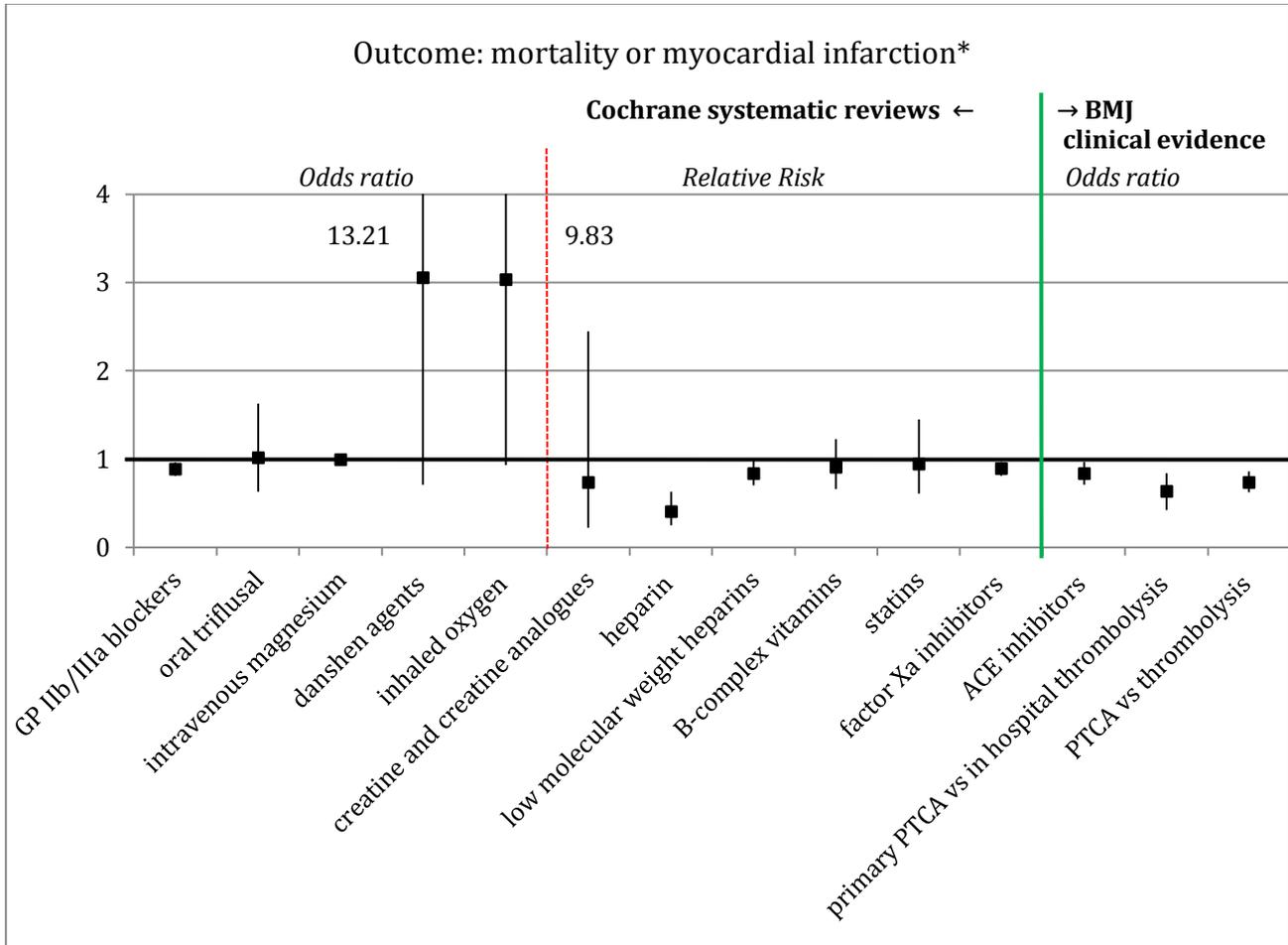
The methods described in this chapter are detailed in the Background Papers and associated Appendices and Annexes. The original burden of disease databases and the

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<sup>c</sup> Most confidence intervals involving ratios are asymmetric so the Relative Risk ratios are not in the middle of each vertical line.

spreadsheets of the Cochrane Database analyses are available on the web site to enable review of the results and further analyses for different countries or regions.

Figure 4.2: Trial results for different myocardial infarction treatments



RR or OR <1 favours the intervention (less mortality or myocardial infarction).

#### 4.11 Data sources for R&D funding

Donors interested in funding R&D of products for neglected diseases must currently make substantial investment decisions in the absence of accurate data regarding funding flows, gaps and duplications. Information that is available is often out of date, patchy and unreliable or cannot be compared across surveys due to different accounting and reporting methodologies. In some areas there is an almost total lack of information.

The goal of the G-FINDER survey is to help funders to better target their investments into neglected disease product R&D.<sup>10</sup> G-FINDER tracks global investment annually in

this area. It is hoped that by providing funders with better information, the G-FINDER survey will stimulate increased efficiency and investment into neglected disease product R&D. The G-FINDER survey includes 31 neglected diseases, and the pharmaceutical tools used to prevent, control and treat these, including medicines, preventive and therapeutic vaccines, diagnostics, microbicides and vector control products. The survey encompasses R&D funding for these products from basic research through clinical trials.

### 4.12 Conclusions

The methodology described above serves as the basis for determining priorities for a public-health-based research agenda for the EU. This is accomplished using in-depth analyses to decide which pharmaceutical gaps warrant further study. As discussed in Chapter 3, the prioritization scheme employs several different conceptual frameworks. The "ethical/moral" conceptual framework for prioritization is summarized in Chapter 3. The "evidence-based" framework, which is described in more detail in this Chapter, combines burden of disease and risk factor analysis with clinical efficacy measurements. This is further updated by informed judgments about future clinical and epidemiological scenarios and by in-depth (Background) reviews of recent science, drug development and market analyses for multiple disease areas.

### References

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- <sup>7</sup>*The 10/90 Report on Health Research 2001-2002*. Geneva, Global Forum for Health Research, 2002. Available at <http://www.globalforumhealth.org> Last accessed 1 March 2004
- <sup>8</sup>The Cochrane Library, from the Cochrane Collaboration. Available at [www.thecochranelibrary.com](http://www.thecochranelibrary.com).

<sup>9</sup> *BMJ Clinical Evidence* reviews. Available at <http://clinicalevidence.bmj.com/x/index.html>.

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# 5. Demography, Global Burden of Disease and the Preliminary List of Priorities.

[See Background Paper 5 \(BP5 PreliminaryList.pdf\)](#)

## 5.1 Introduction

This chapter provides summary results of the data collected on demographic changes in Europe and the world and on the burden of disease. Detailed tables of summary results are included. The purpose of the analysis reported in this chapter is to produce a Preliminary List, which provides the basis for in-depth studies of diseases and risk factors reported in Chapter 6 ([see also Background Paper 5](#)).

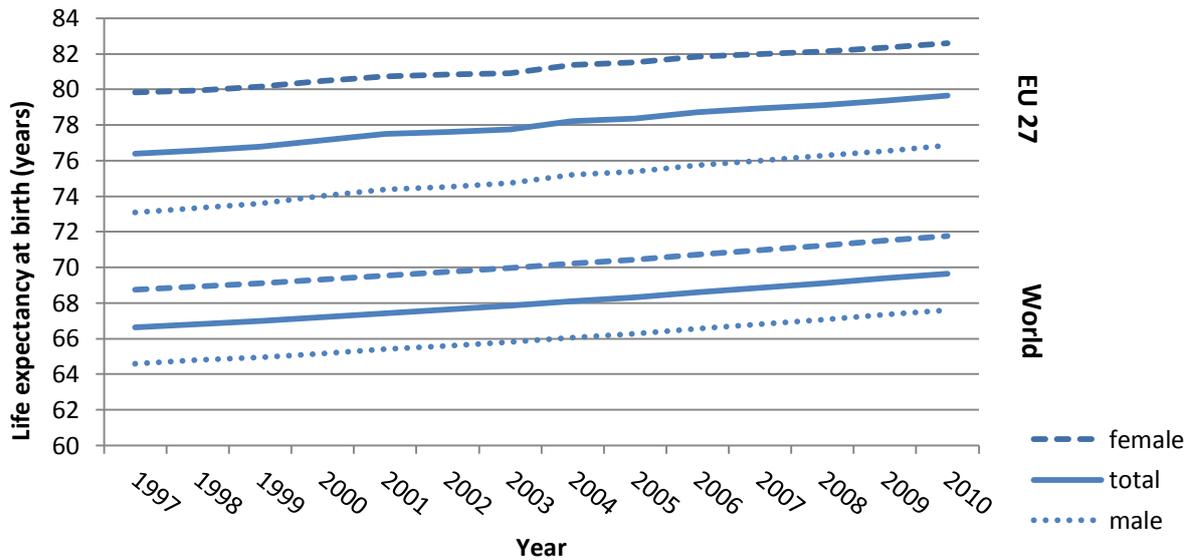
## 5.2 Demographic indicators and trends

Development, industrialization, urbanization and ageing are all factors in an epidemiological and demographic transition which is impacting on the disease burden in countries throughout the world. The global population is predicted to be 9.6 billion by 2050, up from about 7 billion today.<sup>1</sup> The overwhelming majority of population growth in the future will occur in low- and middle-income countries. The increase in population growth within these countries will have a substantial impact on health as more pressure is put on water supply, sanitation, health care facilities, nutritional resources and education. Unfortunately, the countries most affected by these transitions will be the ones with the least means to cope with these challenges.

### 5.2.1 Global demographic trends

Over the past 50 years, average life expectancy at birth has increased globally by almost 20 years.<sup>1</sup> As life expectancy increases and fertility rates drop, the global population is rapidly ageing, and mortality and morbidity are increasingly shifting to older age groups (see Background Paper 5, Figure 5.4). During the period 1997 to 2010, average life expectancy worldwide increased by about three years from 66.6 years to 69.6 years (see Figure 5.2.1). Meanwhile, in the EU27 countries, although absolute life expectancy is higher than that for the world, the absolute increase over time is about the same: up from an average of 76.4 years in 1997 to 79.6 years in 2010.

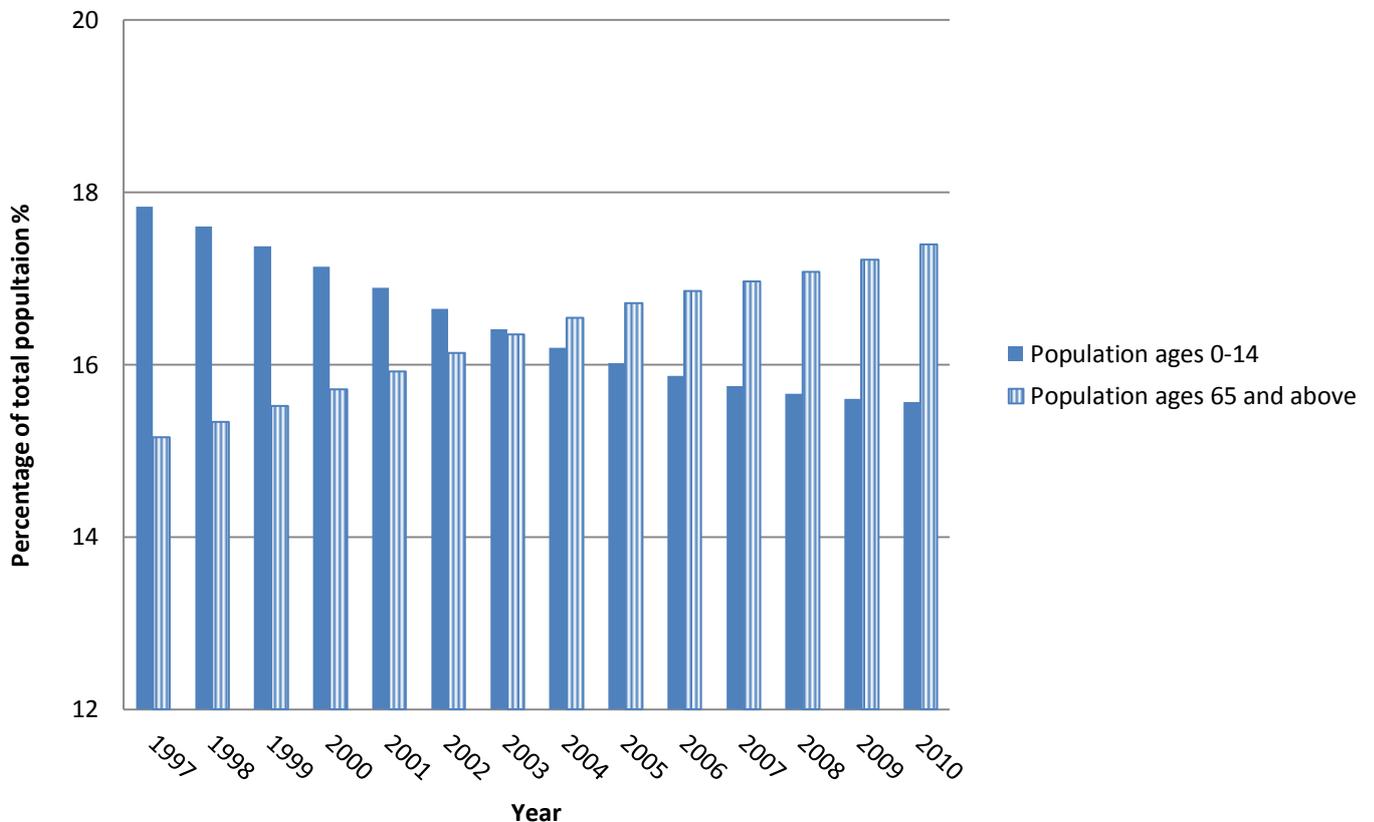
Figure 5.2.1: Average life expectancy at birth within EU27 and the world, 1997-2010



Source: Data from *the World Bank. World Development Indicators*. Available at: <http://databank.worldbank.org> Last accessed September 18, 2012

Lack of family planning resources and poor health literacy are related to poor health outcomes and result in higher fertility rates in low-income countries. In Niger, for example, women still have on average 7.1 children, compared with an average of 1.1 children in Latvia. Because of the low fertility rates and improvements in health care in high-income countries, population ageing is even more pronounced in the EU Member States. Since the original Priority Medicines Report in 2004, for the first time ever, the population of the EU countries includes a higher percentage of people aged 65 and older than of children aged under 15 (see Figure 5.2.2). Elsewhere, in low- and middle-income countries, there are still many more children aged under 15 than there are people aged 65 and over. But even in these countries, the percentage of children aged under 15 has declined from 31% in 1997 to 27% in 2010.

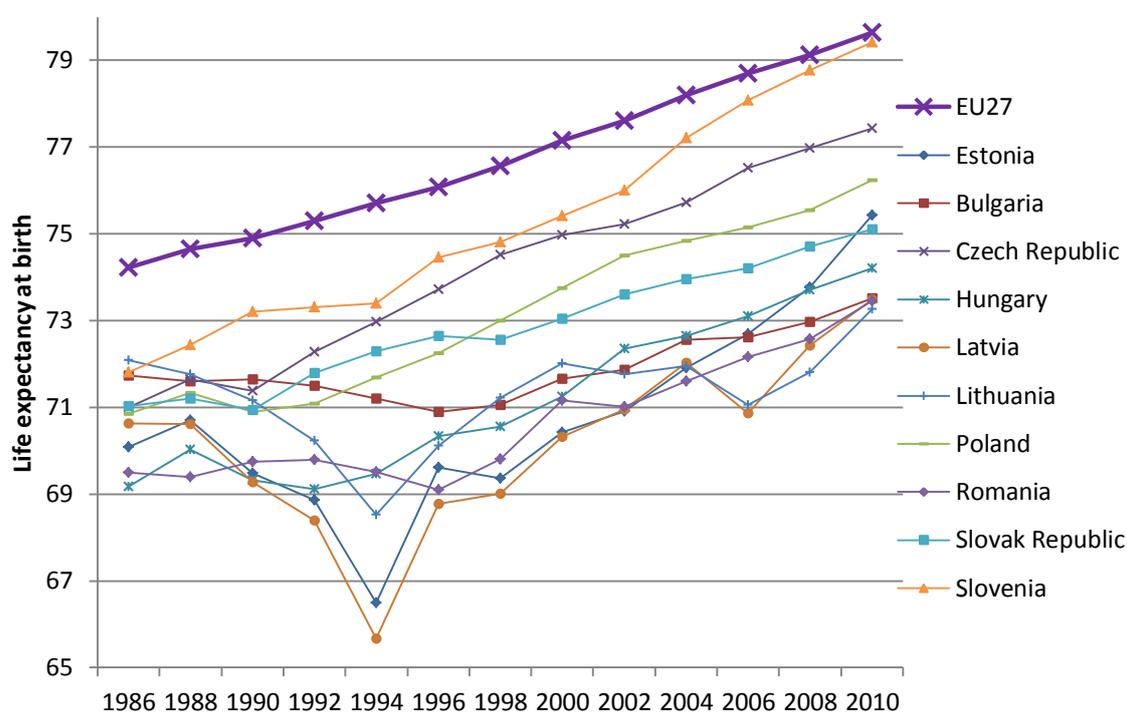
**Figure 5.2.2: Shift in young and elderly population for the European Union - 1997 to 2010**



Source: Data from the World Bank. World Development Indicators. Available at: <http://databank.worldbank.org> Last accessed September 20, 2012

Within Europe, there are significant differences in life expectancy and fertility rates between the EU Member States. For example, in Eastern Europe, after the break-up of the Soviet Union, there was a clear drop in average life expectancy for the three Baltic States (Estonia, Latvia, Lithuania) in comparison to the EU27 average. This drop started in 1988 and reached its lowest point in 1994 before rising again from the mid-1990s onwards (see Figure 5.2.3).

Figure 5.2.3: Life expectancy at birth: Central and Eastern European countries and EU27 average

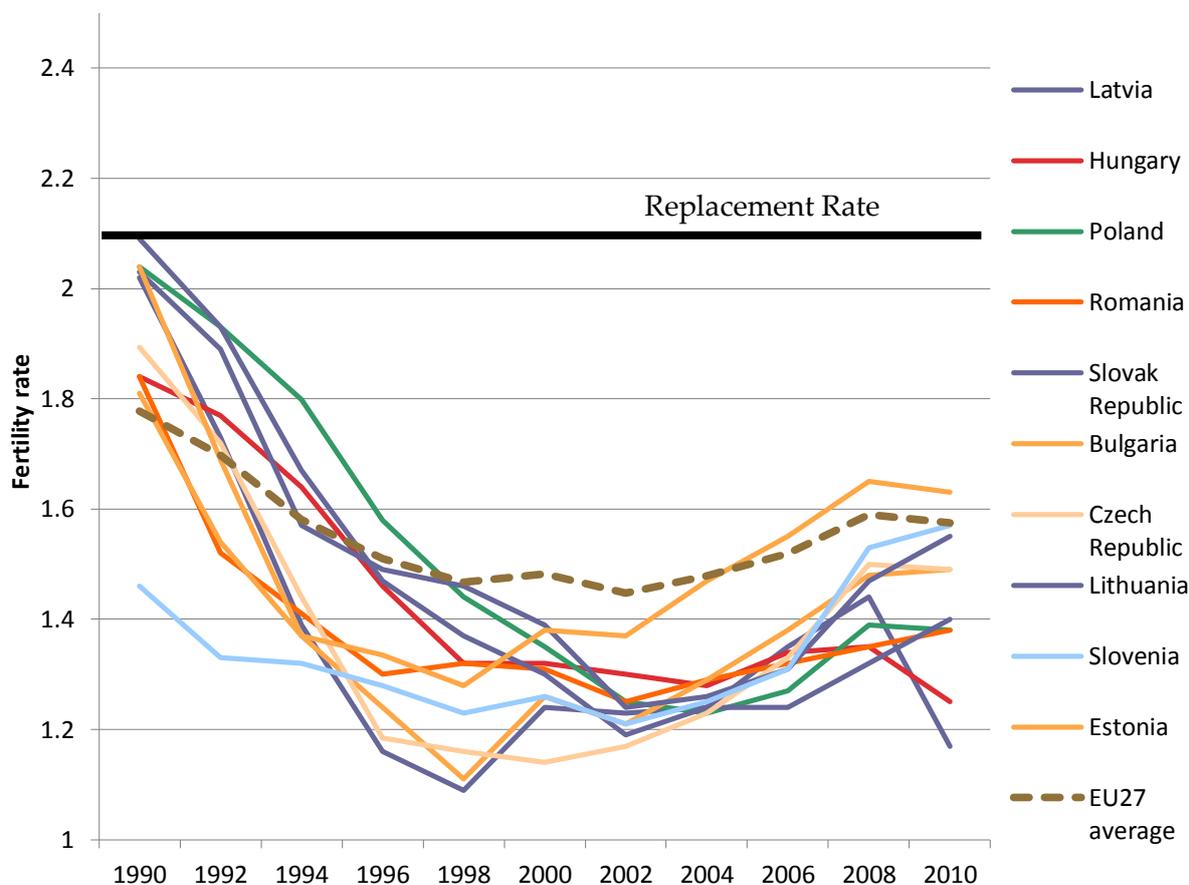


Source: Data from the World Bank. World Development Indicators.  
 Available at: <http://databank.worldbank.org> Last accessed October 9, 2012

Even two decades after the political transition in these countries, changes can still be mirrored in the patterns of life expectancy. Estonia continued to have a steady and rather dramatic increase in life expectancy from 2000 to 2010, while Latvia and Lithuania experienced a second drop in life expectancy around 2006.

As elsewhere in the world, the overall increase in life expectancy in Europe has been accompanied by a decline in fertility rates. However, fertility trends among European countries differ widely. The situation in the eastern European countries is marked by a steep decline in fertility, which began in the 1970s and accelerated in the early 1990s after the break-up of the Soviet Union.<sup>2</sup> Today, fertility rates in the Eastern European countries are among the lowest in Europe and are less than the replacement rate of 2.1 children (see Figure 5.2.4), which means that, without substantial immigration or changes in fertility rates, the population of these countries will shrink in the future. Eastern Europe is the first region in Europe in which such a substantial decrease in population is predicted by 2050. As elsewhere in Europe, this decrease in fertility and increase in life expectancy will lead to a rapid ageing of the population, putting pressure on pension systems and demand for health care.

**Figure 5.2.4: Fertility rates of Eastern European countries in comparison to the average of the European Union, 1990-2010**



Source: Data from the World Bank. World Development Indicators.

Available at: <http://databank.worldbank.org> Last accessed 21 December 2012.

Note: \*Replacement level fertility is the level of fertility at which a population exactly replaces itself from one generation to the next. In developed countries, replacement level fertility can be taken as requiring an average of 2.1 children per woman. In countries with high infant and child mortality rates, however, the average number of births may need to be much higher.

Although the overall increase in life expectancy can be seen as a great success and proof of global development and improved living standards, population ageing has profound implications for disease burden. As people live longer they spend more years with sickness and disabilities related to chronic noncommunicable diseases (NCDs) such as cardiovascular diseases, cancers and diabetes. In addition, the shift in the *dependency ratio*, with large numbers of older adults for every working person (see Figure 5.2.2), will make it difficult for countries to finance the health care needs that come with this increased burden. This is especially problematic in low- and middle-income countries, where infectious diseases still account for another large portion of the disease burden. In these countries, the growing epidemic of chronic NCDs puts pressure on existing health systems, which now have to address both infectious (communicable) and NCDs, a problem known as the *double burden of disease*.<sup>3</sup>

Another important trend contributing to the change in burden of disease is urbanization. Over the past decade, for the first time in world history, the majority of the world's population lived in urban areas.<sup>4</sup> Cities offer the lure of better employment, education, health care and culture; and they contribute disproportionately to national economies.<sup>4</sup> However, rapid and unplanned urban growth is often associated with slums, poverty, eating unhealthy foods, environmental degradation and population demands that cannot be met, such as safe drinking water, sanitation, processing of waste disposal and treatment of disease.

### 5.2.2 Disease trends

#### *Noncommunicable diseases*

The recent *Global Burden of Disease Study 2010 (GBD 2010)*<sup>5</sup> found that in 2010, 54% of all global DALYs were due to NCDs, compared with 35% due to communicable, maternal, neonatal and nutritional disorders, and 11% due to injuries. With declining fertility rates and improvement in health care in many low- and middle-income countries, the global burden of NCDs is predicted to catch up with the European pattern in the near future.

Noncommunicable diseases are today the main cause of death in EU countries. In the countries of the former Soviet Union, the risk of death related to ischaemic heart diseases and diseases of the circulatory system increased sharply at the beginning of the 1990s, soon after the break-up of the Soviet Union, and began decreasing in the mid-1990s.<sup>6</sup> Traditional risk factors such as smoking, diets rich in saturated fats, alcohol consumption (specifically binge drinking) and psychosocial factors are thought to be related to the elevated levels of cardiovascular morbidity and mortality in Eastern Europe compared to the levels in Western European countries.<sup>7</sup>

Cancers account for a substantial amount of the chronic disease burden in Europe. (See Background Paper 6.4 Cancer.) Over the past 25 years, the number of lung cancer deaths among men has decreased steadily in most western European countries with the exceptions of France, Portugal and Spain. Meanwhile, lung cancer deaths among women are on the increase almost everywhere. Although the exact reasons for this increase remain unclear, the growing number of female smokers must contribute to this ([see also Background Paper 6.17 on tobacco use cessation](#)).

Diabetes, which is associated with an increase in obesity, is among the leading causes of mortality and disease burden within the EU.<sup>8</sup> In 2009, there were over 31 million people living with diabetes in the EU27 and this number is expected to more than double by 2030, with an estimated 64.2 million people affected.<sup>8</sup> Estimates and projections point to a Europe-wide epidemic of the disease in the coming years (for more details see Background Paper 6.4 on diabetes and Chapter 6.18 on obesity).

Neuropsychiatric conditions account for almost 20% of the total DALY burden in the EU27 countries (see Background Paper 5, Tables 5.1 and 5.4). Of these conditions,

unipolar depressive disorders are ranked highest for burden of disease (measured in DALYs) in the EU, while Alzheimer disease and other dementias are ranked highest for mortality. The consequences of rapid economic and societal change as observed in the countries of Central and Eastern Europe, have been accompanied by a decline in population mental health. This is shown in the increasing rates of alcohol-use disorders, violence and suicide (see Background Paper 5). As the population ages, the incidence of both dementia and other mental health problems, such as depression, are likely to increase even more.

Chronic obstructive pulmonary disease (COPD) is another large disease burden in Europe, where the prevalence of clinically relevant COPD ranges from 4% to 10% of the adult population. In 2008, the countries most affected by COPD were Ireland and Romania, with rates of more than 80 cases per 100 000 population. (See Background Paper 6.13). Just as with lung cancer, there has been a moderate decrease in overall mortality from COPD in most Western European countries, while there was a considerable increase in mortality for females aged over 55 in some Northern European countries, such as Denmark (see Background Paper 6.13) associated with an increase in female smoking rates.

There are some striking trends in the incidence of chronic liver disease and cirrhosis of the liver in European Member States. While the EU as a whole has experienced declines in mortality from both chronic liver disease and cirrhosis of the liver, Eastern European countries have shown a steady increase, especially during the period immediately after the break-up of the Soviet Union. In Europe, deaths from cirrhosis of the liver are mainly related to excessive alcohol consumption<sup>9</sup> (see Background Paper 6.14).

### *Communicable diseases*

With regard to communicable diseases, there is concern at the recent increase in HIV, tuberculosis (TB) and sexually transmitted infections (STIs), in some EU States. In the WHO European Region (which includes all EU27 countries), the number of newly diagnosed HIV infections has increased since 2004, mainly due to the high rate of new HIV cases in Eastern Europe.<sup>10</sup>

Tuberculosis (TB) accounts for the second most important infectious disease burden in Europe. In 2009 to 2010, TB notification rates dropped in 22 Member States, with declines of more than 10% in Estonia, Finland, Greece, Ireland, Malta and Slovakia. However, over the same period, increases of at least 10% were observed in Belgium, Cyprus and Hungary.<sup>11</sup> Almost all EU Member States report decreasing numbers of TB cases among people of national origin, but only six countries observed a decrease among people of foreign origin.<sup>12</sup>

Overall, the TB notification rate in the EU and the European Economic Area (EEA) continues to decline. While country-specific rates have fallen fastest in the WHO's five "high priority" countries (Bulgaria, Estonia, Latvia, Lithuania and Romania), these

countries still have notification rates several times higher than those in the low-incidence countries (see Background Paper 6.8 for a more extensive overview of the latest developments in TB control).

In 2010 in the EU27 countries, the overall prevalence of HIV among notified TB cases was 6%. However, HIV/TB prevalence is still three times higher in Ireland and Portugal and appears to be on the rise in Latvia.

Respiratory infections pose significant challenges. Recorded since the middle of the 18<sup>th</sup> century, new influenza virus subtypes have caused major global outbreaks at unpredictable intervals. The “Spanish flu” of 1918 was one of the most severe, causing an estimated 2.64 million excess deaths in Europe. Another important aspect of the influenza burden is therefore the threat of the emergence of new virus subtypes capable of causing influenza pandemics, as occurred in 2004 with the H1N1 pandemic. Meanwhile, the incidence of pneumonia varies across different age groups, with very young children and elderly adults mainly affected. Limited data, disaggregated by age, suggest that countries in Eastern Europe have much higher rates of pneumonia mortality in children aged under one than Western European countries <sup>13</sup> ([see Background Paper 6.22](#)).

Mortality data for acute respiratory infections, pneumonia and influenza in children aged under five show that central Eastern European countries and the Baltic States, as well as Portugal, have dramatically lowered death rates from these diseases in the last 30 years ([see also Background Paper 6.22 on pneumonia](#)).

### 5.3 Burden of disease

#### *Disability Adjusted Life Years (DALY)*

For a summary measure of population health, the WHO Global Burden of Disease studies use Disability Adjusted Life Years (DALYs), which are the sum of Years of Life Lost (YLL) due to premature mortality and Years Lived with Disability (YLD). Disability in this sense refers to any short-term or long-term health loss, other than death (see Background Paper 4.5 for more methodological detail on DALY measurement).

Globally, five disease groups account for 60% of the total burden of disease as measured in DALYs. Table 5.3.1 shows that infectious and parasitic diseases are ranked number one worldwide (18% of the total disease burden), followed by neuropsychiatric conditions (14%), cardiovascular diseases (10.5%), unintentional injuries (9.2%) and perinatal conditions (8%). The European Region has a slightly different mix of diseases to account for almost 70% of its burden of disease. Cardiovascular diseases are the biggest contributors with 23%, followed by neuropsychiatric conditions (19.6%), malignant neoplasms (11.7%), unintentional injuries (8.5%) and sense organ diseases (5.8%).

## 5. Demography, GBD and the Preliminary List of Priorities

**Table 5.3.1: Projected burden of disease (DALYs) by cause and region, for the year 2008<sup>a,b</sup> (all disease groups)**

<i>Cause<sup>d</sup></i>	European region <sup>c</sup>			World		
	<i>DALYs</i>	<i>% of total</i>	<i>Rank</i>	<i>DALYs</i>	<i>% of total</i>	<i>Rank</i>
Cardiovascular diseases	33 268 978	23.04	1	153 058 636	10.48	3
Neuropsychiatric conditions	28 321 309	19.61	2	205 008 966	14.04	2
Malignant neoplasms	16 846 698	11.67	3	82 854 986	5.67	7
Unintentional injuries	12 236 784	8.47	4	134 860 922	9.24	4
Sense organ diseases	8 357 085	5.79	5	91 384 277	6.26	6
Infectious and parasitic diseases	6 836 269	4.73	6	262 939 655	18.01	1
Digestive diseases	6 131 603	4.25	7	39 416 099	2.70	11
Respiratory diseases	5 760 454	3.99	8	62 475 621	4.28	9
Musculoskeletal diseases	5 396 694	3.74	9	31 954 450	2.19	13
Intentional injuries	5 088 711	3.52	10	49 067 868	3.36	10
Perinatal conditions	3 241 918	2.24	11	117 215 604	8.03	5
Diabetes mellitus	2 638 147	1.83	12	21 702 445	1.49	16
Respiratory infections	2 413 742	1.67	13	81 583 751	5.59	8
Congenital anomalies	1 722 790	1.19	14	23 749 043	1.63	15
Nutritional deficiencies	1 571 779	1.09	15	32 304 144	2.21	12
Genitourinary diseases	1 270 976	0.88	16	14 950 971	1.02	17
Endocrine disorders	1 167 886	0.81	17	10 071 712	0.69	18
Oral conditions	892 325	0.62	18	8 311 704	0.57	19
Maternal conditions	644 559	0.45	19	31 087 899	2.13	14
Skin diseases	327 180	0.23	20	4 075 555	0.28	20
Other neoplasms	277 506	0.19	21	2 065 985	0.14	21
<b>All Causes</b>	<b>144 413 392</b>	<b>100.0</b>		<b>1 460 140 289</b>	<b>100.0</b>	

<sup>a</sup> Source: The Global Burden of Disease: 2004 update, World Health Organization, 2008

<sup>b</sup> Ranked in order of importance for the European region

<sup>c</sup> Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.

<sup>d</sup> See annex 5.6 for details on specific diseases included according to the International Classification of Diseases (ICD)

Ischaemic heart disease and cerebrovascular disease are the biggest contributors to the burden of cardiovascular diseases, both for the WHO European Region and the world. For neuropsychiatric conditions, the major contributors are unipolar depressive disorders, Alzheimer disease, other dementias and alcohol use disorders. However, alcohol-use disorders are ranked much lower for the world than they are for the WHO European Region. Malignant neoplasms account for a high disease burden within the WHO European Region - mainly due to cancers of the trachea, bronchus and lung. Hearing loss contributes to the high burden of sense organ diseases, which are mainly problems of the elderly and therefore occur in the WHO European Region. The high

global burden of infectious and parasitic diseases is mainly due to HIV/AIDS, diarrhoeal diseases, malaria and tuberculosis. Perinatal conditions, which account for a high burden in the world, but not in the European region, consist of prematurity and low birth weight, birth asphyxia, birth trauma and neonatal infections.

### *Risk factors*

The percentage of disease burden that can be attributed to various risk factors for both the WHO European Region and the world is, unlike the DALY burden, quite different for each (see Table 5.2). Major risk factors at the global level are: being underweight; having unsafe sex; and unsafe water, sanitation and poor housing. In the WHO European Region, there is little under nutrition but a considerable number of people who are overweight or obese, and physical inactivity appears to be a key risk factor unique to this region. Alcohol use is the second most important risk factor in WHO Europe. It is not surprising therefore, that other related risk factors such as high blood pressure, high cholesterol and high blood glucose are also represented in the list. Tobacco use remains the number one risk factor on the European list, despite the important progress in reducing the prevalence of smoking in a large number of European countries.

**Table 5.2: The leading risk factors for the Burden of disease, 2004, ranked in order of per cent of total DALY<sup>a</sup>**

WHO European Region <sup>b</sup>		World	
<i>Risk factor</i>	%	<i>Risk factor</i>	%
Tobacco use	11.7	Underweight	5.9
Alcohol use	11.4	Unsafe sex	4.6
High blood pressure	11.3	Alcohol use	4.5
Overweight and obesity	7.8	Unsafe water, sanitation, hygiene	4.2
High cholesterol	5.9	High blood pressure	3.7
Physical inactivity	5.5	Tobacco use	3.7
High blood glucose	4.8	Sub-optimal breastfeeding	2.9
Low fruit and vegetable intake	2.4	High blood glucose	2.7
Occupational risks	1.7	Indoor smoke from solid fuels	2.7
Illicit drug use	1.6	Overweight and obesity	2.3

<sup>a</sup> Source: Global Burden of Disease, 2004 update, World Health Organization published 2008.

<sup>b</sup> Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.

## 5. Demography, GBD and the Preliminary List of Priorities

### *Mortality*

Four major disease groups (cardiovascular diseases, infectious and parasitic diseases, malignant neoplasms (cancers) and respiratory diseases) account for a little over 65% of all deaths worldwide (see Table 5.3).

**Table 5.3: Estimated total deaths by cause and region for the year 2008<sup>a</sup>**

<i>Cause<sup>c</sup></i>	EU27 <sup>b</sup>			World		
	<i>Deaths</i>	<i>% of total</i>	<i>Rank</i>	<i>Deaths</i>	<i>% of total</i>	<i>Rank</i>
Cardiovascular diseases	1 981 443	41.52	1	17 326 646	30.46	1
Malignant neoplasms	1 267 412	26.56	2	7 583 252	13.33	3
Neuropsychiatric conditions	257 311	5.39	3	1 310 002	2.30	10
Respiratory diseases	240 503	5.04	4	4 233 863	7.44	4
Digestive diseases	234 544	4.92	5	2 206 300	3.88	8
Unintentional injuries	168 908	3.54	6	3 618 666	6.36	5
Respiratory infections	147 180	3.08	7	3 533 652	6.21	6
Diabetes mellitus	109 753	2.30	8	1 255 585	2.21	11
Genitourinary diseases	87 979	1.84	9	1 021 935	1.80	12
Infectious and parasitic diseases	72 261	1.51	10	8 721 166	15.33	2
Intentional injuries	66 003	1.38	11	1 510 352	2.65	9
Other neoplasms	37 976	0.80	12	188 227	0.33	17
Endocrine disorders	33 568	0.70	13	318 248	0.56	16
Musculoskeletal diseases	23 216	0.49	14	167 814	0.29	18
Perinatal conditions	12 504	0.26	15	2 603 140	4.58	7
Congenital anomalies	12 440	0.26	16	428 161	0.75	13
Nutritional deficiencies	9 490	0.20	17	418 081	0.73	14
Skin diseases	8 509	0.18	18	74 138	0.13	19
Maternal conditions	467	0.01	19	361 361	0.64	15
Oral conditions	202	0.00	20	3 937	0.01	20
<b>All Causes</b>	<b>4 771 786</b>	<b>100.00</b>		<b>56 888 289</b>	<b>100.00</b>	

<sup>a</sup> Source: The Global Burden of Disease: death estimates for 2008, World Health Organization

<sup>b</sup> Current EU member states: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

<sup>c</sup> See Annex 5.1 for details on specific diseases included according to the International Classification of Diseases (ICD)

Cardiovascular diseases are ranked number one as a cause of deaths worldwide, accounting for over 30% of mortality. Infectious and parasitic diseases come second with over 15% of mortality (due mainly to diarrhoeal diseases, HIV/AIDS and TB), followed by malignant neoplasms (13%) and respiratory diseases (7%). Neuropsychiatric diseases, which are ranked very high in DALY burden, account for only 2.3% of all deaths. This can be explained by the fact that this burden consists mainly of unipolar depressive disorders that do cause major disability, but not death. In the EU27 countries, four disease groups account for almost 80% of total mortality: cardiovascular diseases, malignant neoplasms, neuropsychiatric conditions and respiratory conditions. Ischaemic heart disease and cerebrovascular disease are the

most important contributors to cardiovascular mortality both for the European Union and the world. Trachea, bronchus and lung cancers are accountable for most of the malignant neoplasm burden in both regions. Neuropsychiatric conditions account for a substantial number of deaths in the EU countries, in contrast to the number of deaths they cause worldwide. This is due to the high prevalence of Alzheimer disease and other dementias in these countries. Mortality due to respiratory conditions is related to COPD and lower respiratory infections, both in Europe and the world.

### 5.4 A commonality of interest: Europe and the world

Table 5.4.1 shows the diseases and conditions that appear in the top 20 DALY rankings for Europe and the world. Of these, 13 diseases and conditions are in the top 20 DALY ranking for both Europe and the world: ischaemic heart disease, cerebrovascular diseases, unipolar depressive disorders, alcohol use disorders, hearing loss, road traffic accidents, COPD, HIV/AIDS, refractive errors, lower respiratory infections, diabetes mellitus, self-inflicted injuries, and violence.

Of the common conditions not found in the original 2004 Report, most remarkable is an increase in the DALY burden due to HIV/AIDS in the WHO European Region since 2004. This increase in Europe makes HIV/AIDS an even more important health priority worldwide. Another new common condition is refractive errors that now appear on the European DALY ranking for the first time. Because of the ageing population these problems are predicted to further increase in importance in the coming years. The two other new common conditions are alcohol use disorders and lower respiratory infections. Alcohol use disorders were already a problem in the European countries in 2004, but have now appeared on the global DALY ranking for the first time. Lower respiratory infections are an increasing disease burden in Europe, mainly due to pneumonia in the elderly population. Elsewhere, children account for a large share of the global pneumonia burden.

## 5. Demography, GBD and the Preliminary List of Priorities

**Table 5.4: Top 20 causes of projected burden of disease (DALYs) for the year 2008 for WHO European Region and the world<sup>a</sup>**

*Commonality of interest indicated with shade*

WHO European Region <sup>b</sup>			World		
Cause <sup>c</sup>	DALYs	% of total	Cause	DALYs	% of total
<i>Ischaemic heart disease</i>	16 377 272	11.3	<i>Lower respiratory infections</i>	78 870 694	5.4
<i>Cerebrovascular disease</i>	9 310 100	6.4	<i>Unipolar depressive disorders</i>	68 895 978	4.7
<i>Unipolar depressive disorders</i>	8 380 707	5.8	<i>HIV/AIDS</i>	64 661 516	4.4
<i>Alcohol use disorders</i>	4 753 251	3.3	<i>Ischaemic heart disease</i>	64 242 816	4.4
<i>Hearing loss, adult onset</i>	3 896 935	2.7	<i>Diarrhoeal diseases</i>	55 970 960	3.8
<i>Road traffic accidents</i>	3 405 803	2.4	<i>Cerebrovascular disease</i>	47 529 750	3.3
<i>Alzheimer and other dementias</i>	3 286 741	2.3	<i>Road traffic accidents</i>	45 932 901	3.1
<i>Trachea, bronchus, lung cancers</i>	3 210 541	2.2	<i>Prematurity and low birth weight</i>	40 719 981	2.8
<i>Osteoarthritis</i>	3 138 042	2.2	<i>Birth asphyxia and birth trauma</i>	38 592 986	2.6
<i>Chronic obstructive pulmonary disease</i>	2 911 003	2.0	<i>Neonatal infections and other conditions</i>	37 902 638	2.6
<i>Self-inflicted injuries</i>	2 904 536	2.0	<i>Chronic obstructive pulmonary disease</i>	33 144 764	2.3
<i>Cirrhosis of the liver</i>	2 712 366	1.9	<i>Malaria</i>	32 342 149	2.2
<i>Diabetes mellitus</i>	2 638 147	1.8	<i>Hearing loss adult onset</i>	28 858 571	2.0
<i>HIV/AIDS</i>	2 598 495	1.8	<i>Tuberculosis</i>	28 697 686	2.0
<i>Refractive errors</i>	2 311 894	1.6	<i>Refractive errors</i>	28 646 307	2.0
<i>Lower respiratory infections</i>	2 178 547	1.5	<i>Alcohol use disorders</i>	24 163 164	1.7
<i>Colon and rectum cancers</i>	1 888 989	1.3	<i>Childhood-cluster diseases</i>	23 193 908	1.6
<i>Violence</i>	1 845 980	1.3	<i>Diabetes mellitus</i>	21 658 468	1.5
<i>Falls</i>	1 763 223	1.2	<i>Violence</i>	21 546 654	1.5
<i>Breast cancer</i>	1 718 856	1.2	<i>Self-inflicted injuries</i>	18 626 664	1.3
Total of top 20 causes	81 231 428	56.2	Total of top 20 causes	748 387 874	51.3
Overall total	<b>144 413 392</b>	100	Overall total	<b>1 460 140 289</b>	100

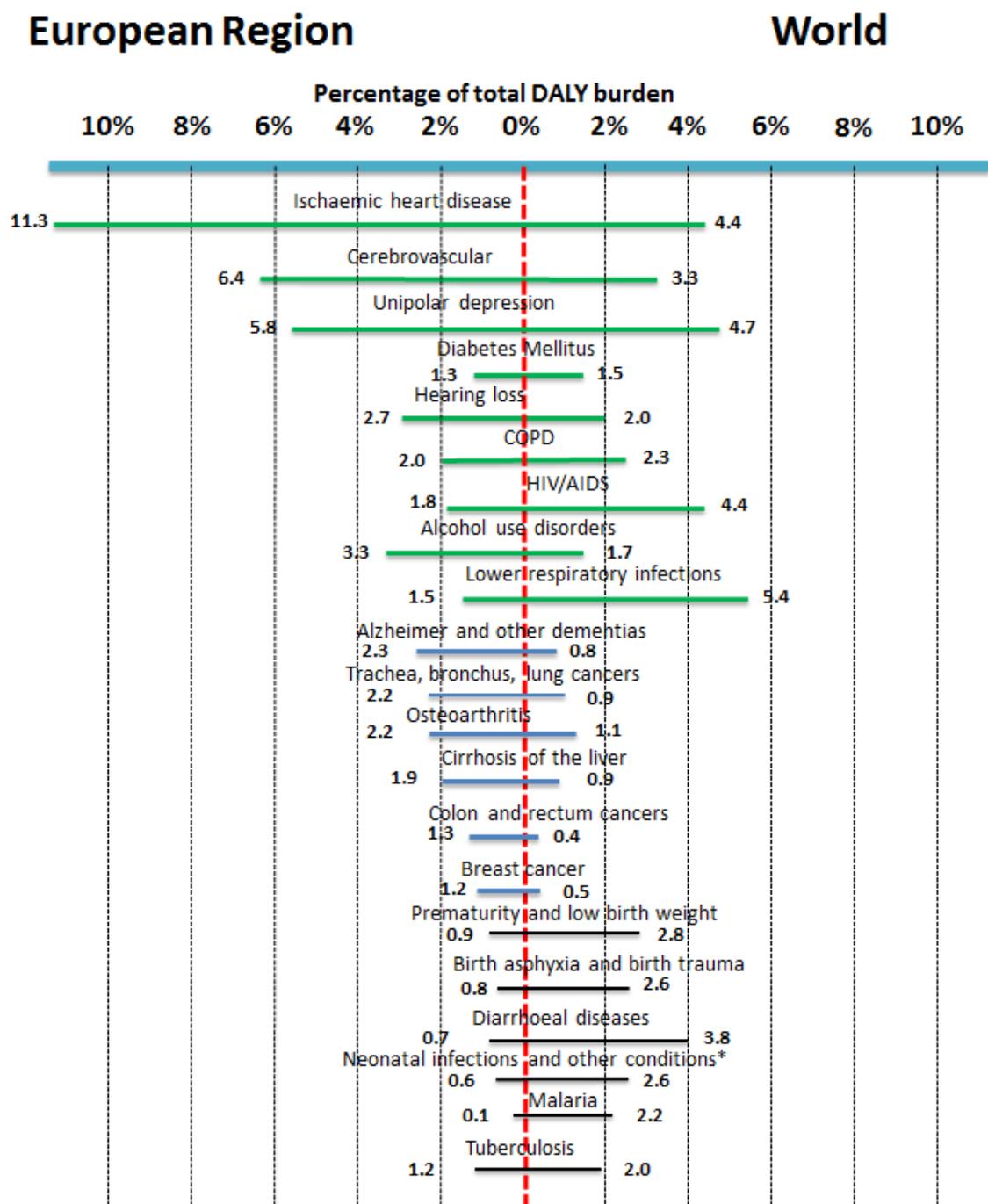
<sup>a</sup> Source: The Global Burden of Disease: 2004 update, World Health Organization

<sup>b</sup> Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.

<sup>c</sup> See annex 5.1 for details on specific diseases included according to the International Classification of Diseases (ICD), causes that have been grouped as 'other' have not been taken into account, since burden of individual diseases within this cluster are presumed to be small.

The commonality of interest can be visualized in Figure 5.4.1, which lists for the Preliminary List diseases their percentage of total DALY burden for the WHO European Region, as compared to their percentage of the total global DALY burden. Figure 5.4.1 shows only those diseases that are amenable to pharmaceutical interventions. The green bars show the distribution of those high burden diseases that are common to both the WHO European Region and the world.

Figure 5.5: Distribution of attributed percentage of DALYs for the top 20 high-burden diseases and conditions (excluding conditions that are not affected by pharmaceutical interventions) for the WHO European Region and the world.



Source: The Global Burden of Disease: 2004 update, World Health Organization, 2008

\* See annex 5.1 for included conditions

Green indicates diseases that appear in the top 20 DALY ranking of both regions

Blue indicates diseases that appear in the top 20 DALY ranking of the European region

Black indicates diseases that appear in the top 20 DALY ranking of the world

Ischaemic heart disease and cerebrovascular diseases clearly still cause a greater burden in the European Region than worldwide. Lower respiratory infections and HIV/AIDS on the other hand show a much higher percentage worldwide than in Europe. The blue and the black bars represent diseases that are in the top 20 ranking for one of the two regions, but not for both. This again shows the difference between infectious (communicable) diseases such as TB appearing high on the ranking for the world, and NCDs such as osteoarthritis causing a high burden in the WHO European Region.

For mortality, commonalities are slightly different (see Background Paper 5, Table 5.7) with common conditions being: ischaemic heart disease, cerebrovascular disease, trachea, bronchus and lung cancers, COPD, lower respiratory infections, hypertensive heart disease, diabetes mellitus, cirrhosis of the liver, stomach cancer, nephritis and nephrosis, self-inflicted injuries, and liver cancer. Three of these conditions, cirrhosis of the liver, nephritis, nephrosis, and liver cancer, have been newly identified as common conditions since the 2004 Priority Medicines Report. While cirrhosis of the liver was already a high burden in Europe in 2004, it is new in the global ranking.

### 5.5 The Global Burden of Disease Study 2010

The Global Burden of Disease Study 2010 (GBD 2010), which was published in *The Lancet* in late 2012,<sup>5</sup> is a completely new global burden of disease assessment exercise. It uses a different methodology from the 2004 WHO Global Burden of Disease study and so the results are not directly comparable (see Chapter 4.4 and Background Paper 5). While the results show many similarities, there are also some differences:

#### *Europe: DALY*

- Unlike the 2008 projections in the WHO 2004 study ([see Chapter 4 for methodology](#)), low back pain, anxiety disorders, migraine and neck pain now appear on the GBD 2010 list.
- Refractive errors do not appear in the top 20 for the GBD 2010 study (the condition is ranked 85th and accounts for 0.23% of all DALYs) while it was ranked 19th for the WHO 2004 study and accounted for 1.6 % of all DALYs in the WHO projections for 2008.
- Hearing loss does not appear in the GBD 2010 ranking, possibly because individual causes of hearing loss were reported (as a cluster of conditions) instead of “hearing loss”.

### *Global: DALY*

- Alcohol use disorders is ranked 37th in the GBD 2010 as opposed to 17th in the 2008 projections of the WHO 2004 study.
- Neck and back pain are now represented for the first time, just as in the European regions (Central Europe, Eastern Europe and Western Europe).
- Six diseases and conditions that appear in the top 20 of the GBD 2010 DALY ranking do not appear in the WHO 2008 DALY projections. These are: anemia, malnutrition, trachea, bronchus and lung cancers

Overall, the number of deaths measured in the GBD 2010 is lower than that of the 2008 WHO actual measurements (52 769 679 as compared to 56 888 289).

### *Europe: Mortality*

- There are differences and commonalities between the 2010 mortality ranking of the European regions and the 2008 ranking for the EU27.
- Conditions that appeared on the 2008 ranking but not on the 2010 ranking are: nephritis and nephrosis, lymphomas, liver cancer, bladder cancer and leukaemia.
- For the 2010 global ranking, the first 16 conditions of the top 20 are almost identical to the 2008 ranking.

While these differences between GBD lists have led to the addition of five conditions to the preliminary list, some conditions which appeared in the 2008 list but not the 2010 list have been retained since the different methodologies used may have led to these conditions being downgraded. In addition, if a condition was reviewed in the 2004 Report this section was updated and not deleted.

## **5.6 Preliminary List**

A total of 24 diseases, disease groups and risk factors were selected for the Preliminary List and for subsequent in-depth analysis (see Chapter 6). Based on the findings of these in-depth studies, a Final List of priorities was then drawn up, based on burden of disease, pharmaceutical gaps, social solidarity and epidemiological projections ([see Chapter 9](#)).

### *Preliminary List based on burden of disease and mortality*

Based on the burden of disease and mortality ranking for both Europe and the world, the following diseases and conditions were selected:

- ischaemic heart disease, diabetes, cancer, stroke, HIV/AIDS, TB, malaria, Alzheimer disease and other dementias, osteoarthritis, chronic obstructive pulmonary disease, alcohol use disorders (alcoholic liver diseases and alcohol dependency), hearing loss, depression, diarrhoeal diseases, lower respiratory infections, neonatal conditions and low back pain.

### *Preliminary List based on projections [\(see Chapter 4\)](#)*

- antimicrobial resistance, pandemic influenza.

### *Preliminary List based on social solidarity [\(see Chapter 4\)](#)*

- rare diseases, postpartum haemorrhage and maternal mortality, neglected tropical diseases.

### *Preliminary List based on risk factors [\(see Chapter 4\)](#)*

- smoking, obesity.

## 5.7 Conclusions

This chapter provides an overview of the demography and burden of disease in the EU Member States and the world as a whole. It highlights a shift towards a double burden of disease in low- and middle-income countries, making many chronic diseases a priority not only for EU countries, but in low- and middle-income countries as well.

Since the publication of the 2004 Priority Medicines Report, more commonalities of interest have emerged between Europe and the world. In large part, this is due to the ageing of the global population (including Europe), the rise in chronic NCDs in middle-income countries and the increase in some infections such as HIV/AIDS, TB and pneumonia in the elderly in Europe. The burden of disease is globalizing and converging.

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# 6. Priority diseases and reasons for inclusion

## 6.0 Introduction

This chapter provides an in-depth review of the various diseases or conditions that have been selected as part of this priority-setting exercise based on the methods described in Chapters 4 and 5. These conditions have been grouped according to the nature of the pharmaceutical gap(s) associated with them. Many conditions such as cancer fall into multiple gaps as mentioned in the Executive Summary.

The first series of conditions, infections due to antibacterial resistance and pandemic influenza, are associated with a pharmaceutical gap in that many pharmaceutical treatments for them are already ineffective and many others will soon become ineffective. Both pose enormous threats to global public health which will require major multisectoral responses.

The second series of conditions, cardiovascular disease (CVD), HIV/AIDS, cancer, depression, diabetes, pneumonia/diarrhoeal/neonatal conditions, malaria, tuberculosis, neglected tropical diseases and postpartum haemorrhage include chronic diseases with a clear "commonality of interest" in both Europe and the world (e.g. CVD, cancer, depression) and infectious diseases which mainly affect people in low- and middle-income countries (e.g., HIV/AIDS, malaria, tuberculosis). The characteristic that is common to all these conditions is their pharmaceutical gap. For these conditions, treatment exists but the delivery mechanism or the formulation needs to be more appropriate for patient use. For example, there continues to be a need for paediatric dosages of cancer medicines; antidepressants often cause side-effects; oxytocin, which is used to prevent postpartum haemorrhage, is not heat-stable, and nor is insulin — making them both difficult to use in developing countries, where they are needed most.

The next series of conditions are characterized by the third pharmaceutical gap: a treatment does not yet exist or the existing treatment(s) is insufficiently effective. These conditions are stroke, osteoarthritis, Alzheimer disease (AD) and other dementias, chronic obstructive pulmonary disease (COPD), hearing loss, low back pain and rare (orphan) diseases. Despite substantial investments in research, progress towards developing curative treatment or medicines to slow or reverse the progression of these conditions has been disappointing. In addition, these are diseases where basic research is needed to establish biomarkers.

The final group consists, not of diseases *per se*, but global risk factors for disease. These risk factors are amenable to pharmaceutical treatment but such treatment is either non-existent or inadequate. These are treatments for cessation of tobacco use, alcohol use disorders and obesity.

This chapter should be read in conjunction with the background documents which provide additional details for all of the statements made in this summary chapter. In addition, some themes are revisited in Chapters 7 and 8.

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### 6.1 Antibacterial drug resistance

[See Background Paper 6.1 \(BP6\\_1AMR.pdf\)](#)

#### *Background and developments since 2004*

The 2004 Priority Medicines Report underlined the major threat to global health from increasing resistance to antimicrobial drugs: *“The discovery of antibiotics in the mid-twentieth century led to a revolution in the management and treatment of infectious diseases. Today, we are witnessing the emergence of drug resistance along with a decline in the discovery of new antibacterials ... As a result, we are facing the possibility of a future without effective antibiotics ...”*.<sup>1</sup>

In 2013 the situation remains a continuing cause for concern:

- Gram-negative bacteria are now showing increasing resistance to antibiotics. In Europe, bacteria including *Escherichia coli* and *Klebsiella pneumonia* collected from normally sterile sites (blood or cerebrospinal fluid) have demonstrated resistance to antibiotics.
- The number of new molecular entity (NME) antibiotics approved by the U.S. Food and Drug Administration (FDA) has remained very low over the past two decades (see Background Paper 6.1, Annex 6.1.21). Ten new antibacterials (i.e. excluding antivirals, antifungals, antiprotozoals and vaccines) were approved by the FDA between 2004 and 2012 and 13 were approved between 1996 and 2003. These are NMEs, which are defined by the FDA as medications containing an active substance that has never before been approved for marketing in any form in the United States. There have been no novel mechanism agents for Gram-negative organisms for decades.
- Research has revealed that there is a low possibility, if at all, of reversing antimicrobial resistance (AMR) once it has been established in both community and non-community settings.<sup>2</sup>
- There is now more extensive data supporting the increasing economic burden of AMR - due in part to the doubled increase in hospital length of stay, additional discharge costs to facilities, extra medical care needed and

## 6. Priority diseases and reasons for inclusion

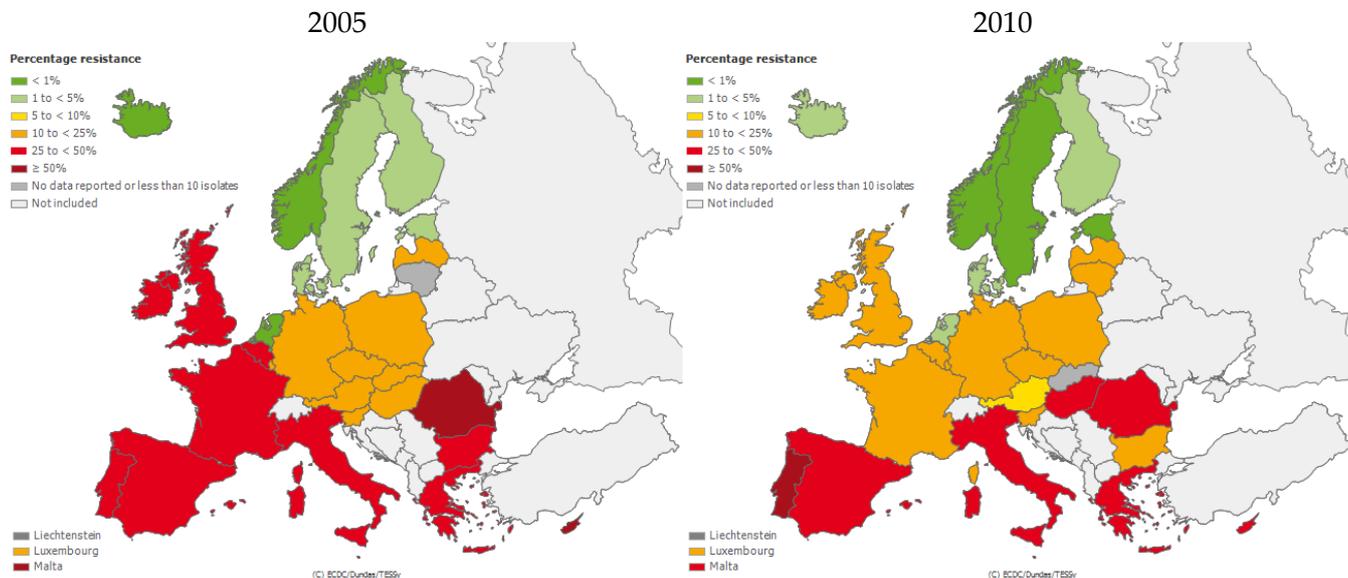
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productivity loss. The societal costs to the EU, Norway and Iceland due to AMR in 2007 were estimated to be in excess of €1.5 billion per year.<sup>3</sup>

There have also been a number of success stories since 2004. Surveillance programmes have been initiated at local, national, and international levels. Successful programmes have led to better interventions aimed at assessing AMR and ensuring more appropriate antibiotic prescribing. The adoption in November 2011 of the Communication from the Commission to the European Parliament and the Council on an Action Plan against the rising threats from Antimicrobial Resistance has significantly strengthened and coordinated action against AMR.

- The Action Plan has 12 concrete actions to combat AMR and two of these in particular should be noted, the actions on collaborative antibiotic research and development (Action 6) and coordination of research efforts (Action 11).
- There have been major improvements in the development of diagnostic tools. Inexpensive and readily available diagnostic tools are now available for a variety of infectious diseases. Some of these tools are able to distinguish between viral and bacterial infections, while others are able to distinguish between bacterial species (see Background Paper 6.1, Annex 6.1.7). Point-of-care diagnostics remain an unmet need.
- Since 2004, various national and international organizations have responded to the issue of AMR through numerous meetings, task forces, workshops, and publications (see Background Paper, Annex 6.1.1).<sup>4</sup> Several major publications addressing AMR and its public health threat are in print.<sup>5,6,7</sup>
- One success in efforts to slow the development of AMR in Europe is the overall decline in the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in this region since 2005 (see Figure 6.1.1). However, this decline has not occurred in all European countries (see Background Paper, Annex 6.1.10).

**Figure 6.1.1: Proportion of meticillin-resistant *Staphylococcus aureus* isolates in participating countries, 2005 and 2010**



Source: EARS-interactive database. Available at:

<http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx>

### Control strategies

#### European Union

European Union efforts to combat AMR are extensive and have expanded (see Background Paper 6.1, Annex 6.1.15). In 2011, the European Commission (EC) issued an “Action plan against the rising threats from Antimicrobial Resistance”. The EC proposed the implementation of a five-year Action Plan to combat AMR, based on 12 key actions.<sup>8</sup> In particular, the actions related to research activities promoting public-private collaborative research and development to bring new antibiotics to patients (Action 6) and the reinforcement and coordination of research efforts (Action 11) are already well advanced in their implementation. The Innovative Medicines Initiative (IMI) has recently launched a €223.7 million programme to combat AMR. Under its 7<sup>th</sup> Framework Programme (FP7), the EC currently funds numerous projects that aim to develop control strategies, diagnostics, drugs and new therapies. There are numerous national antibiotic stewardship campaigns, including the European Antibiotics Awareness Day.

The European Technology Platform on Nanomedicine has also been established in an effort to create diagnostic tools that can identify a disease at the earliest possible stage – thereby facilitating the appropriate use of antibiotics.<sup>9</sup> Top Institute (TI) Pharma, a non-profit organization whose mandate and vision is based on the 2004 Priority Medicines Report, has also provided support for projects concerning MRSA and multidrug-resistant (MDR) pathogens.<sup>10</sup>

### **World Health Organization**

The WHO has been heavily involved in the range of national and global activities outlined above. In addition, the WHO has published various recommendations to deal with AMR (see Background Paper 6.1, Annex 6.1.18).

### **World**

China's activities concerning AMR are rather recent but expanding. In 2004, China created its first AMR surveillance programme and national guidelines for appropriate antibiotic use. Elsewhere, Israel has had success with a national campaign promoting prudent antibiotic use,<sup>11</sup> and numerous other countries have also implemented stewardship campaigns and other control strategies. In India, the Chennai Declaration proposes a plan to create a road map for tackling the challenge of AMR in India.<sup>12</sup>

### *Other approaches*

#### **Vaccines**

There are several FDA-approved vaccines addressing bacterial pathogens (see Background Paper 6.1, Annex 6.1.24 and Table 6.1.3). Accumulating literature is providing evidence that vaccination has potential advantages for primary prevention of AMR. Protein-based vaccines usually target multiple immunogenic epitopes, suggesting that several mutations are required before the immune response to the vaccine may no longer recognize the bacterial pathogen. By preventing infections in the first place, vaccines do not allow bacteria to replicate in the host, thereby limiting the selection process of variants to the initial phases of the infection. However serotype replacement, as observed for pneumococcal strains, can undermine vaccine effectiveness. Bacteriophages may be used in the future for the treatment of antibiotic-resistant organisms.

#### **Diagnostics**

The development and validation of new diagnostic tests can in principle help determine whether antibiotics should be prescribed at all. When antibiotic treatment is needed, such tools can help determine which antibiotics should be prescribed. In addition, rapid tests can help control the spread of infections if an infection is diagnosed early enough. (See Background Paper 6.1, Annex 6.1.7).

#### **Alternatives to antibiotics**

Over the past five years progress has been made towards the development of one possible alternative to antibiotics: antivirulence drugs that would not kill but rather deprive bacteria of their virulence functions so that they can be eliminated by the immune system.<sup>13</sup>

Another alternative approach was recently demonstrated in a proof-of-concept trial in which bacteriophages were genetically engineered to reverse a pathogen's drug resistance, thereby restoring its sensitivity to antibiotics.<sup>14</sup>

Elsewhere, another approach is based on the broad and diverse biological functions of endogenous peptides called cationic antimicrobial peptides (CAMPs), which are found in most animal cells that host microbes. These CAMPs are currently being widely used as blueprints for the development of innovative therapeutic agents that may be used as antimicrobials.<sup>15</sup>

### **Incentivizing R&D**

Numerous incentives for drug development have been proposed and implemented (see Background Paper, Annex 6.1.22). The Innovative Medicines Initiative (IMI) has recently launched research calls under the new theme NewDrugs4BadBugs (ND4BB), which aims to bring new antibiotics to patients by funding research in which small and medium-sized enterprises (SMEs) and academics work in close collaboration with large pharmaceutical companies in order to establish a vibrant antimicrobial drug discovery hub. In July 2012, the United States enacted the Food and Drug Administration Safety and Innovation Act (user fee legislation) which included the GAIN Act. The GAIN Act will provide an additional five years of data exclusivity, priority review and fast track status for new antibacterials that target qualifying pathogens.<sup>16</sup>

### ***Remaining challenges***

Although there are some achievements in the containment of AMR in Europe, much remains to be done. For this reason it is concluded that the containment of AMR remains a high priority. Continued action is needed on many fronts: to stimulate basic and applied research and development of new medicines and other treatment options in response to increased resistance; to reduce inappropriate use through the use of evidence-based public health interventions; to improve prescribing and dispensing practices; and to conduct high-quality surveillance of antibacterial resistance and of antimicrobial consumption patterns in hospitals and the community.

### ***Research needs***

Collaborative, global and more concerted efforts are needed to address the public health threat that AMR poses. The EU should continue its extensive contributions and collaborations in this regard and can provide ongoing leadership in research in the following areas:

#### **Diagnostic and therapeutic tools:**

- Development and use of cost-effective and point of care diagnostic tools to encourage prudent and appropriate antibiotic use.
- Priority development of antibiotics against Gram- negative bacteria.
- Replenishment of the antibiotic development pipeline, possibly using new business models for R&D, in order to develop new products with novel mechanisms of action to address the already heavy burden of AMR.

### Health systems:

- Establishment and implementation of a multi-faceted approach using standardized surveillance coupled with appropriate antimicrobial stewardship campaigns at country level.
- Allocation of public funding to continue providing evidence/data on antimicrobial resistance to treatment for vaccine-preventable diseases in order to assess the potential impact of comprehensive vaccination policies in reducing antimicrobial resistance.

### Prescription interventions:

- Promotion of strategies designed to modify physician antimicrobial-prescribing practices towards an approach based on simplicity rather than complexity.
- Approaches to encourage improved adherence to veterinary “judicious use” guidelines.
- Promotion of investment in research and development of future innovative vaccines capable of targeting and preventing antibiotic-resistant bacteria.

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## 6.2 Pandemic influenza

[See Background Paper 6.2 \(BP6\\_2Pandemic.pdf\)](#)

### *Background and developments since 2004*

The WHO estimates that annual influenza epidemics account for about 3 to 5 million cases of severe illness and 250 000 to 500 000 deaths worldwide.<sup>1</sup> However, the disease burden of influenza is difficult to quantify as patients may have a wide range of symptoms that can lead to under-diagnosis. In addition, patients are not laboratory-confirmed as having influenza, diagnostics tests are not 100% sensitive or virus-specific, and influenza can be masked by other comorbidities. Despite a substantial increase in laboratory testing during the most recent pandemic in 2009, recorded hospitalizations and deaths are a crude underestimation of the true pandemic burden.<sup>2</sup>

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There are three types of influenza virus that affect humans (A, B and C) but only one of these, type A, has been known to cause pandemics.<sup>3</sup> Influenza A viruses circulate naturally in a global avian reservoir. However, some viral strains have crossed the species barrier, infecting pigs, horses, and, most notably, humans.<sup>4</sup> Many RNA viruses such as influenza have high mutation rates which can lead to new, distinct antigenic variants.<sup>4</sup> Genetic diversity among influenza viruses accounts for the recurring seasonal influenza epidemics of varying patterns and severity, as well as the continuing risk of the emergence of a novel pandemic strain.

The 1997 A (H5N1) influenza outbreak in Hong Kong was the first known incidence of a purely avian virus causing severe human disease and death.<sup>3</sup> By 2006, the A (H5N1) virus had spread across 54 countries spanning three continents.<sup>3</sup> Inefficient human-to-human transmission was the only factor preventing H5N1 from becoming a pandemic virus. However, there is a substantial possibility that, in the event of the correct combination of genetic modifications, this rapidly replicating and highly mutable virus could re-emerge as a pandemic virus.

### *The 2009 influenza A (H1N1) pandemic*

In early April 2009, a new influenza A (H1N1) virus emerged in Mexico and the USA and rapidly advanced beyond the possibility of successful containment. The virus spread worldwide through human-to-human transmission, and on 11 June 2009 the WHO elevated the influenza pandemic alert level to Phase 6, officially declaring a global pandemic – the first in the 21<sup>st</sup> century.<sup>5</sup> Box 6.2.1 outlines a generally accepted understanding of the 2009 influenza pandemic. The inability to predict which specific subtype will trigger the next pandemic demonstrates the need to address the gaps in knowledge in order to more effectively manage the next pandemic.<sup>5</sup>

The economic impact of an influenza pandemic includes direct health care costs as well as the indirect costs of work absenteeism and loss of productivity. Studies evaluating economic impact on interpandemic seasonal influenza epidemics demonstrate that the most significant expenses are the indirect costs, accounting for more than 80% of the total societal cost of interpandemic seasonal influenza epidemics.<sup>6</sup> However, total economic burden can be difficult to quantify as recent studies conclude that the global economic impact from the 2009 H1N1 pandemic still remains unknown.<sup>5</sup> One study conducted in the United Kingdom used a computational general equilibrium modelling experiment to estimate the economic impact and found that depending on the severity of the disease (low to high fatality scenarios), a pandemic could result in losses of between 0.5% and 4.3% in the United Kingdom Gross Domestic Product (GDP).<sup>7</sup> While this range of economic loss may not seem dramatic, a strained economy and indirect costs may compound the impact of disease.

### Box 6.2.1 General summary of the 2009 H1N1 influenza pandemic <sup>8</sup>

- The pandemic virus was less virulent than was anticipated in many pandemic preparedness plans.
- Highest disease incidence was in 0 to 4 year old age group although cumulative incidence of infection was in school-aged children.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths typically associated with seasonal influenza.
- The majority of deaths occurred at a younger age than typically seen with seasonal influenza.
- Although older adults had lower morbidity rates, this population had the highest case fatality ratio.
- Pregnant and postpartum women and indigenous populations, recognized risk groups during interpandemic seasonal influenza seasons, were also at increased risk for a severe outcome.
- Intensive care units were burdened by the increase in the number of young adults with severe disease due to the pandemic virus, though this was not experienced in all countries.
- Although the 2009 pandemic influenza A (H1N1) seems to have replaced all seasonal influenza A (H1N1) subtypes, it has not replaced influenza A (H3N2) subtypes, which have continued to co-circulate as a small proportion of all types influenza A viruses. This is contrast to previous pandemics where the pandemic virus replaced all influenza A viruses.
- When the H1N1 vaccines were produced they were highly antigenic and only a single dose was required for most individuals.
- Unlike the pattern for interpandemic seasonal influenza A (H1N1) viruses, no significant neuraminidase resistance of the 2009 pandemic influenza A (H1N1) has been reported to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region.

### *Influenza vaccines*

Vaccination is considered to be the most effective way to prevent the spread of influenza and to mitigate the severity of illness and impact of the disease.<sup>5</sup> The EU has instituted procedures, managed by the European Medicines Agency (EMA), to expedite the authorization and availability of vaccines in the event of an influenza pandemic.<sup>9</sup>

Interpandemic Seasonal influenza immunization presents substantial challenges, including the need for annual vaccination, the co-circulation of multiple virus strains, antigenic variation in the influenza virus, and the broad age spectrum of people affected by the disease. The development of pandemic influenza vaccines brings additional challenges, including the need to: induce a broad spectrum and long-lasting immune response; ensure a much more rapid manufacturing time; and increase

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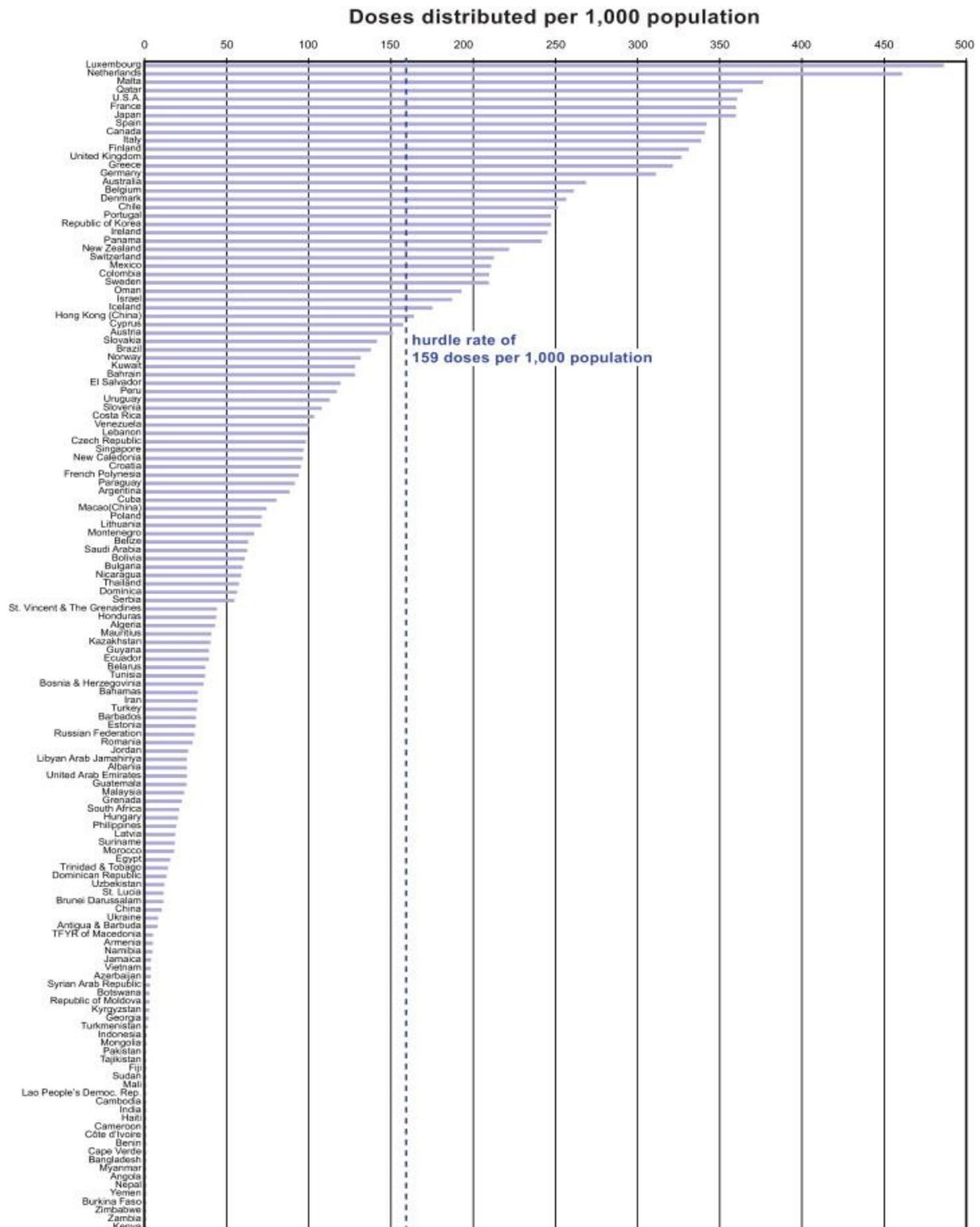
production capacity so it is large enough to reach populations at risk worldwide. These challenges have led to the use of a myriad of approaches to influenza vaccine development.<sup>10</sup>

During the 2009 influenza A (H1N1) pandemic, monovalent vaccines without adjuvants were used in the United States and Australia (and to a limited extent in Europe).<sup>11</sup> In contrast, within the EU, adjuvant vaccines were more widely used. Adjuvants are compounds that enhance the ability of a vaccine to elicit strong and robust immune responses.<sup>12</sup> At the time of the pandemic, adjuvant vaccines had been approved by the EMA for use in all populations whereas the United States had not approved the use of any adjuvant influenza vaccines.<sup>5</sup> Available data in 2010 demonstrated that pandemic influenza vaccines were safe and well tolerated.<sup>5</sup> However, Pandemrix, one of the adjuvant vaccines used in the EU was found to have an association with narcolepsy in children.<sup>13,14</sup> Future studies are needed to further elucidate the role of adjuvants in the possible association with narcolepsy prior to further use of adjuvants in pandemic vaccine development.

Equitable access to influenza vaccines is a key component of global prevention and control strategies for influenza. In 2003, the World Health Assembly (WHA) adopted a resolution on the “Prevention and control of influenza pandemics and annual epidemics,” which called on Member States with influenza vaccination policies to increase vaccine coverage for all high-risk individuals. The results from a 2010 study (involving 157 countries) indicated that the global distribution of influenza vaccines increased by 72% between 2004 and 2009 (from 262 million doses to 449 million doses, respectively).<sup>15</sup> However, despite encouraging growth at national, regional, and global levels, none of these countries distributed sufficient vaccines to immunize half of its total population and one-third of countries did not distribute enough vaccine to protect even 1% of their population. Meanwhile, only 20% of the countries achieved the study “hurdle” rate of 159 doses per 1000 population (see Figure 6.2.1).<sup>15</sup> Low vaccination uptake rates in many countries and disproportionate global production capacities continue to be two important factors contributing to low global vaccine coverage.

Efforts to increase vaccine coverage rates require public education campaigns and additional funding for immunization. In addition, efforts are needed by health care workers to proactively recommend immunization to people at-risk.<sup>15</sup> Continued efforts to increase vaccine coverage are critical. The use of seasonal influenza vaccines not only protects against annual epidemics, but also provides the foundation for pandemic preparedness. It is important to note that the use of annual seasonal vaccines sustains production capacity and facilitates the global capability to respond during a pandemic.

Figure 6.2.1 Global interpandemic influenza vaccine dose distribution per 1000 population (2009)



Source: Palache, A. Seasonal influenza vaccine provision in 157 countries (2004–2009) and the potential influence of national public health policies. *Vaccine* 29, 9459–9466 (2011)

### *Antiviral therapeutics*

Current antiviral therapy remains unchanged since 2004 with four commercially licensed products including: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantadine). Only one of these products, oseltamivir, was included on the WHO Model List of Essential Medicines for selected high-risk patients. The increasing use of these antiviral agents has led to the emergence of drug-resistant variants of the virus and reduced drug efficacy.<sup>16</sup> There is a need for the development of new antiviral agents that are active against all virus strains and subtypes.

### *Diagnostics*

Rapid and accurate laboratory diagnosis of viral infection is critical to reducing the disease burden of influenza and its associated social and economic consequences. Rapid influenza diagnostic tests (RIDTs) are simple-to-use, point-of-care antigen tests that can generate results in 10 to 30 minutes. However, studies on the use of RIDTs to diagnose seasonal influenza have demonstrated high specificities but varying levels of sensitivity.<sup>17,18,19</sup> Most of the currently used RIDTs are not able to distinguish between the different influenza A virus subtypes.

Rapid influenza diagnostic tests are useful in patient and outbreak management as they enable clinicians to initiate prompt infection-control measures and provide earlier access to antiviral treatment for high-risk populations. However, the 2009 influenza A (H1N1) virus pandemic underlined the importance of precise assays with brief turnaround times and the ability to differentiate influenza strains in order to accurately monitor the spread of an outbreak and ensure effective clinical management of patients.

### *EU-funded pandemic influenza projects*

The European Commission's current 7<sup>th</sup> Framework Programme (FP7), which supports health research, is providing significant funding for R&D in emerging epidemics of infectious diseases including influenza. EU-funded influenza projects relate to the pre-clinical and clinical development of new, innovative, safe, and effective vaccines and diagnostics.<sup>20</sup> Research is also focused on the development of "universal" influenza vaccines, designed to provide longer-lasting and broader protection against multiple strains of influenza virus, with the ultimate aim of protecting against both seasonal and pandemic influenza. Various complementary scientific aspects such as basic virology, diagnostics, epidemiology, pathogenesis, surveillance, immune responses, animal viruses, novel drugs, clinical management of patients, behavioural aspects and optimized communication strategies are also covered by FP7 research.<sup>21</sup>

### *Remaining challenges*

Following the initial outbreak of avian influenza in 1997, the threat of a potential influenza pandemic was widely recognized by key stakeholders. A substantial amount

of financial support and research has since been allocated to increasing pandemic influenza preparedness at the international level. The subsequent emergence of the 2009 A (H1N1) influenza pandemic challenged these efforts in every aspect of pandemic preparedness. Fortunately, the new virus appeared to be less virulent than anticipated.

The EU has recognized the public health impact of influenza through the establishment of a wide range of influenza-related surveillance networks, consortiums, and research projects. The information collected through these will provide the basis for an improved response to the next influenza pandemic. However, the prevention and control of influenza requires immense efforts and collaboration during the interpandemic seasonal and pandemic periods. Cooperation and collaboration between all key stakeholders will provide the foundation for a rapid and effective response in the event of a future pandemic.

### *Research needs*

Research should be prioritized in the following areas:

- The virology and pathogenicity of influenza viruses in order to predict and prepare for the next pandemic.
- Improved quantification methods to more accurately assess the economic burden of influenza.
- Understanding barriers to uptake for seasonal immunization, combined with evaluation of interventions to increase uptake.
- Global and country-level vaccine coverage information and monitoring systems.
- Rapid scale-up of vaccine production in case the next pandemic is caused by a subtype that is less antigenic and requires two doses of vaccine.
- Vaccine “platforms” that produce safe, effective, and cross-strain vaccines with long-lasting protection against influenza.
- New antiviral agents with broad reactivity against all virus strains and subtypes.
- The ability of RIDTs to accurately detect and distinguish between different influenza virus subtypes.

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## 6.3 Ischaemic heart disease

[See Background Paper 6.3 \(BP6\\_3IHD.pdf\)](#)

### *Introduction*

This chapter addresses cardiovascular disease (CVD) with a focus on the development, justification and evidence for the polypill in the secondary prevention of ischaemic heart disease (IHD). The reason for this is that the 2004 Priority Medicines Report highlighted this as a priority, leading to significant research funding being invested in this area, including the funding of two large-scale clinical trials. One of these studies (the UMPIRE trial) has since reported positive results, as outlined in more detail in Background Paper 6.3.

This report updates the information on this topic and therefore continues to focus on secondary prevention among patients who have already suffered a cardiovascular event. The majority of such patients have IHD, but a significant minority have cerebrovascular disease or peripheral vascular disease.

In addition to secondary prevention with the polypill, a number of other pharmacological approaches to prevention and treatment of IHD will need to be researched in order to provide more effective, safer and individualized intervention strategies. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; and regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD.

### *Background*

The 2010 Global Burden of Disease Study reported that, in line with global trends, the largest single cause of death in the combined regions of Central, Eastern, and Western Europe was IHD (26.6% of all deaths), followed by cerebrovascular diseases with 11.0% of the total number of deaths.<sup>1</sup> For the world, IHD accounted for 13.3% of mortality again followed by stroke with 11% of global mortality. In 2010, in Europe, IHD accounted for 13.8% of the total European disease burden (DALYs).<sup>2</sup> For the world the equivalent figure was 5.2%. (See Table 5.8 of the Background Paper.)

Fifty-seven per cent of CVD deaths (19% of global deaths) can be attributed to eight risk factors associated with poor diet and low rates of physical activity: high blood pressure; high blood glucose; physical inactivity; overweight and obesity; high cholesterol; and low fruit and vegetable intake.<sup>3</sup> The 2010 Global Burden of Disease Study reported that the two leading risk factors for global disease burden overall were

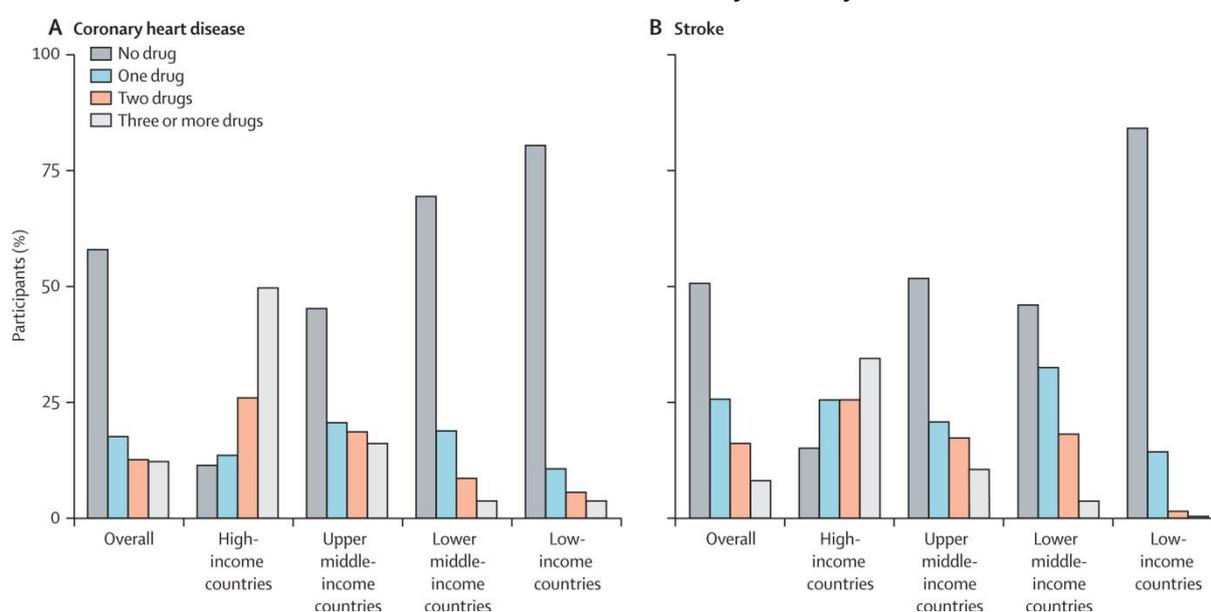
## 6. Priority diseases and reasons for inclusion

high blood pressure (9.4 million deaths and 7% of global DALYs) and tobacco smoking, including second-hand smoke (6.3 million deaths and 6.3% DALYs), both of which are key factors in increasing the risk of CVD. In Europe, the leading risk factor was also high blood pressure, with smoking ranked either second or third (depending on the region of Europe).

Studies have shown that adherence to lifestyle guidelines advocating moderate physical activity, a cardio-protective diet and abstinence from smoking can reduce the incidence of CVD by more than 80% compared to the rest of the population. However, studies have also shown that neither the general population nor (more surprisingly) people with established CVD typically adhere to these recommended guidelines.

Evidence for the effectiveness of blood pressure lowering, cholesterol lowering and anti-platelet medications in preventing both initial and subsequent cardiovascular events is compelling, with hundreds of thousands of patients analyzed in meta-analyses and reviews over the last 10 years. Although most people with established CVD in high-income countries have been started on recommended medications, significant numbers of people in high-income countries<sup>4,5,6</sup> and even larger numbers in low- and middle-income countries either do not receive or do not remain adherent to these treatments in the long term<sup>7,8,9</sup> (see Figure 6.3.1).

**Figure 6.3.1: PURE study: Number of drugs\* taken by individuals with established cardiovascular or cerebrovascular disease by country economic status.**



Source: Yusuf S et al. *Lancet*, 2011<sup>9</sup>

Note: \*For coronary heart disease (A), drugs counted were aspirin,  $\beta$  blockers, ACE inhibitors or ARBs, or statins. For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (e.g.,  $\beta$  blockers, diuretics, and calcium-channel blockers).

ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

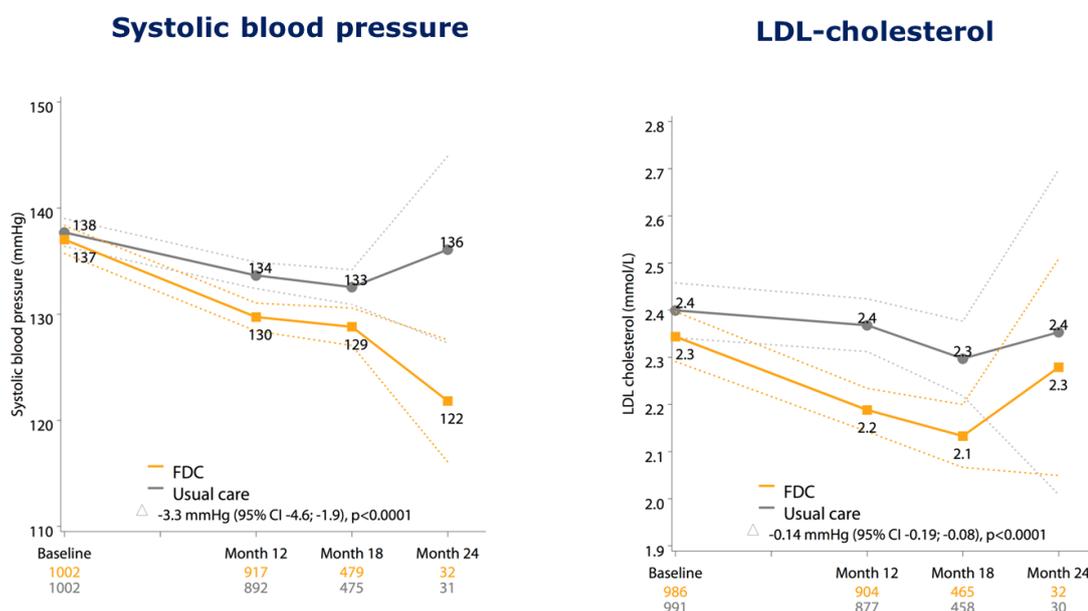
Within Europe, the EUROASPIRE III study<sup>10</sup> showed that the majority of coronary patients who required blood pressure lowering and lipid-lowering medications were not receiving them on a long-term basis; and if patients were receiving them, they were not reaching their blood pressure and lipid targets, suggesting either poor adherence by the patient or inadequate prescriptions by physicians. Various factors may underlie the suboptimal treatment of high-risk patients, such as the need for doctors to navigate complex guidelines, low continuation rates by patients, inequities in health care, and resistance to costs by both doctors and patients.

Practical and affordable approaches are needed to close these treatment gaps. Combination pills or 'polypills' may have a role to play in closing these treatment gaps in ischaemic and cerebrovascular disease, and their use has been advocated for more than a decade.<sup>11,12,13</sup> The use of a polypill containing off-patent generic medicines would reduce the complexity, number and costs of medication regimens and could potentially improve adherence and reduce the number of cardiovascular events.

### *Developments since 2004*

The 2004 Priority Medicines Report<sup>14</sup> strongly recommended that the EC should fund research into the development and testing of combination pills in secondary prevention of CVD. Since then, multiple short-term trials have been conducted on the use of various polypills compared with either a placebo or no treatment. While many of the patients involved in these trials suffered from IHD, some of the patients included were suffering from cerebrovascular disease. These trials have shown that the short-term reductions in CVD risk factors are of approximately the size expected from the individual agents, after taking into account loss to follow-up and non-adherence. Following on from these studies, the EC FP7-funded "Use of a multidrug pill in reducing cardiovascular events" (UMPIRE) trial was the first long-term trial reported that tested the impact on adherence to recommended medicines of a polypill in patients at highest risk of CVD. This 2000-patient randomized controlled trial compared the polypill to usual care and showed improvement in adherence of one-third, which corresponds to 4.6 patients needing to be treated with the polypill in order to gain one additional adherent patient. Reductions in SBP of 2.6 mmHg and LDL-cholesterol of 0.11 mmol/L in the polypill group were also seen and these were sustained throughout follow-up (see Background Paper 6.3).

Figure 6.3.2: Systolic blood pressure and LDL-cholesterol by treatment group over follow-up in the FP7-funded UMPIRE trial\*



Source: personal communication, S Thom

Note: \* Systolic blood pressure (panel A) and LDL-cholesterol (panel B) values shown at baseline, during follow-up and at end of study (EOS) in the polypill and usual care groups.

These improvements were seen even though the trial population had higher than average usage rates for the individual classes of medication at baseline and the “newer” statins (atorvastatin or rosuvastatin) comprised over 70% of the statins prescribed in the usual care comparison group. Even larger benefits were seen in the small group of patients who were not adherent to all three medication classes at baseline.

### Remaining challenges

The recommendations of the 2004 Priority Medicines Report have led to advancements in polypill research over the past nine years and demonstration of the effectiveness of such a strategy in improving adherence. However, there is now a need for committed funding to assess the size of the benefits and risks of implementing a polypill strategy on a large scale.

The scale of funding required to further develop the evidence base that has already been achieved in the area of polypill research is unlikely to be committed to by major pharmaceutical companies as their focus lies in the development of newer patent-protected products which are likely to have higher profit margins. Meanwhile, generic pharmaceutical companies do not have the research budgets that would enable them to invest in such large-scale clinical trials. Major public funding commitment is therefore needed to ensure that what has been achieved so far is built upon and to provide the evidence necessary for regulatory approval in both Europe and worldwide. The

potential benefits (both in economic and health gains) of the widespread use of polypills for secondary prevention are enormous.

### *Research needs related to the polypill*

Many of the factors involved in scale-up are system-level (including training, education, task shifting, and electronic decision support), and many of the patients, clinicians and environments most in need of adherence-improving strategies are those least likely to join a standard clinical trial. Therefore the area would be well served with a very large implementation trial or a series of sister trials. The UMPIRE trial showed improvements in risk factor reductions that would be expected to result in a 10% to 15% reduction in cardiovascular events in that trial population. However, that benefit might be at least twice as great among a group not already taking all the indicated medications. This would require trials involving tens of thousands of participants in order to reliably assess cardiovascular outcomes and assess consistency in different patient groups and in different health systems.

Other issues that require further research in this area (as part of the above-mentioned implementation research or as separate trials) include:

- Potential additional benefits from newer agents now off-patent
- Careful attention to new evidence on the side-effects of statins
- Number of dose versions
- Low-dose versus high-dose polypills
- Specific populations (e.g. diabetes polypill, hypertension polypill)
- Use in acute care (e.g. immediately after a heart attack versus use in chronic care).

### *Other research needs related to ischaemic heart disease.*

As mentioned in the introduction, there are many other areas of research into pharmacological approaches to IHD that may need to be supported. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; as well as regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD. While these areas have not been investigated in the background paper or in this chapter, opportunities for research may exist that are not being addressed by the pharmaceutical industry.

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### 6.4 Diabetes

[See Background Paper 6.4 \(BP6\\_4DM.pdf\)](#)

#### *Background*

Diabetes and diabetes-related illnesses place an enormous burden on the health care systems of countries throughout the world. In 2008, diabetes accounted for about 2% of the burden of disease (DALYs) in the WHO European Region<sup>1</sup> and about 1.5% worldwide. At the global level, diabetes accounted for 2% of all deaths – about the same as in the EU27. In 2012, there were an estimated 370 million people with diabetes worldwide and nearly five million deaths due to diabetes and diabetes-related illnesses (see Appendix 6.4.1).

Over time diabetes can damage the heart, blood vessels, eyes, kidneys and nerves. The disease is a considerable cause of premature mortality. Due to increases in life expectancy, urbanization, rates of overweight and obesity, and the prevalence of diabetes. The disease burden for diabetes is likely to worsen, particularly in low- and middle-income countries.

There are primarily two types of diabetes. Type 1 diabetes is an autoimmune disease in which the pancreas can no longer produce insulin. As a result, the body cannot control blood sugar levels. The key characteristics of type 1 diabetes are its onset mostly in young people and the extremely wide global variation in the incidence of the disease. There is a comprehensive lack of knowledge about the cause of this disease,<sup>2</sup> and it remains an epidemiological puzzle. The overall standardized incidence varies from 0.1:100 000 per year in the Zunyi region of China to more than 40:100 000 per year in Finland.<sup>2</sup> Type 1 diabetes appears to be on the increase in almost all populations. In Europe, the incidence of (childhood onset) type 1 diabetes continues to rise but the increase is not necessarily uniform. This pattern of change suggests that key risk exposures differ over time in different European countries.<sup>3</sup>

Type 2 diabetes (previously called adult onset) is a metabolic disorder in which the body gradually becomes insensitive to the action of insulin with decreased beta cell mass and progressive beta cell failure so that blood sugar control is also compromised. Overall, the prevalence of type 2 diabetes dominates the total diabetes burden. In developed countries, most people with diabetes are aged over 60 years, while in developing countries the disease mainly affects people of working age (40 to 60 years).

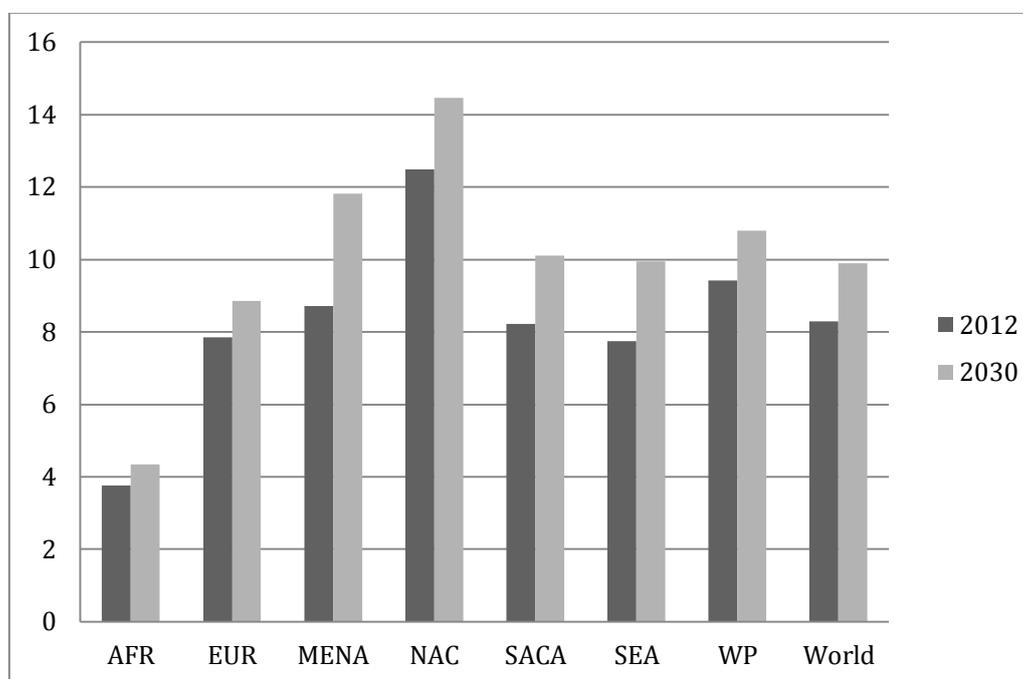
#### *Developments since 2004*

The most recent global projections<sup>4</sup> for diabetes are far higher than predictions made around the time of the 2004 Priority Medicines Report. In 2012, of the estimated 370 million people affected by diabetes worldwide, about half live in the Western Pacific, South Asia, and Eastern Mediterranean regions. See Appendix 6.4.1 and Figure 6.4.1

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below (created from recent data assembled by the International Diabetes Federation (IDF) at Appendix 6.4.2). The IDF regions are not coincident with WHO regions.

**Figure 6.4.1: Median Regional Diabetes Prevalence (%)**



Source: Adapted from recent data assembled by the International Diabetes Federation (IDF): Appendix 6.4.2 at IDFAAtlas5E\_Detailed\_Estimates.xls

Note: WP: Western Pacific; SACA: South and Central America; AFR: Africa; MENA: Middle East and North Africa; NAC: North America and Caribbean; SEA: Southeast Asia; EUR: Europe

It is estimated that from 2012 to 2030 the total number of people with diabetes worldwide will increase by about 180 million (from 371.33 million to 551.87 million). This dramatic increase of 48% from 2012, at an annual growth of 2.7%, is twice the annual growth of the total global adult population.<sup>5</sup> Of this global increase, 42% is projected to occur in India and China alone.<sup>6</sup> In low- and middle-income countries, adult diabetes numbers are likely to increase by over 60% from 2012 to 2030, compared to 20% in developed countries, while the total adult populations are expected to increase by 36% and 2% respectively.<sup>4</sup>

With increasing levels of obesity among children, there is an alarming trend for juveniles to develop type 2 diabetes. Predictions from the United States suggest that within 10 years, normal adult onset type 2 diabetes might become the most common form of newly diagnosed diabetes in adolescent youth.<sup>7</sup>

### *Remaining challenges*

In view of the burden and associated costs of diabetes, the ongoing epidemic represents a major public health problem requiring effective control. There is currently a large gap between the prevalence of diabetes and treatment rates, with an estimated 30% to 50% of diabetes cases remaining undiagnosed and therefore untreated.<sup>4</sup>

People with type 1 diabetes require lifelong insulin replacement and face the additional complications of diabetes-related diseases. At present, there is no real ability to provide effective, long-term, tight blood sugar control through insulin replacement therapy. Moreover, insulin requires refrigeration and this creates an access problem in many low- and middle-income countries. Primary prevention of the disease may depend on the determination of autoantibody combinations conferring a high risk of progression to diabetes, which typically become established within the first three years of life. Therefore, ideally, primary prevention should be attempted as early in life as possible (i.e. soon after birth).<sup>8</sup> Safety is the major criterion for any form of primary prevention, since only a small percentage of those at risk would be expected to develop diabetes. Meanwhile, metabolic testing of young people with type 1 diabetes can identify those at imminent risk of progression, which helps to stage the disease process. Major studies have demonstrated the feasibility of large scale controlled trials in antibody-positive first degree relatives of those with diagnosed type 1 diabetes, but the logistics are difficult and the number of interventions that can be tested is very limited.<sup>9</sup>

Primary prevention of type 2 diabetes has always been centered on control of the energy economy of the body (i.e. achieving a negative calorie balance if weight loss is required and/or optimal intake of carbohydrates and lipids).<sup>10,11</sup> Controlling obesity and increasing physical inactivity can prevent, or at least delay, the development of the disease in many genetically susceptible individuals. However, success in controlling these risk factors on a large scale has been limited. Efforts to control blood sugar levels in type 2 diabetes has become increasingly complex and, to some extent, controversial as there is still debate over how “flexible” or “tight” such control should be. With a widening array of pharmacological agents now available, there is growing concern about their potential adverse effects and uncertainties regarding the asserted benefits of aggressive glycemic control on macrovascular complications.<sup>12</sup> In the long run, many patients with type 2 diabetes will require insulin therapy alone or in combination with other agents to maintain glucose control.

Although blood glucose lowering agents can assist in preventing the onset of type 2 diabetes, a significant percentage of patients do not achieve glucose or weight goals and develop complications. At present, there is an inability to prevent progressive loss of islet B-cell function/mass (affecting prevention and then progression of hyperglycemia). There is also an inability to manage the progressive ineffectiveness of glucose-lowering treatments over time, resulting in the need for multiple therapy (and usually insulin about 10 years after the onset of the disease).<sup>13</sup>

There are considerable gaps in the understanding of optimal applications of existing and new therapies, particularly since many patients will have coexisting conditions that require polypharmacy. The risk of possible drug interactions and the safety of new agents will remain of primary concern. The accumulated evidence for type 2 diabetes suggests that not everyone benefits from aggressive glucose management.<sup>14</sup>

Diabetes is an example of a disease with an unmet global medical need and conforms to the "commonality of interest" principle of the Priority Medicines Project. The dramatic increases in diabetes that are projected over the next several decades require a global strategy for prevention, treatment and medicine development.

### *Research needs*

The availability of heat-stable insulin, for use in developing countries with limited access to refrigeration, and for use by travellers, would be a major public health advance. Another major advance would be the development of glucose-responsive insulin. At present, all insulin treatments for people with diabetes release an amount of insulin at fixed times that is not in proportion to local blood glucose levels, in contrast to people without diabetes, in which the body secretes insulin in proportion to local blood glucose levels. A glucose-responsive insulin for people with diabetes could therefore be a transformative solution, vastly improving the quality of life of people with insulin-dependent diabetes.<sup>15,16</sup>

In addition, there is a need for therapies directed at multiple risk factors for type 2 diabetes, such as dyslipidemia, hypertension and obesity. These have been a major focus of research and therapy. One possible future strategy is the fixed-dose combination 'polypill', whereby several risk factors are treated with a single capsule containing a combination of pharmaceuticals, which can be assembled in various ways. A second pharmacological strategy to reduce the problems associated with polypharmacy for patients with several risk factors is to develop single drugs that have multiple targets or modulate targets that affect several risk factors.

Research is also needed into effective delivery of preventive strategies to delay progression of the disease and its complications. This should integrate individual, clinical, system, and society-level approaches that span the full course of life.

- The evidence base for clinical and public health interventions needs to be expanded to include a much broader spectrum of disciplines including, for instance, experts in behavioural economics, systems dynamics, political science, and urban planning. Integration of surveillance, clinical and population-based epidemiology, health services research and economics is sorely needed.
- Large, long-term intervention studies are needed to identify effective strategies for reducing barriers to diabetes care and improving adherence to treatment and management regimens.
- The gap is large between scientific and technological progress and its implementation. Europe can help reduce this gap by championing international

efforts to assure that children and adolescents around the world do not suffer premature death and disability because their diabetes is mismanaged.

- Although effective preventive strategies exist for type 2 diabetes, the susceptibility genes identified so far do not provide predictive abilities strong enough to warrant genetic screening. Therefore continued research into genetic screening is needed.
- The safety, efficacy, and economic impact of self-adjusting closed-loop control systems are currently unknown and deserve further investigation.
- Translational research, which seeks to understand how advances can be adopted in community-based and often uncontrolled conditions (e.g. resource-poor environments) has received little attention in the diabetes field. Some of the important questions in translational research cannot be addressed in randomized trials.
- Community-based participatory research, issues related to lifestyle, diet, physical activity and cultural preferences should be explored.
- A diabetes registry that keeps track of glycosylated haemoglobin (A1C) values is one example of linking diabetes with key policy decisions. Such a registry was implemented in New York City.<sup>17</sup>

Substantial resources continue to be allocated to diabetes research by public and private funders. By 2019, the global market for diabetes is expected to be worth US\$ 35 billion and the private sector is investing heavily. The pharmaceutical industry considers development of effective diabetes medications to be a major goal. The European Commission (EC), together with support from network organizations, has the opportunity to continue research on genetic and environmental factors in different population groups.

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### 6.5 Cancer

[See Background Paper 6.5 \(BP6\\_5cancer.pdf\)](#)

#### *Background*

Cancer (a term that includes over 100 types of malignancy) is one of the major burdens of chronic disease in Europe and the world (see Chapter 5 and associated Background Paper). It is estimated that in 2012 in the EU27 countries over 700 000 men and over 550 000 women died of cancer. These numbers are slightly higher than those recorded for 2007 (an increase of 1.5% in men and 2% in women). This increase in cancer deaths can be explained by the ageing of the EU population. When these cancer mortality rates are adjusted for age, they are expected to show a substantial improvement, falling from 154 per 100 000 in men in 2007 to 139 per 100 000 in 2012 (a drop of 9.6%) and from 91 per 100 000 to 85 per 100 000 in women (a drop of 6.5%).<sup>1</sup>

In men, improvements in age-adjusted mortality rates (in 2007 to 2012) are expected to include significant reductions for five cancer types: stomach cancer (-20%), leukaemias (-11%), lung and prostate cancer (-10%) and colorectal cancer (-27%). In women, over the same period, age-adjusted mortality rates are also expected to decline for the following cancer types: stomach cancer (-23%), leukaemias (-12%), uterus and colorectal cancer (-11%) and breast cancer (-29%). However, increases are expected in age-adjusted mortality rates for lung (+7%) and pancreatic (+3%) cancers in women.<sup>1</sup>

There is some disparity in cancer mortality rates between the Central European post-2004 EU accession countries (particularly Poland) and countries of the former EU15. This disparity was seen in the early 2000s and is expected to continue, at least in proportional terms. Furthermore, trends in cancer survival rates also vary across the EU.<sup>2</sup> Berrino et al., determined that the relative excess risk of death from cancer was 28% higher in Eastern Europe (based on data from the Czech Republic and Poland) than in Central Europe (based on data from Austria, Belgium, France, Germany, the Netherlands and Switzerland).<sup>3</sup>

It is possible that differences in survival rates between Eastern and Central European countries persist largely because of fewer resources for health care services and recent dysfunction in the health care systems of Eastern European states.<sup>3</sup> In Europe as a whole, the relative excess risk of death was 60% higher for patients aged 55 to 99 years than for those aged 15 to 54 years; and male cancer patients in Europe had a significantly higher risk of dying than women.<sup>3</sup> These regional disparities are inherently subject to controversy. The idea of using cancer survival as a means of measuring the effectiveness of health systems is a major topic of research and discussion.<sup>3,4</sup>

In Europe, any spotlight on high burden cancers such as breast, lung, prostate, and colorectal cancer must also keep a focus on the incidence of rare cancers. In the EU27

countries there are about 500 000 new cases of rare cancers a year (for definitions of rare cancers see <http://www.rarecare.eu/default.asp>). In the EU27 countries today about 4.3 million patients are living with a diagnosis of a rare cancer, accounting for 24% of the total EU cancer prevalence. Over all age groups, five-year survival rates are 48% for rare cancers and 64% for more common cancers.<sup>5</sup> The low incidence of individual rare cancers is a major obstacle to conducting clinical trials to develop effective treatments ([see also Chapter 6.19 on rare diseases](#)).

Meanwhile, there are an estimated 175 000 new cases of childhood cancers every year worldwide.<sup>6</sup> Although 80% of children in developed countries now survive cancer as a result of the latest treatment regimens, 60 000 children in developing countries die each year from cancers that are often curable.<sup>6</sup> In the 1990s, overall survival rates for children with cancer were 64% in Eastern Europe and 75% in Western Europe, with differences between regions for all tumour groups. There is a critical need for better access to care and for more research in childhood cancer. It is important to close the gaps in survival rates among children with cancer both at the European level and worldwide.<sup>6,7</sup> In this context, for both adults and children, there is a need for research in survivorship issues as the long-term side-effects of cancer therapies is an important research subject. In addition, quality of life issues such as end of life care and palliative therapy are worthy of research.

### *Developments since 2004*

Since the 2004 Priority Medicines Report, there have been a number of major therapeutic breakthroughs. An increasing number of targeted therapies – in combination with chemotherapy – have proved to be effective against common cancers. These include:

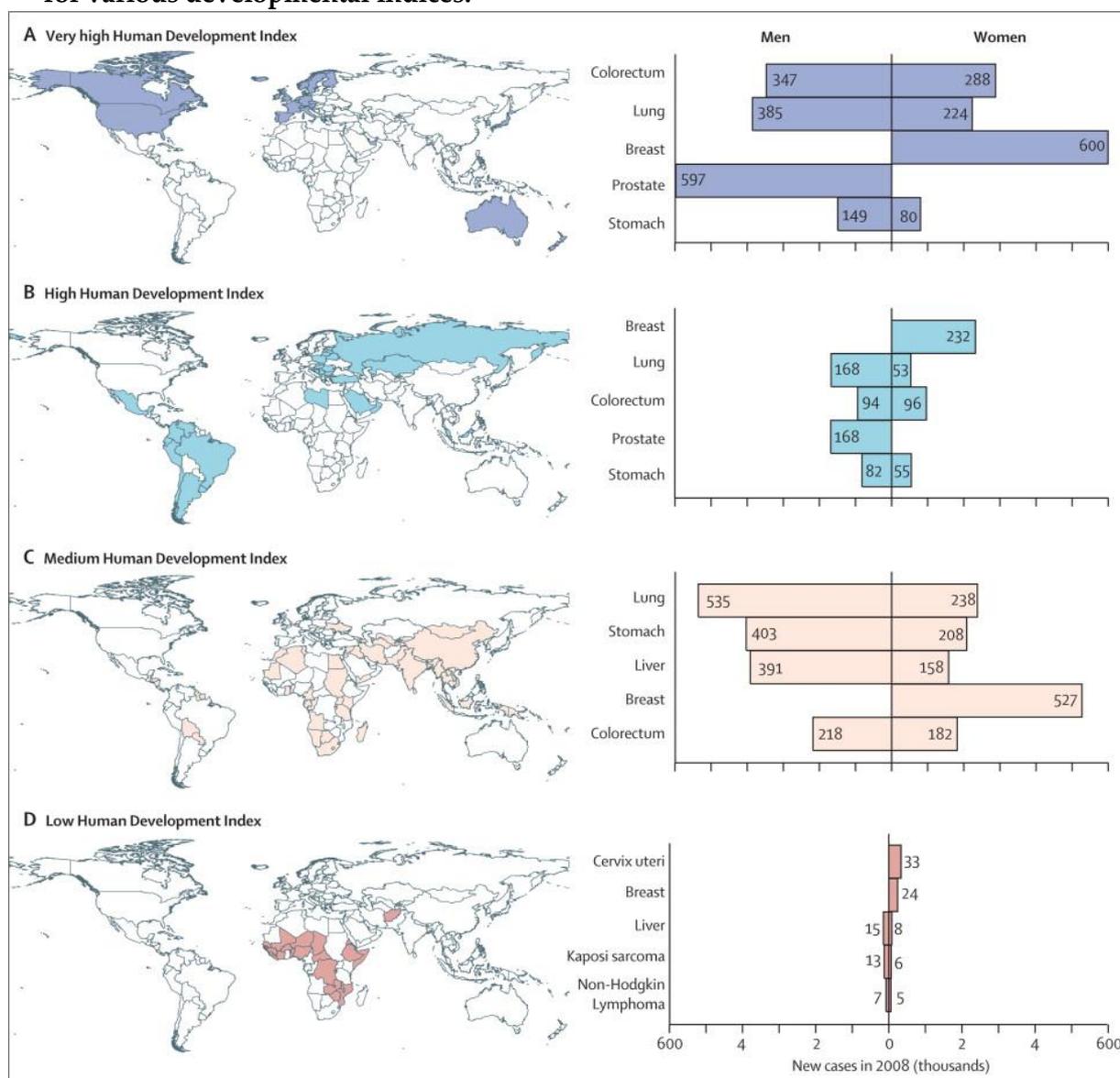
- Efforts to attack more than one target in a molecular pathway that is critical for tumour survival and growth can now be achieved through the use of multi-targeted drugs. These include: regorafenib (for patients with metastatic colorectal cancer or GI stromal cancer); and crizotinib (which offers promising activity against neuroblastoma).
- Targeted agents have also shown benefit when used as monotherapy (e.g. for anaplastic lymphoma kinase gene-mutated non-small cell lung cancer) where the pace of research progress in this area has been remarkable.
- In 2005, the first vaccine to prevent infection with human papillomavirus (HPV), which is present in virtually all cervical cancers, was approved by the U.S. Food and Drug Administration (FDA). The viral strains used in the HPV vaccine together account for approximately 70% of cervical cancer cases worldwide. In February 2013, the GAVI Alliance announced it would provide HPV vaccine as part of its portfolio.
- In 2009, trastuzumab (Herceptin®), which is widely used to treat HER2-positive breast cancer, was proven effective as the first targeted therapy for stomach cancer.

- In 2010, the FDA approved sipuleucel-T (Provenge®), a cancer vaccine for metastatic hormone-refractory prostate cancer. This is a true *therapeutic vaccine* in that it boosts the body's immune system to attack cancer cells in the body.
- The entire cancer therapeutics field is moving more toward targeted therapies and immunotherapy. The monoclonal antibody ipilimumab was approved by the FDA in March 2011 to treat patients with late-stage melanoma that has spread or cannot be removed by surgery. This is an area of high unmet medical need.

In many of the countries where social and economic transition is leading to a shift in the pattern of disease, the cancer burden is also changing. The result is a reduction in infection-related cancers and an increase in cancers that are more associated with reproductive, dietary, smoking and hormonal factors. Targeted interventions can lead to a decrease in the projected increases in cancer burden through effective primary prevention strategies, together with the implementation of vaccination, smoking prevention, early detection and effective treatment programmes (see Figure 6.5.1).

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**Figure 6.5.1: Major cancers (by incidence in 2008: male/female) for various developmental indices.**



Source: Bray F et al. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol*, 2012, 13 (8): 790-801.

### Remaining challenges

Cancers are a global public health concern, in large part because of the preventable nature of some of the most common cancers and the high treatment costs of many cancers, which are rarely affordable by patients themselves and can only be made universally accessible through health insurance or national health schemes.<sup>8</sup> Of these, tobacco use probably remains the most important avoidable cancer risk. In the twentieth century, approximately 100 million people worldwide died from tobacco-associated diseases (cancer, chronic obstructive lung disease, heart disease and stroke) ([See Chapter 6.17](#)).

The pharmaceutical industry has invested heavily in finding new pharmaceutical treatment options and the EU does not at present match the private or public funding levels of the United States with regard to cancer therapeutic research and development.

It is entirely possible that in resource-constrained countries without specialized services, cancer could be partly prevented and treated using lessons learned from the public health battle against HIV/AIDS, for example by using primary and secondary caregivers to screen and continue treatment, use of generic drugs, and application of regional and global mechanisms for financing and procurement.<sup>9</sup> In those countries with national health insurance, cancer treatment can be included in the insurance cover, with an emphasis on a benefits package targeting the poorest populations. The availability of expensive immune and targeted therapies should not be limited to patients in high-income countries. However, access will depend on efforts to reduce costs, increase access to health services and strengthen health systems in low- and middle-income countries.

For the EC, in the period 2014 to 2020, one challenge will be to understand the inequalities between EU countries in levels of cancer control and care, including screening and follow-up for breast, cervical and colorectal cancer. Identification and promotion of good practice in prevention, diagnosis, treatment and care of all cancer types, including paediatric cancers, across the EU will be important. In addition, collaborations between EU countries can provide the “economies of scale” needed to manage this condition more effectively across all parts of the health care system.

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### 6.6 Acute stroke

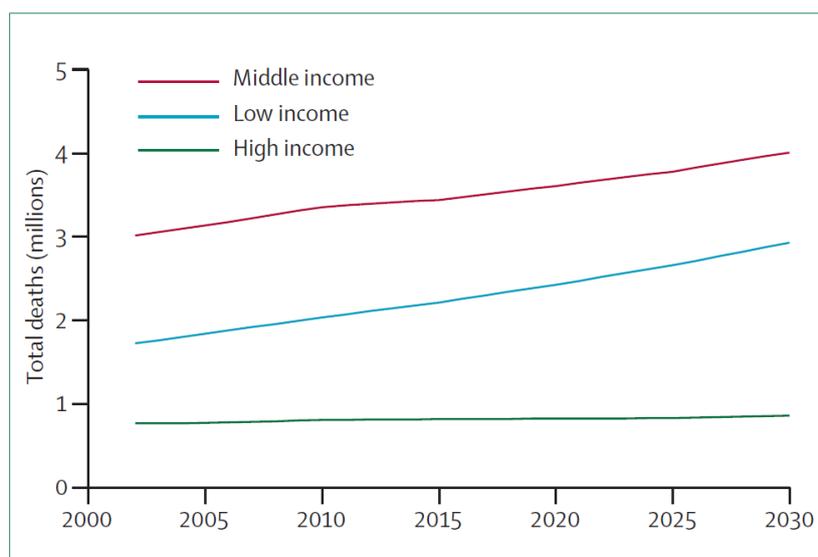
[See Background Paper 6.6 \(BP6\\_6Stroke.pdf\)](#)

#### *Background*

A stroke is caused by either a sudden reduction in the blood supply to the brain or by a haemorrhage. An acute stroke refers to the first 24-hour-period of a stroke event. Most strokes (87%) are ischaemic (caused by thrombosis or embolisms) and the rest (13%) are haemorrhagic (caused mainly by rupture of blood vessel or aneurysm).<sup>1</sup> Eight to twelve per cent of ischaemic strokes and 37% to 38% of haemorrhagic strokes result in death within 30 days.<sup>2,3,4</sup> Within the European Union, hospital discharges for cerebrovascular diseases almost doubled during the last 15 years of the twentieth century. It is projected that in the coming years the major increase in the global stroke burden will be in low- and middle-income countries.

Stroke is the second leading cause of disability in Europe after ischaemic heart disease (IHD) and is the sixth leading cause worldwide (See Background Paper 6.6, Table 6.6.7). Women have a higher lifetime risk of stroke than men: about one in five women (20% to 21%) and one in six men (14% to 17%) will suffer a stroke in their lifetime, according to a 2006 study.<sup>5,6</sup> The prevalence of stroke events is expected to increase across the globe as the global population aged over 65 increases.<sup>7,8</sup> The number of stroke events in Europe is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025, largely due to the ageing population.<sup>9</sup> In the EU27 countries, the annual economic cost of stroke is an estimated €27 billion: €18.5 billion (68.5%) for direct costs and €8.5 billion (31.5%) for indirect costs. An additional €11.1 billion is calculated for the value of informal care.<sup>10</sup>

**Figure 6.6.1: Projected trends for stroke deaths by World Bank income group 2002-30**



Source: Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol*, 2007, 6:182-187.<sup>11</sup>

The successful management of acute stroke is based on imaging such as magnetic resonance imaging (MRI) and computerized tomography (CT) followed by two main strategies: vascular recanalization and supportive care. The restoration or improvement of perfusion to the ischaemic area is a key therapeutic strategy. Secondary prevention strategies that reduce the rate of ischaemic stroke recurrence include aspirin and dipyridamole.<sup>12</sup> Current stroke therapy is mainly based on general care and rehabilitation. The main modifiable risk factors for stroke prevention are high blood pressure, diabetes, smoking, and heavy alcohol use.<sup>13,14</sup>

### ***Developments since 2004***

Since 2004, there has been little progress in the R&D of medicines for treating acute stroke (particularly in the field of neuroprotection) and surprisingly low levels of funding for this – only 10% of the investments in medicines R&D for IHD or cancer over the past 30 years.

Several large-scale, EU-funded projects established under the EC Seventh Framework Programme (FP7) are currently under way, and will provide further insight into the future of stroke care.<sup>15</sup>

### *Remaining challenges*

Despite improvements in care, the sequelae of stroke remain a major problem. While 50% to 70% of those who survive an ischaemic stroke will recover functional independence within three months of onset, 20% will require institutional care. The economic impact of stroke care goes beyond the costs of sophisticated acute care, and includes costly secondary prevention (carotid endarterectomy) and the high cost of prolonged high-dependency institutional chronic care and rehabilitation. Neither mortality rates nor hospital discharge rates accurately reflect the level of disability among stroke survivors, which is mainly borne by patients and their families.<sup>16</sup>

Major improvements are needed in the chain of care for identification of stroke by relatives (education); early treatment (possibly with aspirin); the prompt referral to an accident and emergency facility (mobile units); accurate diagnosis and fast appropriate treatment (protocols and specialized units); improved access to expanded and more efficacious therapeutic options; and prompt referral to rehabilitation services.

Meanwhile stroke research remains severely underfunded, despite its high burden both in Europe and worldwide.

### *Research needs*

#### **Priority research topics**

- A breakthrough therapy has yet to be approved and there are still no highly effective acute therapies available. Research for more efficacious therapeutic options to prevent stroke sequelae are crucially needed. This includes the use of stem cells, and the search for new neuroprotective agents. Promising research is being done in the areas of hypothermia (therapeutic cooling), stem cell therapies, and a polypill for secondary prevention of stroke.
- More clinical trials that focus on the elderly and patients with comorbidities are needed.
- Due to lack of advancement in pharmaceutical treatments for acute stroke, there should be an emphasis on prevention and improving health approaches such as specialized stroke units.

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## 6.7 HIV/AIDS

[See Background Paper 6.7 \(BP6\\_7HIV.pdf\)](#)

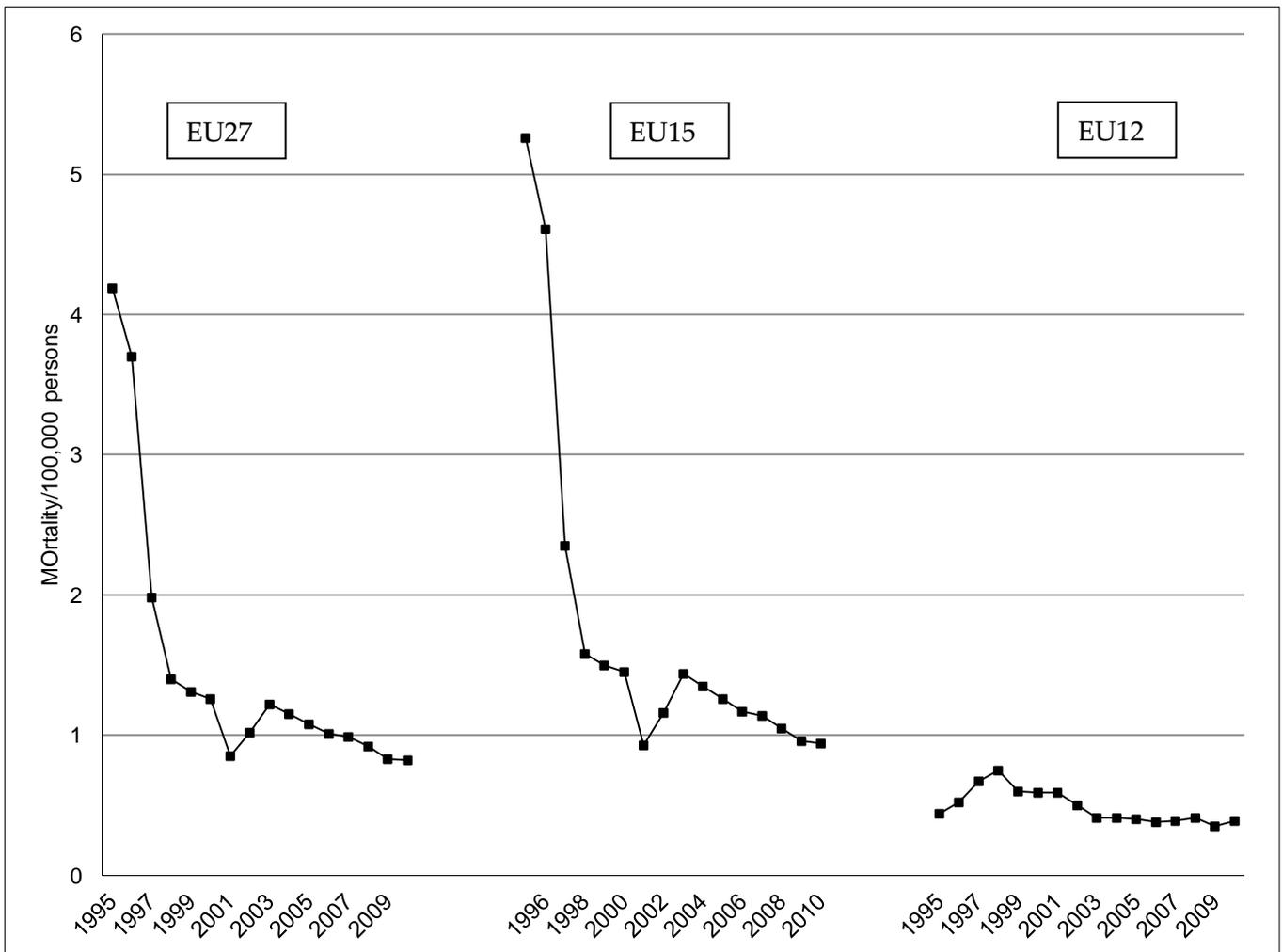
### *Background and developments since 2004*

#### *Europe*

##### **Western and Central Europe**

Since the mid-1990s, AIDS-related mortality rates have fallen dramatically in Western and Central Europe (in both the EU27 and EU15 countries), due to the widespread availability of ART from the mid- to late-1990s (see Figure 6.7.1)

**Figure 6.7.1: Standardized death rates (per 100 000 people) for HIV/AIDS among country-components of the European Union**



Source: European mortality database, WHO European Regional Office

Note: "EU 27" is the 27 Member States of the EU; "EU 15" are those countries that were EU Member States before May 2004; "EU12" are the 12 new Member States of the European Union as from 1 May 2004 or from 1 January 2007. (see Background Paper, Annex 6.7.1).

With the roll-out of antiretrovirals (ARVs) there was a general expectation that the widespread availability of antiretroviral therapy (ART) would act as an incentive for individuals to get tested for HIV and that, once diagnosed, the drugs would help them stay healthy for a longer period of time.<sup>1</sup> However, in Western and Central Europe many people are still not being tested and are unaware that they are living with HIV.<sup>2</sup>

Opportunities to diagnose HIV infections are often missed, particularly in routine health care settings and testing among injecting drug users is particularly low. Late diagnosis of HIV infection, when the CD4 count is low, has serious implications for both the individual and for public health. Although treatment reduces transmission rates, a late diagnosis means that a person is more likely to develop an AIDS-related illness, less likely to respond to ART and more likely to die as a result.<sup>3</sup> Since people are more likely to take precautions to prevent transmission if they are aware of their HIV status, late or no diagnosis will increase the risk that HIV will be transmitted, which has wider public health implications.<sup>4</sup>

Early diagnosis of HIV infection is essential so that patients are referred promptly for evaluation, provided treatment (if indicated), and linked into counselling and related support services to help them reduce the risk of transmitting the virus to others. It is particularly important to diagnose HIV during the early acute stage of the disease when people are most infectious but test negative for HIV antibodies and therefore may continue to engage in high-risk behaviours associated with HIV transmission. There is a critical need to encourage wider uptake of voluntary testing for HIV to ensure earlier access to counselling and treatment (as needed). It would appear that uptake of testing increases when “opt-out policies” are in place – whereby a test is routinely performed unless the patient chooses to opt out. Meanwhile, there is evidence that in some European countries, migrants from countries with generalized HIV epidemics are disproportionately affected by HIV and do not access testing or treatment services as readily as other populations.<sup>5,6</sup>

The prevalence of HIV in the over 50 years age group is increasing due both to the ageing of adult populations living with HIV and to the diagnosis of new cases in later life. Older adults are vulnerable to late or missed diagnosis and poorer treatment outcomes, due to the misconception that they are not at risk. As the HIV population ages, older patients increasingly have to contend with the development of chronic diseases (such as cardiovascular disease, osteoporosis and dementia) and with treatment complications.<sup>7</sup> The management of older adults with HIV and multiple comorbidities presents challenges for both infectious disease physicians and geriatricians.<sup>7</sup>

### *Russia Federation, Eastern Europe and Central Asia*

Around 1.5 million people in the Russia Federation, Eastern Europe and Central Asia were living with HIV at the end of 2010, with the region having a prevalence of 0.9 percent.<sup>8</sup> In the Russian Federation and Ukraine in 2009, the prevalence of adult HIV

infection was 1% and 1.1% respectively. It has been estimated that over two-thirds of the area's infected people live in the Russian Federation, and combined with Ukraine, these two countries account for almost 90 per cent of the region's newly reported HIV diagnoses. They also have twice as many people living with HIV as all of Western and Central Europe combined. In St Petersburg, in the Russian Federation, for example, the incidence of HIV among people who inject drugs was 8.1 per 100 person-years in 2009, almost twice the rate five years earlier (see Background Paper 6.7, Appendix 6.7.1). Unlike most other regions, the number of people dying from HIV-related causes continues to rise in these regions (see Background Paper 6.7, Appendix 6.7.1). There is concern at the increasing incidence of HIV infection among people who inject drugs. In 2007, injecting drug users accounted for 57% of new HIV infections reported in this region.<sup>9</sup> Since 2005, newly reported HIV cases have also been increasing in the smaller epidemics in Central Asia (Kyrgyzstan, Tajikistan and Uzbekistan). The use of contaminated drug-injecting equipment remains the main route of transmission in this region (see Background Paper 6.7, Appendix 6.7.1).

### *HIV/AIDS at the global level*

The most recent (2012) UNAIDS report, *Together We Will End AIDS*, shows more than 50% reduction in the rate of new HIV infections across the 25 low- and middle-income countries worst affected by HIV (see Background Paper 6.7, Appendix 6.7.1). More specifically, the number of people dying each year from HIV-related causes worldwide was down from a peak of 2.3 million in 2005 to an estimated 1.7 million in 2011. This is most evident in sub-Saharan Africa, where an estimated 550 000 (or 31%) fewer people died from HIV-related causes in 2011 than in 2005, when the number of HIV-related deaths peaked. In addition, in some of the countries with the highest HIV prevalence in the world, rates of new HIV infections have been cut dramatically since 2001; by 73% in Malawi, 71% in Botswana, 68% in Namibia, 58% in Zambia, 50% in Zimbabwe and 41% in South Africa and Swaziland.

Elsewhere, in the Middle East and North Africa, the available evidence points to an ongoing increase in the number of people newly infected with HIV. In these regions in 2011, there were an estimated 36 000 new cases among adults, a 29% increase since 2001.

In Latin America, widespread access to ART has helped reduce the number of people dying from HIV-related causes to 57 000 in 2011, down from 63 000 in 2001. In Asia, the number of people dying from HIV-related causes has remained stable at about 330 000 deaths in 2011, the largest number of deaths outside sub-Saharan Africa.

The prevalence of HIV-related tuberculosis (TB) remains a serious challenge in many countries as TB is the leading cause of death among people living with HIV. More than 80% of the people living with HIV and TB are in sub-Saharan Africa.

Meanwhile, HIV continues to have a disproportionate impact on sex workers, men who have sex with men, and people who inject drugs. HIV prevention and treatment

programmes are largely failing to reach these key populations, particularly in countries of the Middle East, Central Asia and North Africa. (See Background Paper 6.7, Appendix 6.7.1)

### *Paediatric HIV*

There is still a major gap between children and adults in access to ART. In 2011 worldwide, only 28% of eligible children (about 562 000) had access to ART. Although this was higher than the 22% (456 000) in 2010, it was much lower than the 57% coverage among adults in 2011. Despite the continuing low coverage rates for ART among eligible children compared to adults, substantially fewer children are dying from AIDS-related causes: 230 000 in 2011 compared with 320 000 in 2005 (see Background Paper 6.7, Appendix 6.7.1).

In part, this is due to the fact that the cumulative number of new HIV infections averted among children more than doubled between 2009 and 2011 in low- and middle-income countries, as services to eliminate new HIV infections among children were expanded (see Background Paper 6.7, Appendix 6.7.1). Almost 600 000 new HIV infections among children have been averted since 1995 due to the availability of antiretroviral prophylaxis both for pregnant women living with HIV and for their infants. Most of the children involved live in sub-Saharan Africa.

In view of the aggressiveness of HIV infection in infants and young children, national and international guidelines now recommend treatment for all children below the age of 12 months with confirmed HIV infection, regardless of clinical stage or CD4 cell count.<sup>10</sup>

The diagnosis of HIV infection in young infants remains a challenge. The passive transfer of maternal antibodies confounds the diagnosis in children aged under 18 months when they are most vulnerable. The expansion of early infant diagnosis programmes utilizing dried blood spot systems has enabled the identification of infants with HIV, even in remote settings.<sup>11</sup> However, this requires the participation of antenatal and obstetrical services to first identify HIV-positive mothers and to carry out the subsequent follow-up of infants to test them at the appropriate time.

In settings such as sub-Saharan Africa where the prevalence of HIV is high, significant resources are needed to ensure universal antenatal HIV testing, training all health care workers in the management of HIV diagnosis and treatment, and integrating HIV care and treatment into the overall health care system.<sup>12</sup> Routine testing at entry points to care, such as immunization clinics or inpatient wards, is very effective in identifying HIV-exposed and HIV-infected children in countries such as South Africa and Zambia.<sup>13,14</sup>

### *Antiretroviral therapy and therapeutics*

Triple antiretroviral treatments are now standard for people with HIV infection. Without treatment, about 50% of people with HIV will die of AIDS within 10 years. Although the clinical efficacy of existing ARVs has improved dramatically, the HIV genome mutates very rapidly during the course of an infection and the development of resistance to ARVs is common. There is a continuing need to identify which ARVs are most effective and where research is needed to develop new treatments because of the development of resistance. Antiretroviral therapy alone will not end the epidemic and a comprehensive public health approach, involving additional forms of therapy and treatment strategies remains essential.

The HIV-1 life cycle presents many potential opportunities for therapeutic intervention, but not all of these have been exploited. The design of post-entry inhibitors remains problematic; the more advanced inhibitors include agonists of the integrase enzyme, which mediates viral cDNA integration into the host cell's genome. The design of new viral-entry inhibitors also focuses on the escape pathways adopted by the evolving HIV-1 virus in response to inhibition of its normal entry route. The most successful therapeutic approach will likely be a 'cocktail' of inhibitors, which block infection at several points, including the potential escape pathways.

### *AIDS vaccine development*

The AIDS vaccine development effort has faced a number of challenges. The fundamental biological challenge is to achieve better understanding of the basic biology of HIV-1 infection and an effective antiviral immune response.<sup>15</sup>

Current AIDS vaccine candidates are unable to induce broadly neutralizing antibodies against primary HIV isolates or only to a very limited and narrow extent, presenting a major stumbling block in the development of an effective HIV vaccine. The immune response elicited by a successful vaccine may require both antibodies and T cells that recognize, neutralize and/or inactivate diverse strains of HIV, and that reach the site of infection before the infection becomes irreversibly established.<sup>16,17,18</sup>

### *Investment in HIV/AIDS R&D*

In the United States and Europe, the private R&D sector is investing major financial and human resources in addressing HIV/AIDS, with the private sector in the United States by far the larger contributor. Meanwhile, there was a widespread decrease in public funding for HIV R&D in 2011, with 10 of the top 12 funders reducing funding from 2010 (see Background Paper 6.7, Annex 3). Although the U.S. National Institutes of Health (NIH) remained by far the largest funder, contributing 61.4% (US\$ 631.4 million) of the global total, it also registered the biggest drop in funding in 2011, down 3.9% (US\$ 26 million). Of the top 12 funders (see Background Paper 6.7, Figure 6.7.4), only the U.S. Department of Defense and the United Kingdom's Wellcome Trust increased funding. In 2011, the public and philanthropic sectors collectively provided 97.8% of R&D funding for HIV/AIDS, with the public sector providing 84.6%

(US\$ 870.5 million) of total funding and the philanthropic sector providing 13.1% (US\$ 135.2 million). Public funding accounts for the majority of R&D funding for HIV/AIDS. As a result, public sector budget cuts following the global financial crisis have had a large impact.

### *Research needs*

The European Union cannot match the private or public funding levels of the United States for HIV R&D. However, based on the epidemiology of HIV/AIDS both in Europe and worldwide, and the current level of investment by private and public sector institutions, it is believed that the European Union can, from a public health viewpoint, fill gaps in the following areas:

- Target specific populations, especially women, sex workers, injecting drug users, children, adolescents, older adults, and across racial/ethnic groups.
- Conduct studies to evaluate potential differences in response to therapy due to gender and/or racial/ethnic differences.
- Conduct clinical trials involving populations in Africa, possibly with the involvement of the European and Developing Countries Clinical Trials Partnership (EDCTP).
- Promote innovative funding mechanisms to attract additional investigators to undertake multidisciplinary research on the discovery and development of microbicides.
- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III clinical trials of new fixed-dose combination ARVs.

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### 6.8 Tuberculosis

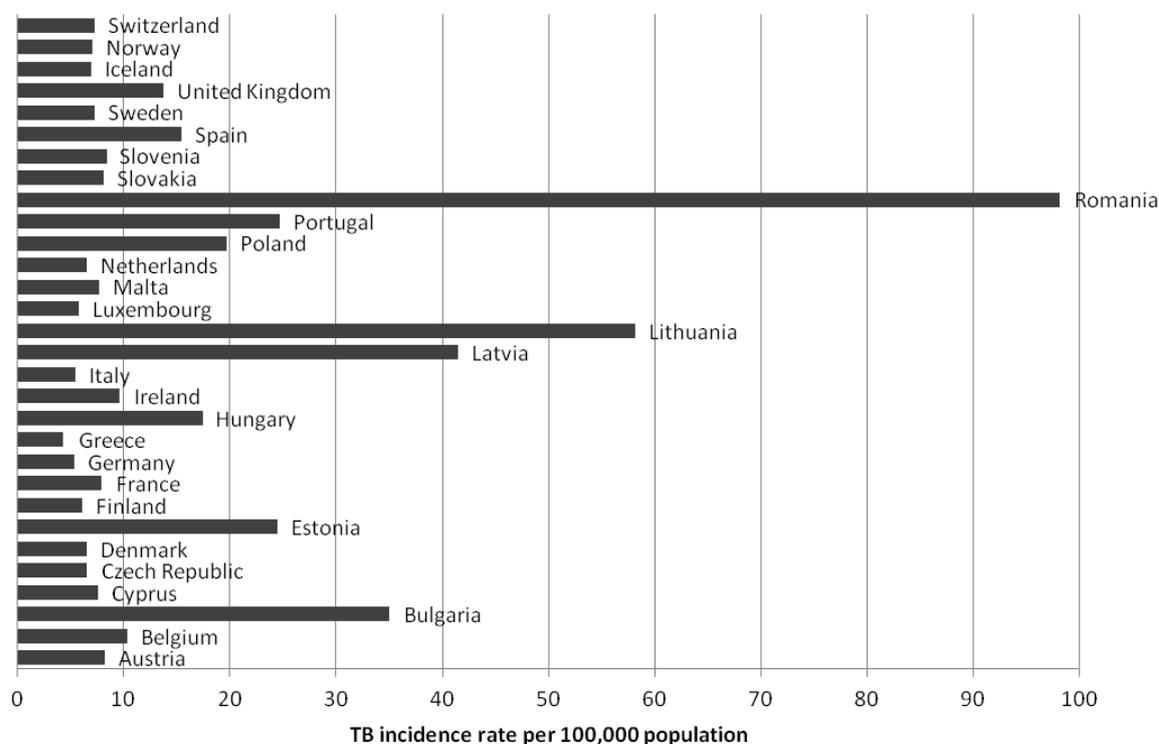
[See Background Paper 6.8 \(BP6\\_8TB.pdf\)](#)

#### *Background and developments since 2004*

The 2004 Priority Medicines Report stated that “*Tuberculosis (TB) is a major and growing threat to public health for Europe and the world, with new epidemiological challenges.*” Since then, the incidence of TB and TB mortality rates have been declining both in the EU/EEA region and worldwide. TB remains largely a disease of poverty, with a high

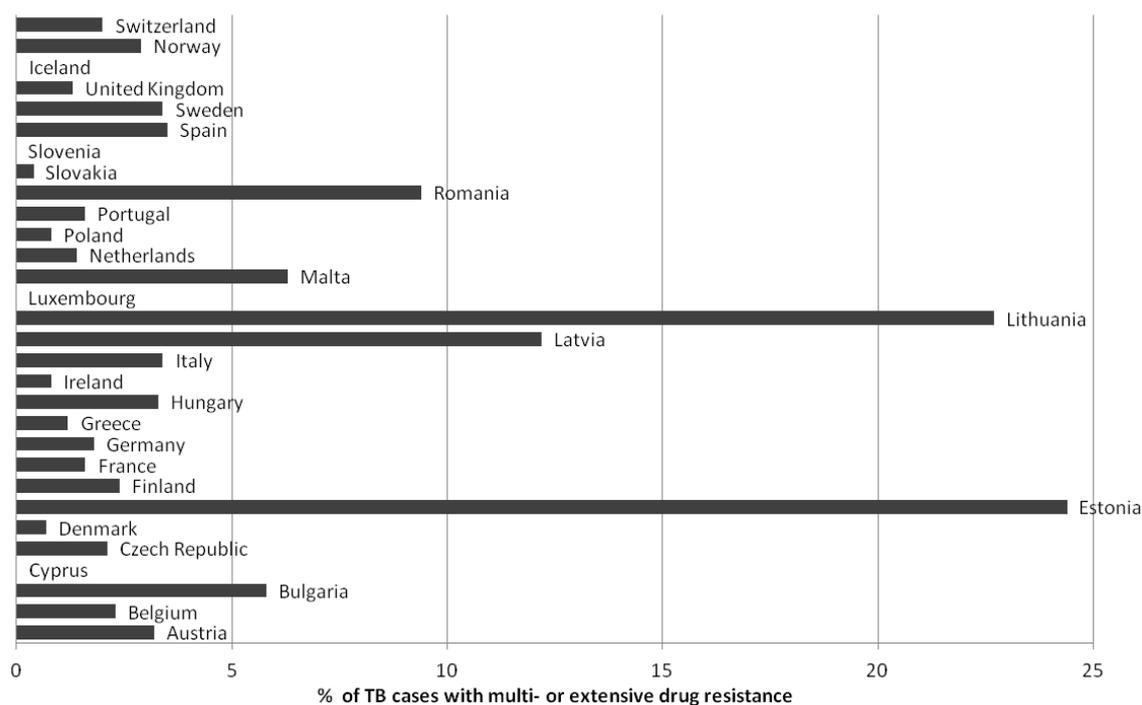
disease burden in low- and middle-income countries and in countries with high HIV prevalence. In 2011, there were an estimated 8.7 million cases of TB and 1.4 million deaths worldwide.<sup>1</sup> Within the EU/EEA, incidence rates vary between countries, with high rates in Romania, Lithuania, Latvia, and Bulgaria (see Figure 6.8.1). Despite the overall decline in TB incidence rates, the increasing incidence of multidrug-resistant TB (MDR-TB) and the emergence of extensively drug-resistant TB (XDR-TB) are major challenges for Europe and the world. It is estimated that 3.4% to 19.8% of TB cases worldwide are multidrug resistant and of these about 9.4% of cases are extensively drug resistant.<sup>2</sup> In the EU/EEA the percentage of drug resistance (both MDR- and XDR-TB) varies from 0% to 24.2% (see Figure 6.8.2).<sup>3</sup>

Figure 6.8.1: TB incidence in the EU/EEA region.



Source: WHO Tuberculosis country data 2010.

**Figure 6.8.2: Drug-resistant TB in the EU/EEA region.**



Source: *European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2012.*

The 2004 Report stated that the available diagnostics, treatments, and vaccines were insufficient to eradicate TB. Although this is still largely true, progress is being made. Efforts and investments from the public and private sectors have increased substantially. In 2011, the largest contributors to TB R&D were the United States National Institutes of Health (NIH), the pharmaceutical industry and the Bill & Melinda Gates Foundation. The EC was the fourth largest funder, but only contributed 4.7% of global funds.<sup>4</sup>

Rapid and accurate diagnosis of TB and determination of a drug resistance profile are the first step in battling TB. The existing methods are slow, inaccurate in high incidence and/or high prevalence HIV settings and require specialized laboratories. Until recently, no rapid point-of-care diagnostic tool existed. In 2006, a rapid test (GeneXpert) with the ability to test for resistance to one first-line pharmaceutical changed the face of TB diagnostics. This test is still expensive and requires the availability of a laboratory, but adjusted pricing ensured a roll-out in several high-burden countries.<sup>5</sup> In South Africa in March 2011, progress has been rapid. By November 2012, 805 571 specimens had been processed with 14.92% positive for TB infection, of which 7.18% were rifampicin-resistant.<sup>6</sup> By December 2012 there were 153 instruments in 108 centres with a 57% implementation rate and a total of 875 964 specimens had been processed.

### *Remaining challenges*

Despite the development of a rapid point-of-care diagnostic test for resistance to TB drugs, determination of a full drug-resistance profile of a patient still takes several weeks and requires specialist laboratories. Thus the search for an appropriate diagnostic tool continues and requires further investments.

The currently available treatments for TB are still inadequate. While most antibiotic treatments last several days, the treatment of non-resistant TB is three to six months. The treatment of MDR-TB and XDR-TB is difficult and expensive, takes a long time (18 to 30 months) and has a relatively low success rate. Due to renewed interest from the pharmaceutical industry, one novel pharmaceutical (bedaquiline), the first in over four decades, was recently approved by the U.S. FDA. Another novel pharmaceutical is currently under evaluation with the FDA and European Medicines Agency. While there are now more TB products in the pipeline, it still needs replenishing and continued incentives are needed for innovation.

The only available TB vaccine is over 100 years old and is not fully protective. The vaccine pipeline has seen some improvement and now includes several candidates. However, no vaccine has successfully reached Phase III of clinical research. Vaccine development is a lengthy and expensive process. The introduction of a new effective TB vaccine will be crucial to the eradication of TB. The current momentum for TB vaccine research needs to be maintained and requires continued funding.

In order to further develop new TB tools, there is a need for better understanding of the TB pathogen. Investments in basic research are required in order to develop more effective animal models and to understand the mechanism of disease.

The R&D landscape has changed over the past decade. Renewed interest from the pharmaceutical industry and public-private partnerships (many of which include pharmaceutical companies) have moved forward the development of TB diagnostics, treatments and vaccines. This has been driven by investments from the public sector, including EC-funded and philanthropic initiatives. In order to see these positive developments through, the current support needs to be continued. Investments in basic research, diagnostics development, novel pharmaceuticals and treatment regimens, and vaccines are essential in order to move towards TB elimination.

### *Research needs*

#### **Basic research**

- How does *Mycobacterium tuberculosis* interact with the immune system during the various phases of progression from infection to disease? What components of the immune system and what components of the pathogen are responsible for the elimination of *M. tuberculosis* or for preventing the reactivation of latent TB infection?
- Can an immune response to the pathogen or a vaccine prevent infection?

## 6. Priority diseases and reasons for inclusion

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- Is persistence a natural occurrence in TB, or does it reflect the inability of current regimens to reach the persisting bacteria?

### Pharmaceuticals

- Carry out early clinical investigation of treatment regimens containing novel and redirected medicines. Shorter and more effective treatments against drug-sensitive and drug-resistant active TB and shorter treatments for drug-sensitive and drug-resistant latent TB infection are necessary. This requires:
  - Testing these regimens in HIV-positive patients and children of all ages;
  - Developing fixed-dose combinations of these new regimens;
  - Developing suitable paediatric formulations;
- Further shorten the treatment of both drug-sensitive and drug-resistant latent TB infection;
- Study interactions between novel TB pharmaceuticals and ARVs;
- Determine which biomarkers or combination of biomarkers would allow for early evaluation of the efficacy of novel pharmaceuticals and regimens, so as to shorten the duration of clinical trials.

### Diagnostics

- Evaluate biomarkers to determine whether they can distinguish different forms of the disease
- Develop rapid diagnostic tools to distinguish between drug-sensitive and drug-resistant organisms. This would include improving existing tools.
- Research into implementation of new diagnostic tools
- Study ways of obtaining better sputum samples, particularly in children.

### Vaccines

- Develop an animal model for use in pre-clinical testing of vaccine candidates
- Establish biomarkers for vaccine-induced protection against TB
- Develop improved vaccines for prime boost vaccination strategies
- Improve the existing vaccine through the use of adjuvants

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## 6.9 Neglected Tropical Diseases

[See Background Paper 6.9 \(BP6\\_9NTD.pdf\)](#)

### *Background*

Currently 17 diseases are recognized as neglected tropical diseases, including Chagas' disease, leishmaniasis, sleeping sickness and Buruli ulcer. They affect more than one billion people, mainly in developing countries, causing great suffering and many deaths. Existing solutions are often ineffective, unaffordable and inappropriate for the needs of the resource-poor populations affected. There is an urgent need for new or improved vaccines, diagnostics and treatments for these diseases.

### *Developments since 2004*

The 2004 Report highlighted the problem of Buruli ulcer, a painful and disabling condition that was primarily treated with wide surgical incision (see 2004 Report Background Paper 6.9). Since then considerable progress has been made in identifying effective treatments for this condition (see Background Paper 6.9, Section 2.2).

In recent years, there has been more commitment towards new R&D initiatives for neglected tropical diseases, both from the public and private sectors, resulting in a well-populated R&D pipeline.<sup>1</sup> There have been efforts to use a two-pronged approach, involving preventative chemotherapy and intensified patient management.<sup>2</sup> As a result, large drug donation programmes have recently been rejuvenated and specific targeted treatments for several neglected tropical diseases have now been prioritized. Both these approaches use existing tools and medicines.

### *Remaining challenges*

There are currently several barriers to the translation of early stage scientific research into effective, affordable and accessible products for neglected tropical diseases. These include the low market value for these products, limited interest from innovators and stakeholders, and a lack of funding.

### *Research needs*

In order to have a major impact on the high global burden of these diseases, there is a need for more R&D of medicines, vaccines and diagnostics. This will require prioritizing R&D efforts towards needs-based agendas and aligning these efforts with existing and planned treatment, control, elimination and eradication programmes. Also needed is greater involvement of the different sectors and pooling of resources, combined with adequate, sustained funding to achieve successful development of products and solutions.

Overall, a public commitment is needed to: develop a global needs-driven (as opposed to market-driven) health R&D agenda for neglected tropical diseases; and create appropriate mechanisms, incentives and monitoring to allow the effective implementation of this agenda towards sustainable, achievable solutions for neglected tropical diseases.

The public health patient-focused needs and programmatic needs (individual disease management or elimination programmes, for example) should be addressed first. A thorough search of the required health tools should be evaluated to develop priority areas for support to fill gaps for product development. Buy-in for these programmes must come from the governments of countries where neglected tropical diseases are endemic, and the regulatory systems in both high- and low-income countries should make this an area where incentives outweigh the burden of product development for these diseases. This analysis should be done for each disease, and resources used to maximize scientific, technological and programmatic opportunities, taking into account the needs of patients from among the poorest communities.

Innovative R&D aimed at radically new products and solutions for neglected tropical diseases, or adaptive R&D designed to make better use of existing medicines, vaccines, diagnostics, and technology platforms, should be supported. In all cases, translational research to transform the results of basic research into useful applications is essential.

The EU, while already supporting some excellent initiatives, should continue to address the problem of neglected tropical diseases. There is a moral and ethical obligation to address the problem of neglected tropical diseases in developing countries. The EU-African, Caribbean, and Pacific Group of States (ACP) Joint Parliamentary Assembly Resolution on poverty-related diseases and reproductive health in ACP states explicitly calls for European action for neglected diseases: “[The Assembly] Calls on the European Commission to include the most neglected diseases, such as sleeping sickness, Chagas’ disease and leishmaniasis, among its priorities and to ensure that effective, appropriate, easy-to-use medicines are developed and placed on the market in the developing countries at an affordable price”.<sup>3</sup> A follow-up United Nations Assembly resolution addressed this point and has led to some efforts in reallocating EU support towards neglected tropical disease R&D (through the EU Framework Programme and government support for product development partnerships (PDPs))<sup>4</sup>. Pharmaceutical industry-driven agendas for the development of new therapeutics (such as the

Innovative Medicines Initiative, IMI) have not yet addressed R&D efforts for these diseases.

Support should be increased substantially and sustained in the Horizon 2020 programme and beyond, and R&D priorities should be based on societal values and health needs and not solely be market-driven. In addition to appropriate (sustainable) funding, governments should establish incentives and obligations to encourage neglected disease R&D in both the public and private sectors. Collaborative efforts are necessary, as the sharing of complementary resources and knowledge and the building of an integrated platform for neglected tropical disease R&D is necessary to keep costs low and impact high. Such a programme could include in-kind contributions from the (local and multinational) pharmaceutical industry, preferential funding of translational research projects (by public-private partnerships, public-driven R&D, integrated academic platforms and PDPs), risk mitigation from drivers of product development, reductions in regulatory costs and barriers and development of alternative, needs-based models for the setting of research priorities.

Organizations active in this area should be encouraged to pool their resources and work together to increase the opportunities for successful results. These include epidemiological tools and data (including drug resistance and monitoring), products developed, operational research outcomes and recommendations for implementation strategies.

Recommendations to help achieve this include:

- **Mobilize and sustain adequate funding** for neglected diseases. Committed funding over a number of years will be needed to support the implementation of a needs-based priority R&D agenda for neglected diseases;
- **Encourage translatable research** using the “3T” approach (Therapeutics, Technology and Transfer) to transform the results of basic research into useful technologies for medical applications, adapted to the needs of neglected tropical disease patients and closely linked to the interventions of existing programmes for neglected tropical diseases;
- **Establish adequate incentives for collaborative research, based on shared values**, including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;
- **Mobilize the pharmaceutical/diagnostics industry by a mix of incentives and obligations** to contribute to the development of needed medical interventions and commit to donate or provide sustained access to medical interventions, **based on shared values**<sup>5</sup>;
- **Engage the innovators** from emerging economies, biotechnology, pharmaceutical/diagnostic companies, small- and medium-sized enterprises (SMEs), PDPs and academic institutions through shared (societal and economic) values;
- **Monitor the performance** of PDPs, integrated academic platforms and pharmaceutical companies (including those in emerging economies) to ensure public accountability for resources spent;

- **Expand the activities of PPPs and integrated academic platforms** to include product development for medicines, vaccines, diagnostics, drug resistance platforms and control strategies for these diseases, together with efforts to strengthen health systems in the disease-endemic countries. Support integrated academic platforms, where product development and operational research is carried out by academic innovators for neglected tropical diseases;
- **Strongly encourage the expansion of the activities of the European and Developing Countries Clinical Trial Partnership (EDCTP)** to include several of the most neglected diseases as well as additional phases of clinical development (Phase I, Phase IV), and link this to the efforts of the pharmaceutical industry-driven non-profit organization TransCelerate<sup>6</sup>;
- **Create a centre for preclinical research** to bridge the continuing gap in the process of developing medicines and vaccines into clinical candidates for neglected tropical diseases. The centre would provide a pool of resources available for preclinical research, which should complement the activities of the EDCTP;
- Investigate the possibility for **centralized technology platforms for adaptive R&D** (for example, adapting existing and new medicines, vaccines and diagnostics to the needs of patients in tropical countries, fixed-dose combinations and paediatric formulations. This should complement the activities of existing organizations and provide a mandate for the recently established TransCelerate.

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### 6.10 Malaria

[See Background Paper 6.10 \(BP6\\_10Malaria.pdf\)](#)

#### *Background*

According to the WHO 2011 World Malaria Report, in 2010, malaria accounted for an estimated 660 000 deaths (between 610 000 and 971 000) and 219 million cases (between

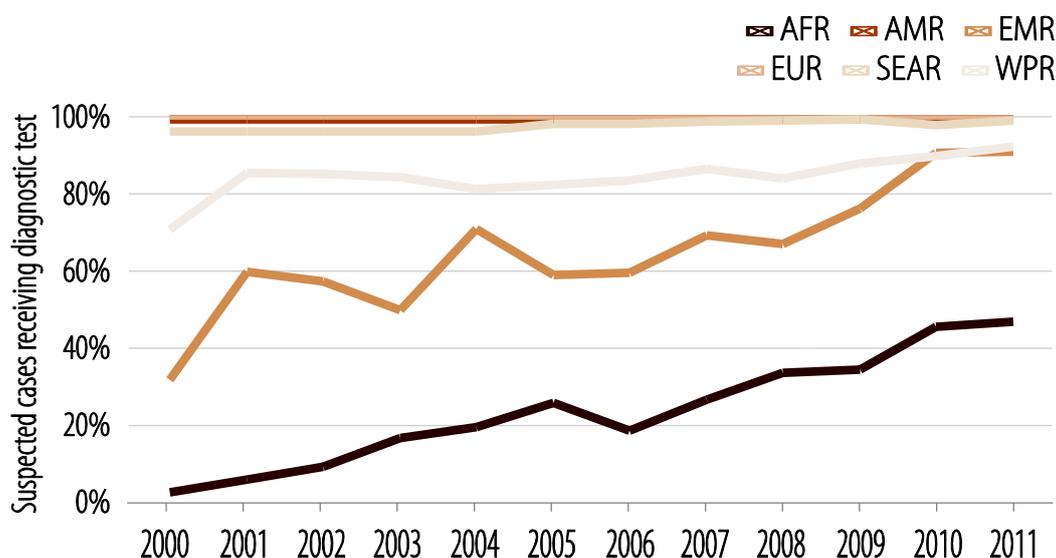
154 million and 289 million) – down from an estimated 800 000 deaths and 230 million cases in the early 2000s.<sup>1,2</sup> Overall, the malaria mortality rate has fallen by 26% since 2000. Almost 80% of cases and 90% of deaths occur in sub-Saharan Africa, and most of these deaths (86%) are in children under the age of five. The most vulnerable populations are children aged under five and pregnant women. The substantial reductions in the malaria burden were gained in countries where integrated control programmes were successful, but there are still many areas where the malaria burden is increasing.<sup>1</sup> In Europe, while the number of imported malaria cases is decreasing, indigenous cases are still being reported in countries where malaria was officially eradicated long ago.<sup>3</sup> In 2008, the Global Malaria Action Plan was launched by the Roll Back Malaria Partnership (RBM), addressing the control, elimination and future eradication of the disease.<sup>4</sup>

The control strategy for malaria involves efforts to control the mosquito vector and provide preventive therapies and/or effective curative treatment. The success of vector control approaches in recent years is due to the global mass campaigns to distribute long-lasting insecticidal nets and carry out indoor residual household spraying.<sup>1</sup> As a result, the percentage of households in sub-Saharan Africa owning at least one insecticide-treated bed net has increased from 3% in 2000 to over 50% in 2011.<sup>1</sup> The intervention of intermittent preventive treatment for pregnant women with sulfadoxine-pyramethamine and seasonal malaria chemoprevention for young children has also been increasingly operated globally.<sup>1,5</sup> Although there are vaccine candidates in pre-clinical or early clinical stage development, the latest Phase III clinical trial of the malaria vaccine candidate RTS,S/AS01 showed modest protection against clinical and severe malaria among infants.<sup>6,7</sup>

### *Developments since 2004*

Since 2004, there have been major improvements in the diagnosis and treatment of malaria. In the WHO African Region, the percentage of suspected cases in public health facilities that received a diagnostic test increased from about 20% in 2005 to 47% in 2011 (Figure 6.10.1).<sup>1</sup> At the same time, there has also been a major improvement in the quality of the rapid diagnostic tests (RDTs).<sup>2</sup> The number of treatment courses of artemisinin-based combination therapies (ACTs) procured by the public sector has increased dramatically from 11 million treatments in 2005 to 278 million in 2011.<sup>1</sup> The increase in procurement and distribution of diagnostics, antimalarials and vector control tools are largely financed by the Global Fund to Fight AIDS, Tuberculosis and Malaria, the (United States) President's Malaria Initiative, and the Affordable Medicines Facility – malaria (AMFm).<sup>8, 9,10</sup>

**Figure 6.10.3: Percentage of suspected malaria cases attending public health facilities that received a diagnostic test, 2000–2011**



Source: NMCP reports

Source: *World Malaria Report 2012*. World Health Organization, 2012

By 1999, the pharmaceutical industry had largely disengaged from innovative drug R&D in tropical diseases due to the lack of market incentives. As a result, the malaria drugs pipeline was virtually empty. However, since the establishment of the Medicines for Malaria Venture (MMV) in 1999, the situation has improved. Using the product development partnership (PDP) model to discover and develop new antimalarials, MMV has created the largest-ever portfolio of malaria drugs, including completely new classes of medicines.<sup>11</sup> Vaccine research has also accelerated in recent decades, including a promising candidate in Phase III trials managed by a public-private partnership, the PATH Malaria Vaccine Initiative.<sup>12</sup> New active ingredients for insecticides and their new formulation have been developed by the Innovative Vector Control Consortium, and many companies have been involved in the R&D of new diagnostic tools.<sup>13,14</sup> The European Commission has also been supporting R&D for basic science, antimalarials, vaccines, diagnostics, and vector control tools under the 6th and 7th Framework Programmes.<sup>15</sup>

### *Remaining challenges*

International funding for malaria control has increased dramatically over the past decade, from around US\$ 100 million in 2004 to a peak of US\$ 2.3 billion in 2011,<sup>1</sup> while global funding for malaria R&D has also been increasing gradually.<sup>16,17</sup> However, it is estimated that US\$ 5.1 billion is required every year to achieve global coverage with malaria interventions.<sup>4</sup> The major challenge to malaria control is the growth of resistance to both insecticides and treatment. The mosquito vector is becoming resistant to insecticides, especially pyrethroids, and cases of parasite resistance to

artemisinin have emerged in the Cambodia-Thailand border region.<sup>18,19,20</sup> To counter this, there is a need for medicines and insecticides with new modes of action, as well as effective monitoring systems.

### *Research needs*

The R&D of new pharmaceuticals is a long process and requires long-term support. Priority needs for research in 2014 to 2020 include:

- new product development
- resistance to pyrethroid insecticides and ACTs
- malaria vaccine development
- improvements in the sensitivity of RDTs in the detection of low-density infections.

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## 6. Priority diseases and reasons for inclusion

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### 6.11 Alzheimer disease and other dementias

[See Background Paper 6.11 \(BP6\\_11Alzheimer.pdf\)](#)

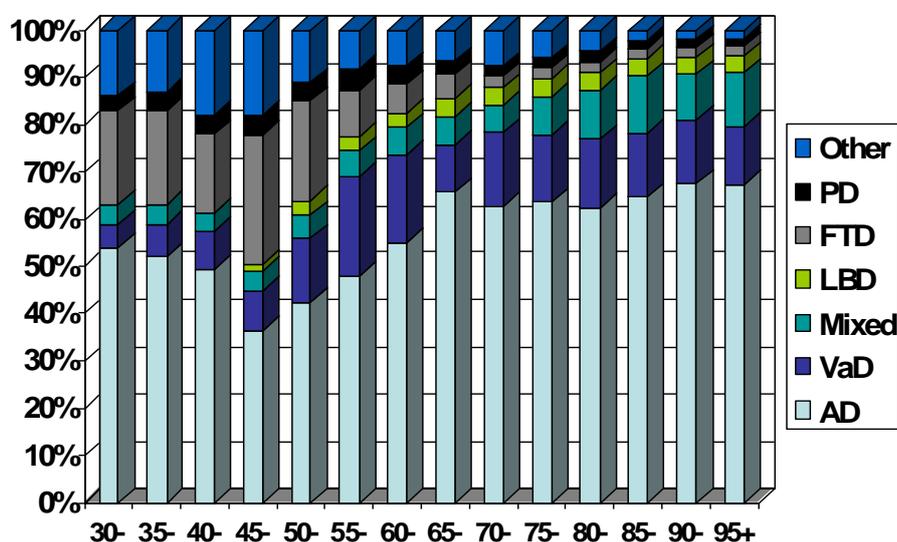
In 2008, the WHO launched the Mental Health Gap Action programme which included dementia as a priority condition. This was then followed by a major report in 2012.<sup>1,2</sup> While improvements in health care over the past century have contributed to people living longer and healthier lives, this has also resulted in an increase in the number of people with noncommunicable diseases, including dementia. Dementia is a syndrome, usually of a chronic or progressive nature, which affects memory, thinking, behaviour

and the ability to perform everyday activities. There are currently no treatments available that can cure or even halt the progressive course of dementia.

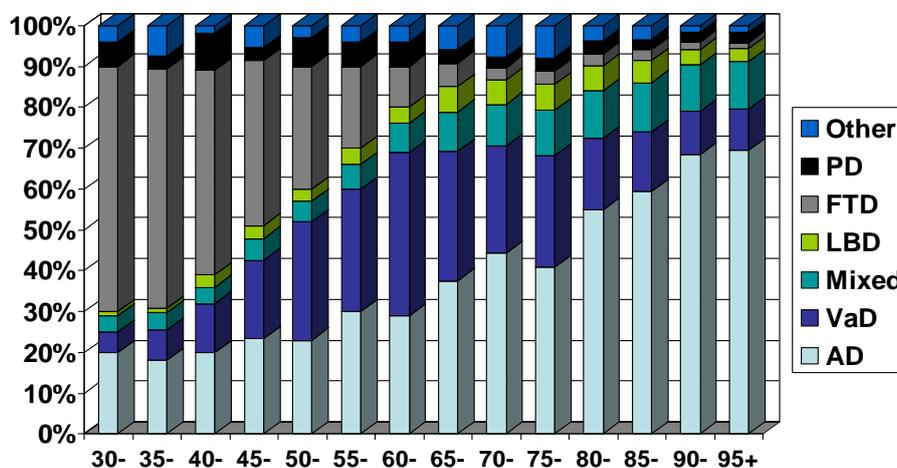
The four commonest subtypes of dementias are Alzheimer disease (AD), vascular dementia (VaD), dementia with Lewy bodies (LBD), and frontotemporal dementia (FTD). Alzheimer disease remains by far the most common form of dementia, as shown in Figures 6.11.1a and 1b.

Figures 6.11.1a and 1b: Dementia cases in the United Kingdom: consensus estimates of the proportion of all dementia cases accounted for by different dementia subtypes, by age and gender

1a) Women



1b) Men



Source: *Dementia: a public health priority*. WHO, 2012.

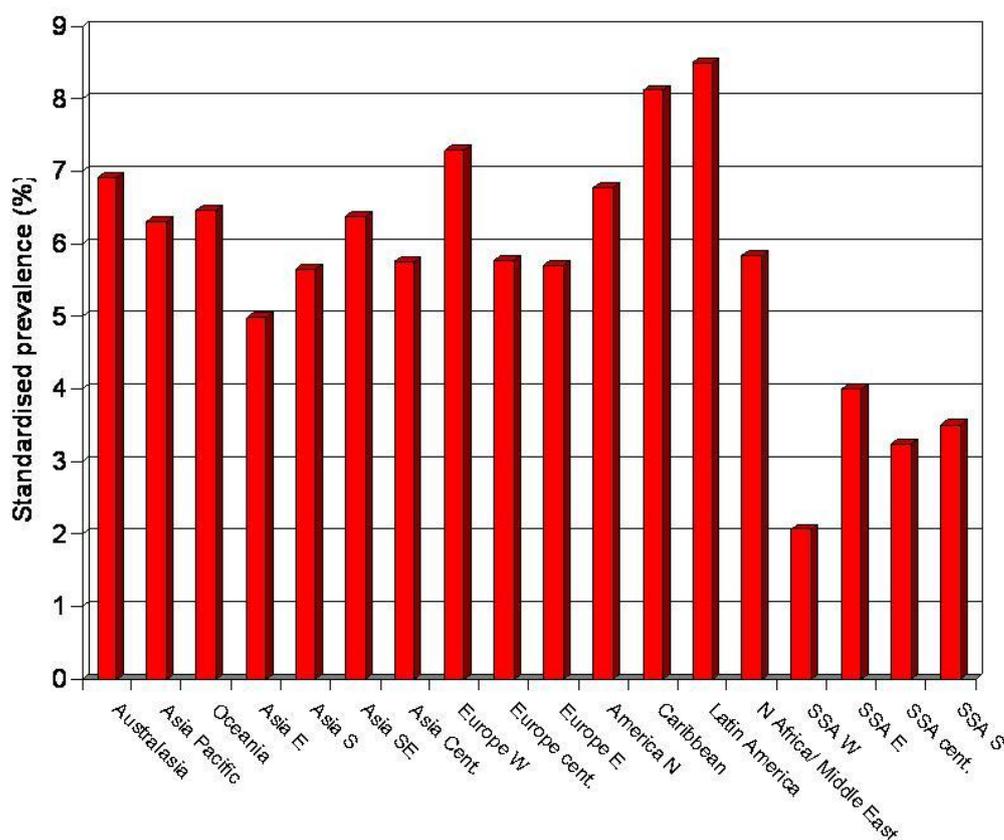
PD. Parkinson's disease, FTD Frontotemporal dementia, LBD Lewy bodies dementia, VaD Vascular disease, AD Alzheimer disease:

The WHO estimates that in 2010, 35.6 million people worldwide were living with dementia. That figure is projected to almost double every 20 years, reaching 65.7 million by 2030 and 115.4 million by 2050.<sup>2</sup> Europe is particularly affected, with an estimated 10 million cases of dementia in 2010 and a projected increase to 14 million in

2030. By 2050, 22% of the world's population will be aged 60 or over, and 80% of this older age group will be in Asia, Latin America or Africa.

In 2010, Western Europe was the region with the highest number of people with dementia (7 million), closely followed by East Asia with 5.5 million, South Asia with 4.5 million and North America with 4.4 million. The nine countries with the largest number of people with dementia in 2010 were China (5.4 million), the United States (3.9 million), India (3.7 million), Japan (2.5 million), Germany (1.5 million), Russia (1.2 million), France (1.1 million), Italy (1.1 million), and Brazil (1.0 million).<sup>2</sup>

**Figure 6.11.2: Estimated prevalence of dementia for people aged 60 and over, standardized to Western Europe population.\***



Source: *Dementia: a public health priority*. WHO, 2012.

Note: \*Regions used here are those used in the *Global Burden of Disease 2010 Study*.<sup>3</sup>

The financial costs of managing dementia are enormous in terms of both public and private resources. The WHO estimates that the total cost of treating and caring for people with dementia is currently more than US\$ 604 billion a year worldwide.<sup>1</sup> In several high-income countries, between a third and one half of people with dementia live in resource- and cost-intensive residential or nursing homes.<sup>2</sup> In the United

Kingdom, a report commissioned by the Alzheimer Research Trust showed that the societal costs of dementia (£23 billion) were almost as much as the combined costs of cancer (£12 billion), heart disease (£8 billion), and stroke (£5 billion).<sup>4</sup>

The exact mechanisms leading to AD are largely unknown, making it difficult to find therapies that can prevent or delay the onset of the disease. Several risk factors have been described, including age, cardiovascular disease, diabetes, hypertension, smoking, obesity and metabolic disorders, as well as a history of brain trauma.<sup>2</sup> Dementia is usually diagnosed on the basis of physical and neurological examinations, as well as standard tests of mental function and brain imaging to detect signs of intellectual impairment. A definitive diagnosis of AD disease can only be made through a postmortem biopsy of the brain. Medicines (such as cholinesterase inhibitors and glutamatergic agents) are used to palliate aggressive behaviours and mood disorders as well as to reduce cognitive disorders.<sup>5</sup>

### *Developments since 2004*

In 2012, the WHO published the report “*Dementia: a public health priority.*”<sup>2</sup> Since 2004, efforts have been intensified in the search for new therapies. Several clinical trials have been launched to investigate new pharmaceutical compounds for AD, as well as immunotherapy and vaccines. Pharmaceutical companies have invested heavily in these research areas, but none of these strategies have proved effective in substantially modifying the outcome of the disease.

### *Remaining challenges*

Alzheimer disease and other dementias have become a major public health concern. As the number of patients with AD and other dementias is expected to rise significantly, there is an urgent need for action. The number of patients affected is increasing substantially and there is no available treatment. However, health care and financial systems both in Europe and worldwide are not adequately prepared to cope with the magnitude of the situation.

While the failure of the most recent clinical trials, as well as the associated high risk and cost, discourage investment from the pharmaceutical industry, there is still substantial involvement in this area with 100 products in development. The lack of biomarkers for therapeutic endpoints remains a major barrier in the clinical development of medicines for AD. The discovery of biomarkers for AD could not only provide the tools to monitor the progression of the disease and the effectiveness of new medicines, but also provide new pathways for research and understanding of AD and other dementias.

### *Research needs*

There is an urgent need for validated biomarkers for measuring and monitoring the progression of the disease, as well as identifying individuals at risk of developing AD.

There are currently no specific markers that can confirm with 100% certainty a diagnosis of AD. Although much work is already under way in the search for new biomarkers, continued efforts are still required. The development of biobanks of material including tissues, blood, urine, and cerebrospinal fluid from patients and healthy volunteers should help identify such markers. In Horizon 2020 support could be provided to such networks. Several EU initiatives such as PredictAD and Pharmacog are also contributing to the search for new therapeutic molecules.

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## 6.12 Osteoarthritis

[See Background Paper 6.12 \(BP6\\_12Osteo.pdf\)](#)

### *Background*

Osteoarthritis (OA) is a long-term chronic disease characterized by the deterioration of cartilage in joints which results in bones rubbing together and creating stiffness, pain, and impaired movement. The disease most commonly affects the joints in the knees, hands, feet, and spine and is relatively common in shoulder and hip joints. While OA is related to ageing, it is also associated with a variety of both modifiable and non-modifiable risk factors, including: obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender.<sup>1</sup>

Osteoarthritis is the single most common cause of disability in older adults.<sup>2</sup> The 2010 Global Burden of Disease Study reports that the burden of musculoskeletal disorders is much larger than estimated in previous assessments and accounts for 6.8% of DALYs worldwide.<sup>3</sup> An estimated 10% to 15% of all adults aged over 60 have some degree of

OA, with prevalence higher among women than men.<sup>4</sup> Across the EU Member States, diagnosed OA prevalence varies from 2.8% in Romania to 18.3% in Hungary.<sup>5</sup>

The prevalence of OA is increasing due to population ageing and an increase in related factors such as obesity. According to the United Nations, by 2050 people aged over 60 will account for more than 20% of the world's population.<sup>6</sup> Of that 20%, a conservative estimate of 15% will have symptomatic OA, and one-third of these people will be severely disabled. This means that by 2050, 130 million people will suffer from OA worldwide, of whom 40 million will be severely disabled by the disease.<sup>6</sup> Costs associated with OA include costs for adaptive aids and devices, medicines, surgery, and time off at work.<sup>7</sup>

Osteoarthritis is currently diagnosed by physical examination and, where necessary, with X-ray, MRI scan and arthroscopy. However, these diagnostic tools have low sensitivity and specificity. There are no biomarkers for OA that can be used in clinical practice at this time. The treatment of OA involves: treating associated pain; viscosupplementation with intra-articular hyaluronate injections; intra-articular corticosteroid injections; joint replacement surgery; and, in rare circumstances, autologous chondrocyte implantation into the damaged areas.<sup>8,9,10</sup>

While protective factors such as exercise, healthy diet, and occupational injuries can all be addressed, many risk factors such as gender, age, and genetics are not modifiable. The physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. Although there is a wide range of devices and palliative medicines available that can relieve pain and improve quality of life, there is no pharmaceutical product that can halt or reverse the onset of OA.

### *Developments since 2004 and remaining challenges*

Both pharmaceutical companies and EU initiatives are actively searching for therapies to treat OA and its associated symptoms.<sup>11</sup> There has been some progress in the search for new biomarkers since 2004 but pharmaceutical development is still limited by the lack of valid biomarkers.<sup>12</sup>

### *Research needs*

Future research should be directed at addressing the gap in diagnostics and biomarkers for OA. This will help improve disease monitoring and help facilitate the development of medicines that can reverse the progression of this high-burden condition. There is currently a need for research in the following areas:

- The cost-effectiveness, safety, and efficacy of the long-term management of OA with the currently available pharmaceutical therapies.
- New imaging technologies, diagnostics, and biomarkers to more effectively measure the status and progression of OA.
- Evaluation of both the impact of risk factors and the effectiveness of potential therapies using these new diagnostics and biomarkers.

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## 6.13 Chronic obstructive pulmonary disease

[See Background Paper 6.13 \(BP6\\_13COPD.pdf\)](#)

### *Background*

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease involving progressive and partly irreversible airway obstruction and persistent, low-grade pulmonary and systemic lung inflammation. The main risk factor for the development of and deterioration of COPD is smoking. However, the disease can also occur in non-smokers and persists even after smoking cessation.

## 6. Priority diseases and reasons for inclusion

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In 2010, COPD was estimated to account for 2.7% of the disease burden and 3.2% of deaths in Europe, and for 3.1% of the global disease burden and 5.5% of deaths worldwide.<sup>1,2</sup> Over the past two decades, there has been a marked increase in COPD deaths (in most, but not all countries), a trend that is predicted to continue. Moreover, the impact of COPD is believed to be underestimated due to a lack of accurate epidemiological data from some countries, misdiagnosis, and inconsistent use of the International Classification of Diseases (ICD) codes when reporting causes of death in patients with COPD.

A number of coexisting conditions not directly related to COPD are associated with the disease, including cardiovascular disease, muscle wasting, type 2 diabetes, and asthma.<sup>3</sup> As a result, deaths in people with COPD are frequently attributed to another cause. In addition, among the coexisting conditions, depression deserves particular attention. COPD (especially at severe levels) leads to impairment in the activities of daily living, social and psychological functioning, and recreational activities. In view of the fragmentary nature of available information on COPD, there is a need for a comprehensive study of the disease, including the coexisting conditions and the burden of illness they cause in people with COPD.

Chronic obstructive pulmonary disease also incurs significant financial costs associated with the care of patients and lost productivity of patients and care takers.<sup>4</sup> However, estimating the costs of COPD is challenging, due to under-diagnosis and the presence of other coexisting diseases, and there appear to be no recent estimates. Many different methodologies are used to estimate the costs of chronic diseases such as COPD.<sup>5</sup> In 2003, the United States National Heart, Lung, and Blood Institute estimated that total costs (direct and indirect) of COPD in the United States were US\$ 32.1 billion, with direct costs of US\$ 18 billion.<sup>6</sup>

The European Lung White Book 2003, estimated that the total annual cost of COPD in Europe was €38.7 billion (including €4.7 billion for ambulatory care, €2.7 billion for medicines, and €2.9 billion for in-patient care) and a total of 28.5 million work days lost due to the disease. As these data exclude mortality costs, the actual cost incurred by COPD may be much higher.<sup>4</sup>

Yet despite the high disease burden and financial costs incurred, efforts to address the problem of chronic respiratory diseases, and COPD in particular, have not received adequate funding in any country, whether for research, prevention, or clinical services.

Smoking cessation is currently the single most effective intervention to improve outcomes in patients with COPD. However, even in the best programmes less than one-third of patients maintain abstinence, and even those people who stop smoking will usually continue to experience shortness of breath and other symptoms as airflow limitation persists.

The overall approach to managing COPD is characterized by a stepwise increase in treatment, depending on the severity of the disease. These treatments fall into three

broad areas: prevention of disease progression; management of stable disease; and management of exacerbations.

In placebo-controlled clinical trials, inhaled anticholinergics and beta-2 agonists have been shown to improve lung function and symptoms and reduce exacerbations in people with stable COPD. While inhaled corticosteroids have been shown to reduce exacerbations in COPD and reduce decline in lung function, the beneficial effects are small. However, the use of combined inhaled corticosteroids plus long-acting beta-2 agonists has been shown to improve lung function, symptoms, and health-related quality of life, and reduce exacerbations, compared with a placebo, and may be more effective than the use of either treatment alone.

### *Developments since 2004*

The fact that in 2013, the available treatments for COPD are still mainly palliative, and that no therapies are available that can halt the decline in lung function or the progressive destruction of the airways, suggests that not much has changed since the original 2004 Priority Medicines Report. Although the understanding of COPD has grown over the past few years, many questions still remain.

### *Remaining challenges*

One of the main challenges in developing new therapeutic agents for the treatment or prevention of acute exacerbations of COPD is that their potential success cannot be known before the outcome of relatively large Phase II trials, assessing clinical outcome over a three to six month period or longer.<sup>2</sup> To date, only two interventions, smoking cessation and long-term treatment with oxygen (in people with hypoxaemia), have been found to alter the long-term course of COPD. Pulmonary rehabilitation, (including patient assessment, exercise training, education, nutritional intervention and psychosocial support), was not found to have an impact on the long-term course of the disease.<sup>7</sup> Current therapies neither arrest nor reverse inflammation and the resulting decline in lung function or health status. New therapies are needed especially for the 10% of COPD patients with refractory asthma whose symptoms cannot be controlled with currently available medicines.

Following significant delays and failures in developing classes such as phosphodiesterase 4 (PDE4) inhibitors, the large pharmaceutical companies have few genuinely novel medicines for COPD in the pipeline. While new treatment initiatives have come from information on the physiology of COPD, to date no new therapy has come from information on pathogenic inflammatory processes.

### *Research needs*

There is a need to develop surrogate markers of inflammation that can predict the clinical usefulness of new management and prevention strategies for COPD, and new clinical end points to assess the impact of different COPD interventions. In addition, standardized methods are needed to enable countries to track trends in the prevalence of COPD and morbidity and mortality over time, in order to plan health care services that can respond to the predicted increases in COPD. This need is especially urgent in low- and middle-income countries, which have limited health care resources.

### *Conclusion*

In the short- and medium-term, prospects for the development of new therapies to treat lung inflammation or reverse COPD remain poor. Therefore the overriding imperative should be to reduce the prevalence and incidence of smoking.

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## 6.14 Alcohol use disorders and alcoholic liver disease

[See Background Paper 6.14 \(BP6\\_14Alcohol.pdf\)](#)

### *Background*

The WHO estimates that alcohol is now the third highest risk factor for premature mortality, disability and loss of health worldwide.<sup>1</sup> Between 2004 to 2006, alcohol use accounted for about 3.8% of all deaths (2.5 million) and about 4.5% (69.4 million) of Disability Adjusted Life Years (DALYS).<sup>2</sup> Europe is the largest consumer of alcohol in the world and alcohol consumption in this region emerges as the third leading risk factor for disease and mortality.<sup>3</sup> In European countries in 2004, an estimated one in seven male deaths (95 000) and one in 13 female deaths (over 25 000) in the 15 to 64 age group were due to alcohol-related causes.<sup>3</sup>

Alcohol is a causal factor in 60 types of diseases and injuries and a contributing factor in 200 others, and accounts for 20% to 50% of the prevalence of cirrhosis of the liver. Alcohol Use Disorders (AUD) account for a major part of neuropsychiatric disorders and contribute substantially to the global burden of disease. Alcohol dependence accounts for 71% of all alcohol-related deaths and for about 60% of social costs attributable to alcohol.<sup>4</sup> The acute effects of alcohol consumption on the risk of both unintentional and intentional injuries also have a sizeable impact on the global burden of disease.<sup>2</sup>

Alcoholic liver disease (ALD) is the commonest cause of cirrhosis in the western world, and is currently one of the ten most common causes of death.<sup>5</sup> Liver fibrosis caused by alcohol abuse and its end stage, cirrhosis, present enormous problems for health care worldwide. Over 60% of patients with cirrhosis of the liver and superimposed alcoholic hepatitis have a life expectancy of only four years. Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD.

### *Developments since 2004*

Despite the high global burden of alcohol-related diseases and injuries, alcohol use remains a low priority for public health policy. In North America, only an estimated 14.6% of people with a lifetime history of alcohol abuse or dependence have received treatment.<sup>6</sup> In Europe, only an estimated 8% of people with alcohol dependence receive treatment.<sup>7</sup> These low figures demonstrate that there are many barriers to treatment.

Several policy options have been tested to reduce alcohol consumption, including: drunk driving reduction; education, communication, training and public awareness; alcohol market regulation; reduction of harm in drinking and surrounding environments; and interventions for individuals.

The currently approved pharmacotherapeutical options for AUD are disulfiram, naltrexone, and acamprosate. Other drugs are being investigated, used off-label

(topiramate and ondansetron) or recently approved in Europe (nalmefene) for use in patients with alcohol dependence who want to reduce their alcohol consumption, either as a treatment goal or as a step towards abstinence. While some of these drugs have shown promise in terms of efficacy (nalmefene, topiramate, and ondansetron), none has been found to be effective when used as a single treatment method, without some form of concurrent behavioural therapy.

Coexisting diseases (especially mental disorders, but also noncommunicable diseases (NCDs) such as cardiovascular disease, cancer, diabetes or liver disorders) are highly prevalent among people suffering from AUD.<sup>8,9</sup> The most recent evidence supports a change from the current practice of treating both diseases (mental disorders and alcohol dependence) separately, to a new approach of incentivizing *better coordination* between clinics and centres to treat addictions.<sup>10</sup> However, effective scaling up of services with improved coordination between health care for AUD and other NCDs has been challenging.

In the United States, there are no therapies for ALD which have been approved by the U.S. Food and Drug Administration (FDA). Although many treatment methods have been tried in patients with alcoholic hepatitis, few of them have been consistently shown to have a beneficial effect<sup>11</sup> and none has achieved consensus status among practising hepatologists. As a result current therapy still focuses predominantly on supportive care.

### ***Research needs***

Although an increase in funding related to alcohol and health has been reported over the last year in the EU, the level of funding seems insufficient in view of the enormous economic and social burden of ALD on the health care system.

More evidence is needed to determine the effectiveness of many of the interventions to reduce harmful alcohol consumption. In addition, health system research is needed to identify appropriate organizational models to effectively coordinate treatment for AUD and other NCDs and to scale these up.

With respect to pharmacotherapy, the development of suitable medications with greater selectivity toward excessive alcohol intake remains a major research goal. Efforts to understand the neurobiological basis and their corresponding effects of the pharmacotherapeutic interventions in individuals with AUD, potentially through the use of new imaging technologies, provides relevant avenues for future research.

Current treatments for alcohol-related cirrhosis of the liver are severely limited. Better understanding is needed in relation to: the pathogenesis of the disease; helping patients to abstain from alcohol (where possible); eradicating existing viruses using interferon, ribavirin, and lamivudine (in cases involving viral hepatitis); liver transplantation;<sup>12</sup> and developing adjunctive pharmacotherapies that can improve survival rates.<sup>12</sup>

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### 6.15 Depression

[See Background Paper 6.15 \(BP6\\_15Depression.pdf\)](#)

#### *Background*

Depression is a common mental disorder that is characterized by loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration, insomnia or hypersomnia, and occasionally suicidal thoughts.<sup>1</sup> Depression often occurs as a result of adverse life events, such as: the loss of a significant person, object, relationship or health. However, it can also occur due to no apparent cause. These problems can become chronic or recurrent and lead to substantial impairment in an individual's ability to take care of their everyday responsibilities.<sup>2</sup>

The ICD-10 classification of mood disorders includes different forms of depression such as: bipolar affective disorder, depressive episode, and recurrent depressive disorder. The American Psychiatric Association's DSM-IV clinical classification for mood disorders divides them into three groups: major depressive disorders (MDD); bipolar disorders; and depression associated with medical illness or alcohol and substance abuse.<sup>3</sup>

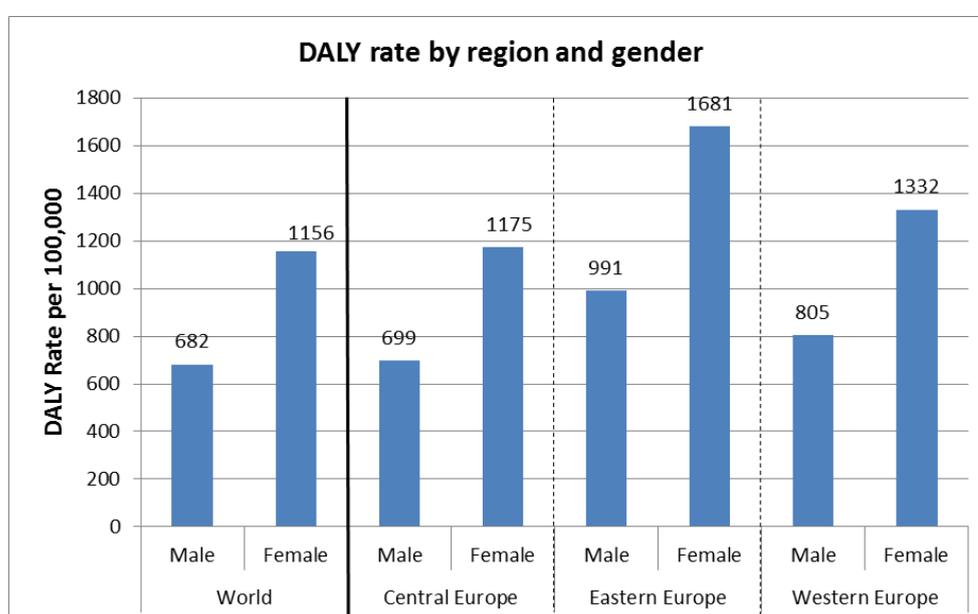
Depression is associated with a combination of genetic, psychological, environmental, and biological factors. Risk factors for depression include pregnancy, childbirth, (peri) menopause, hormonal factors and menstruation, (low tolerance to) stress, impulsive behaviour, alcohol or substance abuse, and family history of depression, alcohol abuse or suicide. Other factors such as poverty, severe or chronic medical conditions, insomnia, being a female, intimate partner violence, (childhood) sexual abuse and tobacco use are also associated with depression.<sup>4</sup>

Depression in young people may be expressed differently from that in adults, with manifest behavioural disorders (including irritability, verbal aggression and misconduct), substance abuse and/or concurrent psychiatric problems, suicidal thoughts, hopelessness, social isolation, overeating and oversleeping, and rage. In the elderly, the physical and behavioural symptoms of depression are usually so intense that they mask the psychological ones, up to the point that they may seem to suffer "depression without sadness". The coexistence of several chronic conditions complicates the diagnosis. Meanwhile, many different classes of drugs that elderly people receive could potentially induce depression.

In 2010, MDD accounted for 2.5% (63.2 million) of DALYs worldwide and 3.4% (8.4 million) in Europe alone.<sup>5</sup> Europe also accounted for more than 13% of the total DALYs caused by MDD worldwide. Between 1990 and 2010, there was a 37% increase worldwide in the number of years of life lived with disability (YLDs) due to MDD (up from 46 million YLDs in 1990 to 63 million in 2010).<sup>6</sup> Depression is more common among females (Figure 6.15.1)

The severity of MDD is associated with increased treatment costs, unemployment, and with reduced performance at work.<sup>7</sup> The available literature on the impact of treatment for all forms of depression on worker productivity costs suggests that the gains made in reduced absenteeism and improved productivity at work may offset the treatment costs. Very little research has been done to estimate the economic burden of depression in Europe. In the United States, the total economic burden of depression was estimated to be US\$ 83.1 billion in 2000, of which US\$ 26.1 billion (31%) were direct medical costs, US\$ 5.4 billion (7%) were suicide-related mortality costs and US\$ 51.5 billion (62%) were workplace costs.<sup>8</sup>

**Figure 6.15.1: DALY rate for Major Depressive Disease per 100 000 by gender and region.**



Source: 2010 *Global Burden of Disease Study*.

Seattle, Washington University Institute for Health Metrics and Evaluation, 2013.

Key interventions for treating MDD are antidepressant medicines and different forms of psychotherapy. Less used interventions are electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).<sup>9</sup>

In the general population, depression is often undiagnosed or misdiagnosed and, even more often goes untreated. Though methods have been developed to help facilitate the diagnosis of depression among patients, it is estimated in New Zealand that 80% of young people who suffer from depressive symptoms that warrant intervention do not receive treatment.<sup>10</sup>

### *Developments since 2004*

During the most recent World Mental Health Day (October 2012), the World Federation for Mental Health called for “*public education and awareness campaigns on mental health in all countries*” so as to “*reduce stigma and discrimination, increase the use of mental health services and bring mental health and physical health care closer to each other.*”

There are currently over 50 projects funded by the EC Sixth and Seventh Framework Programmes (FP6 and FP7) specifically doing research on depression (19 under FP6 and 36 under FP7).

### *Remaining challenges*

Many patients are not able to tolerate available antidepressant medications due to side-effects. Studies show that as many as 50% of subjects may discontinue antidepressant treatments within the first six months of therapy, reporting adverse effects as a major reason for discontinuation. Poor adherence to pharmacological and psychosocial treatments for depression, especially in the elderly, is an additional barrier to the effective treatment of patients suffering from depression. Factors linked to this high non-adherence rate amongst the elderly include lack of information and misperceptions about mental illness and its treatment, stigma, lack of family support, cognitive impairment, and poor physician-patient communication or relationship.<sup>11</sup> Long-lasting (depot) preparations have been suggested as an alternative strategy for non-adherent severely depressed patients.<sup>12</sup>

The development of psychiatric drugs is considered high-risk due to the high failure rates of trials and the high costs associated with a research programme. As a result, many pharmaceutical companies have halted R&D into medications to treat MDD and other mental disorders.<sup>13</sup>

### *Research needs*

In Europe the relative burden of depression is higher than in the rest of the world. Research initiatives through European partnerships are important to help reduce the burden of disease and raise awareness of mental disorders.

Raising awareness and reducing stigma and discriminatory attitudes are important steps towards better diagnosis and treatment. The United Kingdom-based National Institute of Health and Care Excellence (NICE) included research recommendations in their 2009 guidelines on depression, and identified multiple research gaps.<sup>9</sup> These included:

- Optimal treatment of initially poor responders
- Place and cost-effectiveness of cognitive behavioral therapy and antidepressants in different population groups
- Optimal treatment of sub-threshold depressive symptoms

Other research gaps include:

- Identifying the best treatment strategy for different populations and age groups
- Effectiveness of the long-term use of antidepressants
- Development and usage of antidepressant depot preparations
- Clinical research on the impact of genetic variations for personalizing therapy
- Development of new, safer and more effective antidepressants that are based on a completely new mechanism of action.

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### 6.16 Postpartum haemorrhage

[See Background Paper 6.16 \(BP6\\_16PPH.pdf\)](#)

#### *Background*

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths.<sup>1</sup> These deaths have a major impact on the lives and health of the families affected. Between 1990 and 2010, there was a global reduction in maternal deaths and the maternal mortality ratio (MMR) from 543 000 and 400 per 100 000 live births to 287 000 and 210 per 100 000 live births respectively. However, developing countries continue to experience higher numbers of maternal deaths compared to developed countries.<sup>2</sup> In 2010, the MMR in developing countries was 240 per 100 000 live births (284 000 maternal deaths) compared to 16 (2 200 maternal deaths) in developed countries. Thirty-five countries have been identified as either making insufficient or no progress towards achieving the Fifth Millennium Development Goal (MDG5), which aims to reduce the global maternal mortality rate by 75% from 2000 to 2015.<sup>2</sup>

Every year about 14 million women around the world suffer from PPH.<sup>3</sup> The risk of maternal mortality from haemorrhage is 1 in 1 000 deliveries in developing countries (100 per 100 000 live births). Most deaths (about 99%) from PPH occur in low- and middle-income countries compared with only 1% in industrialized nations.<sup>4</sup> However, recent studies have shown an increase in the incidence of PPH in developed countries as well.<sup>5</sup> Therefore, in order to reduce the MMR and achieve MDG5, it is essential to achieve a major reduction in the incidence of PPH.

The WHO and professional bodies recommend active management of the third stage of labour (AMTSL) for all vaginal births in order to prevent PPH.<sup>6</sup> This involves prophylactic administration of uterotonic medicines before delivery of the placenta in addition to other non-pharmacological interventions, such as late cord clamping and controlled cord traction of the umbilical cord (in settings where skilled birth attendants are available). Although AMTSL reduces postpartum blood loss, about 3% to 16.5% of women will still go on to experience PPH and will require treatment.

Oxytocin injection is the recommended first line uterotonic medicine for preventing and treating PPH because it is more effective than ergometrine and other uterotonics and has relatively fewer side-effects. However, oxytocin is unstable at room temperature and requires special temperature storage conditions to remain effective.<sup>7</sup> The cold chain storage required to transport and store oxytocin is unreliable in resource-constrained countries. In addition, the fact that oxytocin must be administered parenterally requires the involvement of skilled health personnel.

### *Developments since 2004*

Following the 2004 Report, in an effort to address the barriers to the use of oxytocin, the TI Pharma Hot Medicines Consortium has initiated studies to develop heat-stable oxytocin formulations.<sup>8</sup> Although progress has been made in improving the stability of oxytocin in the laboratory, a heat-stable oxytocin formulation is not yet available for therapeutic use.

The Program for Appropriate Technology in Health (PATH) has also developed the oxytocin Uniject, a device to ensure safer, accurate and easy dosage of oxytocin, especially in settings where skilled health workers are not available. Recent studies have supported the effectiveness of the oxytocin Uniject when used by trained birth attendants.<sup>9,10</sup> PATH has also incorporated a temperature-time-indicator (TTI) into the Uniject device to monitor the quality of the product in transit and storage.<sup>11</sup> Despite these advances, the oxytocin Uniject is yet to be deployed for use on a large scale.

Based on evidence, the WHO 2012 guidelines for managing PPH advise the use of misoprostol in situations where the use of oxytocin is not possible.<sup>12</sup> Misoprostol is inexpensive (less than US\$ 1 per dose), can be given orally, is relatively stable at room temperature (no need for refrigeration) and has a long shelf life, all of which are major advantages over oxytocin.<sup>13</sup> The slightly lower potency of misoprostol is partly offset by these advantages.<sup>14</sup> However, misoprostol is sensitive to moisture and may degrade in areas of high humidity.<sup>15</sup> It also has side-effects which include transient fever, shivering, nausea, vomiting and diarrhoea. An additional practical problem is that misoprostol can be (mis)used for carrying out abortions and is therefore not marketed or approved in many countries.

The 2012 WHO guidelines also recommend the use of tranexamic acid - an antifibrinolytic agent used in surgery to reduce blood loss - as an alternative treatment for PPH when other uterotonics are unavailable or where the bleeding may be partly due to trauma.<sup>2,12</sup>

### *Remaining challenges*

While substantial progress has been made towards improving on the existing interventions for managing PPH, the burden of PPH still persists because there is no “silver bullet” for either the prevention or treatment of PPH. The current interventions

are inadequate. Efforts to address the following research opportunities will help meet the PPH prevention and treatment needs in most populations.

### *Research needs*

Further research is needed to support the development of heat-stable oxytocin. When developed, the thermostable oxytocin should be packaged in Unijects to provide it with the additional advantage of ease of use in low-resource settings. The use of the currently available oxytocin Uniject with the TTI should be scaled up in low-resource settings in tandem with adequate post-marketing pharmacovigilance.

There is some evidence that sublingual misoprostol is beneficial in the treatment of PPH, especially where there is no access to oxytocin. Research studies are therefore needed to establish a standard safe and effective dose of misoprostol for treating PPH. Evidence is also currently limited on the effectiveness of the use of misoprostol by less skilled or lay caregivers at the community level.<sup>15,16</sup> There is a need for operational research to determine if the benefits of advanced community distribution of misoprostol to pregnant women and to lower cadre health workers at the community level outweigh the potential disadvantages. This study would also inform decisions about the lifting of regulatory barriers that prevent lower cadre health workers from administering oxytocin or misoprostol, especially in low-resource settings.

The potential of tranexamic acid in treating PPH should also be explored. Trials comparing the safety and efficacy of tranexamic acid and tranexamic acid in addition to existing uterotonics would be helpful in understanding the possible benefits of tranexamic acid in managing PPH. Finally, research is needed to discover new, patient-friendly and easy-to-use medicines for preventing and treating PPH.

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## 6.17 Tobacco use

[See Background Paper 6.17 \(BP6\\_17Smoking.pdf\)](#)

### *Background*

Smoking is considered to be the single most important cause of preventable illness and premature deaths worldwide.<sup>1</sup> It is estimated that about 100 million deaths were caused by tobacco addiction in the 20th century. Today, 5.4 million people worldwide die each year from tobacco-related diseases. Unless resolute and urgent action is taken, it is estimated that by 2030 smoking will cause 8 to 10 million deaths a year, over 80% of them in low- and middle-income countries.<sup>2</sup>

In the WHO European Region in 2011, about 32% of the adult population was smoking on a regular basis. Together with the Americas, Europe currently has the highest proportion of all deaths attributable to tobacco (Table 6.17.1).

**Table 6.17.1: Deaths attributable to tobacco use by WHO Region**

WHO Region	Proportion of all deaths attributable to tobacco (%)		
	Men	Women	All adults
<b>Europe</b>	<b>25</b>	<b>7</b>	<b>16</b>
Americas	17	15	16
Western Pacific	14	11	13
South-East Asia	14	5	10
Eastern Mediterranean	12	2	7
Africa	5	1	3
<b>Global</b>	<b>16</b>	<b>7</b>	<b>12</b>

Source: WHO global report: mortality attributable to tobacco (2012).

Data from the Global Adult Tobacco Survey 2009 show that the prevalence of smoking at country level is highly variable, with countries such as the Russian Federation and other Eastern European countries having a higher prevalence (39.1% in the Russian Federation, 30.3% in Poland, and 28.8% in Ukraine) than elsewhere in Europe (25% in Finland, 24% in the United Kingdom, Republic of Moldova, Portugal, Kazakhstan and Iceland, and 21% in Israel).<sup>3</sup> In 2010 in the WHO European Region, 22% of women smoked, compared with only 3.5% in Africa, Asia, and the Middle East. While the use of tobacco products was formerly largely a male phenomenon, the gap in use between male and female adults is now smaller in countries like Austria, Denmark, Ireland, Norway and the United Kingdom. In Norway and Sweden today, more women than

men use tobacco on a daily basis. Meanwhile, in Bulgaria, Croatia, Poland, and Slovenia more girls than boys use tobacco.<sup>4,5</sup>

Stopping smoking is very difficult, often requiring repeated interventions and/or multiple attempts to quit. Only 1% to 5% of smokers attempting to quit on their own (without a smoking cessation programme) succeed.<sup>6</sup> There is a very high relapse rate (93%) after 10 months of follow-up.<sup>7</sup> In Europe, pharmacotherapeutic interventions for smoking cessation have been shown to be both effective and cost-effective in a variety of settings, compared with other interventions within the health system. The medication involved belongs mainly to two distinct groups: nicotine replacement therapy (NRT), involving mainly patches, gum and nicotine inhalers; and non-nicotinic compounds such as bupropion hydrochloride, nortriptyline and, more recently, varenicline tartrate and cytosine.<sup>8</sup>

### *Developments since 2004*

In 2009, NRT products were included in the WHO Model List of Essential Medicines. A systematic review of studies reported a risk ratio (RR) of abstinence for any form of NRT of 1.60 (95% CI: 1.53 to 1.68) compared to no medication for smoking cessation.<sup>9</sup> The use of NRT increases long-term success rates by approximately 50% to 70%, regardless of the setting.<sup>9</sup> Combining a nicotine patch with a rapid delivery form of NRT was more effective for long-term smoking cessation than using a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51); and a combination of NRT and bupropion was more effective than bupropion alone (RR=1.24; 95% CI: 1.06 to 1.45).<sup>9</sup>

### *Research needs*

However, more research is needed in a number of areas. These include efforts to:

- develop more effective medicines to achieve long-term abstinence;
- establish a better definition of the criteria which need to be fulfilled in order to use some of the therapeutic modalities in combination;
- develop “rescue” interventions for smokers, since evidence suggests that smokers who relapse during their cessation attempt are at high risk of future relapses;
- determine the efficacy and effectiveness of existing and new therapeutic modalities for specific patient groups, including adolescents and pregnant women; and
- establish the cost-effectiveness of pharmacotherapy for smoking cessation in low- and middle-income countries in order to inform decision makers about the need for the development of lower-cost therapeutic options for their countries.

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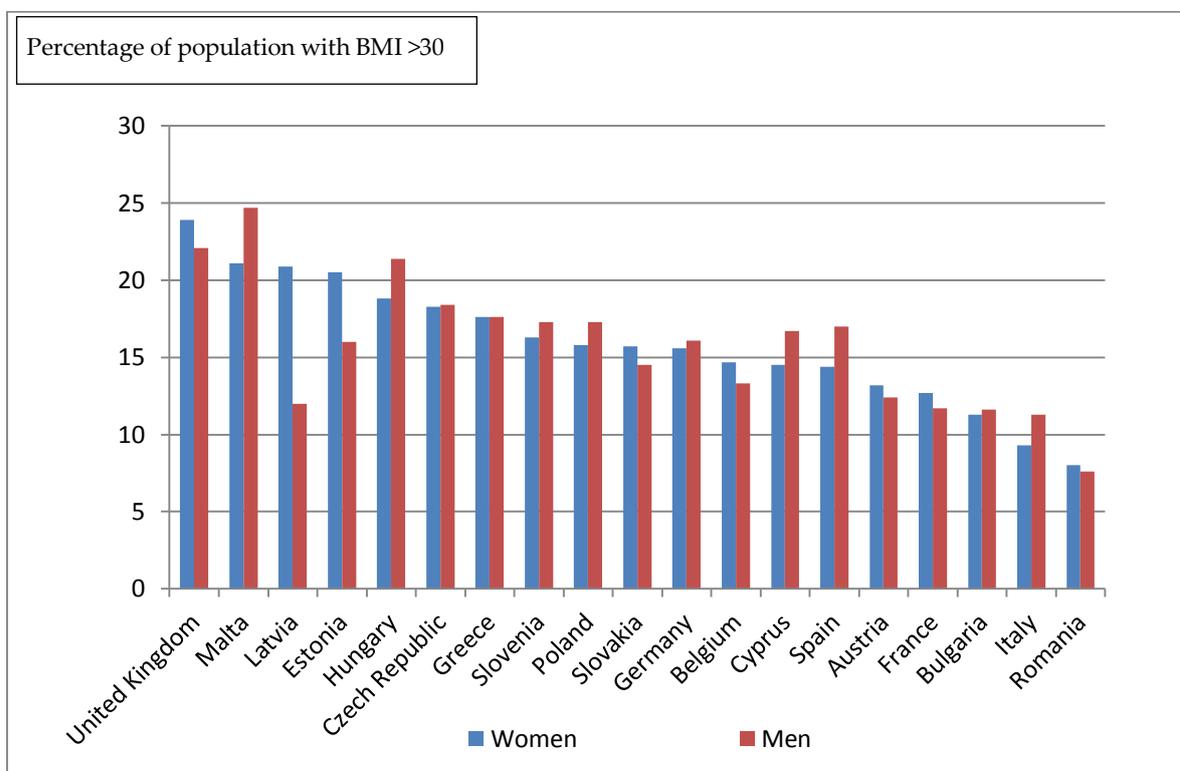
### 6.18 Obesity

[See Background Paper 6.18 \(BP6\\_18Obesity.pdf\)](#)

#### *Background*

Obesity is a chronic disease and one of the most important causes of illness and premature deaths worldwide. Today, over one billion people are overweight and half a billion are obese.<sup>1</sup> According to global projected trends, by 2030 one billion people will suffer from obesity.<sup>2</sup> In more than half of the EU countries one in two people are overweight or obese. Figure 6.18.1 shows the prevalence of obesity in men and women in EU Member States.<sup>3</sup> While the obesity epidemic continues to increase in many European countries, in some it appears to have levelled off.<sup>3</sup>

**Figure 6.18.1: Percentage of population with Body Mass Index (BMI) above 30 (defined as obese), age-standardized estimate, based on available data for EU Member States 2008-2009**



Source: Author's own elaboration based on Eurostat data, Nov 2011<sup>4</sup>

Note: According to Eurostat there was no recent data available for Denmark, Ireland, Lithuania, Luxembourg, Netherlands, Portugal, Finland, or Sweden.

In the United States, obesity has been declared the number one health threat.<sup>5</sup> Non-surgical and non-pharmacotherapeutical options include diet, exercise, behaviour modification, and psychological support.<sup>6</sup> In contrast to experimental settings, in routine primary care it has proved to be difficult to implement life-style interventions that reduce morbidity at population level.

Weight-loss (bariatric) surgery is currently the only intervention that can provide significant and long-term weight loss for the morbidly obese (approximately 20% weight loss after 10 years). It has also been shown to improve diabetes, hypertension and quality-of-life.<sup>7</sup> However, the procedure is associated with surgical risks (mortality less than 1%), long-term digestive problems, and nutritional deficiencies.<sup>8</sup> While savings may be achieved for health care systems six years after the surgery, it is unclear whether these continue after 10 years.<sup>7</sup>

### *Remaining challenges*

Only very limited pharmacotherapeutic options exist, and overall pharmacotherapy has played a minor role in the treatment of obesity.<sup>9</sup> Only one pharmaceutical (orlistat) is currently available in most European countries. Since the weight loss with this medicine is moderate (2.9 kg, 95% CI 2.5 to 3.2 kg), the majority of obese patients remain significantly obese, even with pharmacotherapy.<sup>10</sup> Due to their risk/benefit profile it has been challenging to develop medicines that have gained acceptance by regulatory authorities or remained available for a long time.<sup>11</sup>

### *Research needs*

- Since existing non-invasive therapeutic options have only a moderate effect on reducing obesity-related illness and deaths, there is a continuing need to develop effective and affordable treatment for those affected by obesity in Europe and worldwide.
- More research is needed on adherence and the regaining of body weight after discontinuation of pharmacotherapy, in order to better evaluate its cost-effectiveness.<sup>8</sup>
- Research is also needed into the long-term savings of surgical interventions.

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### 6.19 Rare diseases

[See Background Paper 6.19 \(BP6\\_19Rare.pdf\)](#)

#### *Background*

In the EU, a disease is considered to be rare when the number of people affected is less than 5 per 10 000. There are between 5 000 and 8 000 rare diseases, most of them with a genetic basis.<sup>1</sup> A very rough estimate would be that one out of 15 persons worldwide could be affected by a rare (“orphan”) disease – 400 million people worldwide, of whom 30 million are in Europe and 25 million in the United States.<sup>2</sup> Rare diseases are serious chronic diseases, and may be life-threatening.

In recent decades, considerable attention has been paid worldwide to efforts to stimulate the research, development and marketing of medicinal products for rare diseases, including the use of various regulatory incentives in both the EU and the USA. In the United States, over 400 products have been approved as therapy for more than 200 rare disease indications and in the EU, over 70 products for about 45 indications.<sup>3,4</sup> In addition, the establishment of various (research) programmes and networks has also helped advance understanding and diagnosis of rare diseases.<sup>5</sup> The International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 at the initiative of the European Commission and the U.S. National Institutes of Health with the aim of fostering international collaboration in rare diseases research. However, despite these positive developments, the burden of rare diseases continues to persist for a number of reasons.

Rare diseases present fundamentally different challenges from those of more common diseases, such as asthma. This is most apparent during the clinical development stage when rarity significantly complicates the task. Problems include the small number of patients, the logistics involved in reaching widely dispersed patients, the lack of validated biomarkers and surrogate end-points, and limited clinical expertise and expert centres.

### *Remaining challenges*

For many rare diseases, basic knowledge such as the cause of the disease, pathophysiology, natural course of the disease and epidemiological data is limited or not available. This significantly hampers the ability to both diagnose and treat these diseases. To address this challenge, public funding of fundamental research into the disease process remains necessary both at the national and global level.

Rare disease patients are scattered across countries. As a result, medical expertise for each of these diseases is a scarce resource. Fragmented disease knowledge means that it is critical that investments in fundamental research go hand-in-hand with investments in dedicated infrastructure and international networks (biobanks, registries, networks of expertise). Where needed, these networks can also provide opportunities to train health professionals on rare diseases.

Equally important is the availability of an internationally recognized rare disease classification system which can help generate reliable epidemiological data. Such a system would provide a useful basis for further research into the natural history and causes of rare diseases, and enable monitoring of the safety and clinical effectiveness of therapies and assessment of the quality of care.

Ongoing fundamental research into the disease process will result in the discovery of more targets for drug development for a specific rare disease. In particular, public funding of translational research, including proof of concept studies, might act as a catalyst to translate rare disease research into the development of new medicines. Making a disease easy to diagnose at an early stage will allow the development of prevention strategies that, even in the absence of an underlying treatment, can have a significant positive impact on a patient's life.

Clinical trial funding programmes remain essential for orphan drug development, especially for rare diseases that appear less attractive for the pharmaceutical industry. Of critical importance for marketing authorization and reimbursement is the acceptance of the evidence generated during drug development for rare diseases. When the medical need is great, a treatment can become available at an early stage where evidence is robust, but limited. However, this represents a substantial hurdle for some methodological assessments and the development of alternative methods of evaluation in small and very small populations is desirable. Large multidisciplinary networks should be funded to stimulate collaboration and bring together medical experts, reference centres and patients' groups. This infrastructure is necessary for performance of clinical trials and subsequent monitoring of newly authorized products.

A new generation of more targeted therapies (such as stem cell therapies, gene therapies or therapeutic gene modulations) is in development and new products are becoming available. To allow these targeted therapies for smaller patient groups to

become more common practice, it is critical to continue funding the research and development of these highly innovative therapies.

The use of optimized delivery methods (such as controlled or site-specific delivery) could entail improving the pharmacokinetic profiles of existing orphan drugs with improved efficacy, safety profile, or convenience for the patient.

Another opportunity for research in pharmacological intervention for rare diseases is to pursue the development of molecules developed for one indication that have also demonstrated potential with a favourable benefit/risk ratio for treating a different rare disorder and could be developed for other indications, a practice known as “drug repurposing”. The advantage is that more is known about these molecules and that knowledge can be leveraged in a new development programme.

### *Research needs*

In the area of rare diseases, there are many opportunities for the EU to build on the successful programmes and networks that have been supported so far. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure as well as provision of disease-related information at EU level and beyond (for example, patient experience)
- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase understanding of rare diseases
- Incentives for the development of therapeutics (such as clinical trial funding programmes)
- Assessment methods adapted to small and very small patient populations.

In addition, more support is needed for:

- Translational research to increase the translation of disease knowledge into drug development or health care innovation
- Innovative diagnostic methods for rare diseases to enable early intervention
- Research, infrastructure and implementation of guidelines for medical and psychosocial care for rare diseases
- Incentives for the development of preventive strategies and validated diagnostic techniques
- Research incentives to leverage existing knowledge and optimize the use of existing drugs (innovative delivery systems and drug repurposing) leading to fair prices for repurposed medicines
- Finding methods to provide easy access to available health care for patients, regardless of where they live.

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### 6.20 Diarrhoea

[See Background Paper 6.20 \(BP6\\_20Diarrhoea.pdf\)](#)

#### *Background*

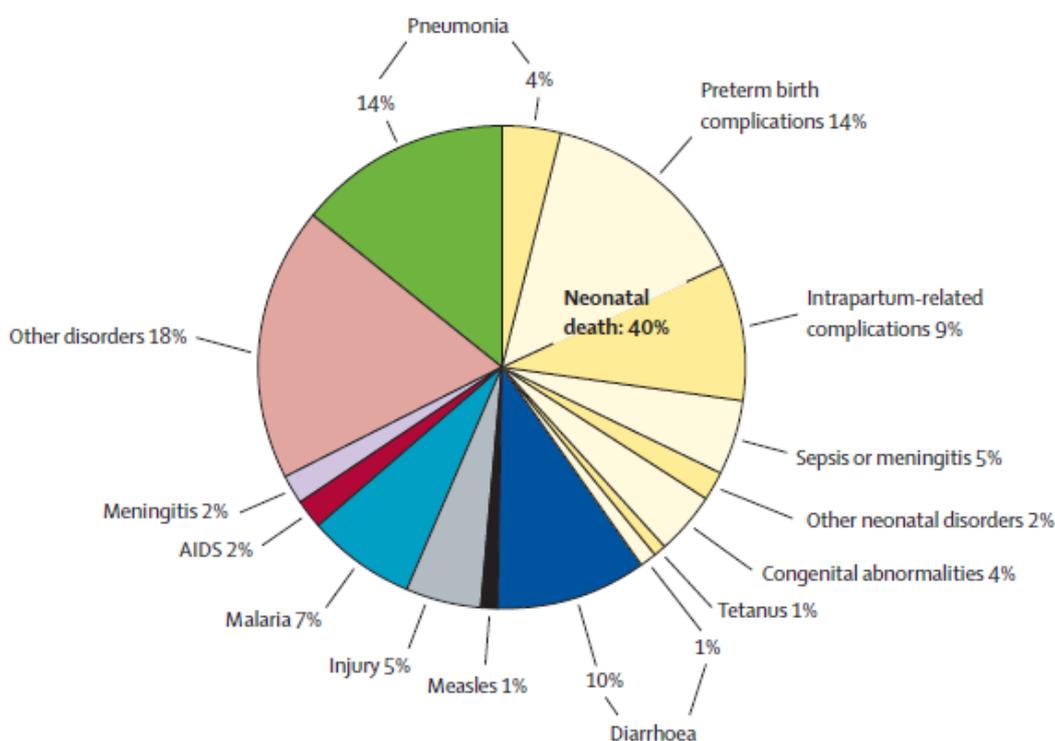
Although diarrhoea is a preventable disease, it remains the second leading cause of death (after pneumonia) among children aged under five years worldwide (Figure 6.20.1).<sup>1,2</sup> It is estimated that in 2010, diarrhoeal diseases accounted for 60.1 million disability-adjusted life years (DALYs) and for 666 000 deaths among children aged under five years - down from 70.6 million DALYs and 782 000 deaths in 2005.<sup>3</sup> The risk factors for diarrhoeal diseases include childhood underweight, suboptimal breastfeeding, unsafe drinking water and sanitation, vitamin A deficiency, and zinc deficiency.<sup>3,4</sup> At highest risk of diarrhoeal diseases are the poorest and most vulnerable children in communities lacking basic human needs such as safe drinking water, adequate sanitation, and optimal nutrition.<sup>1</sup> Around 50% of deaths among children under five occur in sub-Saharan Africa and 40% in South Asia.<sup>5</sup>

Diarrhoeal diseases are caused by a variety of pathogens including viruses (for example, rotavirus), bacteria (cholera, *Shigella* and enterotoxigenic *Escherichia coli* (ETEC)) and protozoa (*Cryptosporidium* and *Entamoeba histolytica*).<sup>1,6</sup> Most pathogens are transmitted from the stool of one person to the mouth of another via contaminated food or water (faecal-oral transmission).<sup>1</sup> Improvements in the supply of drinking water and sanitation, and optimal nutrition can prevent diarrhoea efficiently, and studies have shown that interventions targeting those areas are also cost-effective.<sup>7</sup> Licensed vaccines are available against rotavirus and cholera, and rotavirus vaccine

has been recommended by the WHO since 2006 for use in routine childhood immunization programmes.<sup>8</sup>

Diarrhoeal disease can be treated by using low-osmolarity oral rehydration salts (ORS) together with continued feeding and zinc treatment.<sup>9</sup> Although these treatments are not expensive, the percentage of children with diarrhoea who have access to ORS has only slightly increased over the past decade.<sup>1,5</sup> While antimicrobials are not recommended for routine use, it is recognized that some pathogens, such as *Shigella*, should be treated with antibiotics.<sup>9</sup> However, there has been an increase in cases of multi-resistance to antibiotics, especially for *Shigella*. Diagnosis of diarrhoea relies on assessment for dehydration, types of diarrhoea (watery diarrhoea, bloody diarrhoea and persistent diarrhoea), malnutrition, and non-intestinal infection.<sup>9,10</sup> Diagnostics for point-of-care, such as a rapid diagnostic tool to identify the specific pathogen involved, are not yet available.

**Figure 6.20.1: Global causes of child deaths in 2010**



Source: Liu L *et al.* (2012) Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000.

Data are separated into deaths of neonates aged 0–27 days and children aged 1–59 months. Causes under 1% of deaths are not depicted.

### *Developments since 2004*

Among the handful of funders supporting the R&D efforts against diarrhoea, the European Commission (EC) has been funding about 100 projects, involving basic science, pharmaceuticals, vaccines, and diagnostics under the 6th and 7th Framework Programmes.

According to the G-FINDER survey (which provides information on global R&D funding for 31 neglected diseases), global R&D funding for diarrhoea was an estimated US\$ 113.9 million in 2007 and US\$ 152.2 million in 2011, with a peak of US\$ 180.4 million in 2009 (2009 and 2011 data adjusted for inflation based on 2007).<sup>11,12</sup> In 2011, R&D in diarrhoeal diseases accounted for 5% of the total funds available for research.<sup>11</sup> The majority of diarrhoea R&D funding in 2011 addressed three disease areas: 33.9% for rotavirus (US\$ 51.7million), 17.1% for cholera (US\$ 26 million) and 15.7% for *Shigella* (US\$ 23.9 million).<sup>11</sup>

There are a number of promising vaccine candidates against rotavirus, *Shigella* and ETEC, including some in Phase II clinical trials. Meanwhile, candidate vaccines against *Campylobacter* are currently in the preclinical phase. The need for further research on rotavirus vaccines largely depends on the outcome of current vaccines in terms of their efficacy in endemic regions and their ability to provide cross-protection against a range of rotavirus strains.<sup>13</sup> There are currently fewer medicines in the pipeline, compared with vaccines. However, since 2006, OneWorld Health, a product development partnership (PDP), has been developing new anti-secretory medicines for the treatment of cholera and other diarrhoeal diseases, with funding from the Bill & Melinda Gates Foundation.<sup>14</sup> As a result, a new anti-diarrhoeal medicine was approved by the U.S. Food and Drug Administration (FDA) to relieve symptoms of diarrhoea in HIV/AIDS patients on antiretroviral therapy (ART).<sup>15</sup> Two additional medicine candidates are in Phase I trials.<sup>16</sup> A new diagnostic test which can distinguish between the different pathogens that cause diarrhoeal diseases is also in early development. One of the examples is a disposable diagnostic instrument with microfluidic cards for immunological detection of pathogens.<sup>17</sup>

In April 2013, a Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea was issued jointly by UNICEF and the WHO. This plan sets specific goals for a reduction in the number of deaths and the incidence of diarrhoea by 2025.<sup>18</sup> To address these issues, it sets targets for vaccine coverage, case management, and environmental interventions.

### *Remaining challenges*

From the perspective of the cost-effectiveness of interventions to improve water and sanitation compared with vaccination in endemic areas, the environmental interventions should be prioritized for investment. Access to existing treatment is also highly cost-effective. However, vaccines can greatly reduce the burden of disease and appear to be very effective in areas where access to safe water and sanitation cannot be

guaranteed. There are no vaccines available to protect against several pathogens, such as *Shigella* and ETEC, and more research is needed to develop new vaccines against these pathogens.

### *Research needs*

The development of affordable and easy-to-use diagnostic tools would change the treatment protocol and enable health care workers to provide pathogen-specific treatment. The fact that a number of vaccine and medicine candidates are in Phase I and II trials indicates that more funding is critically needed to bring these candidates into larger scale clinical trials. Research needs include:

- Basic research for cholera, *Shigella* and *Cryptosporidium*
- Vaccines for *E. coli* (ETEC), cholera, *Shigella* and *Cryptosporidium*
- New pharmaceuticals for the treatment of cholera, *Shigella* and *Cryptosporidium*, including ones against drug-resistant strains (see [Chapter 6.1](#))
- Diagnostics (point-of-care).

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### 6.21 Hearing loss

[See Background Paper 6.21 \(BP6\\_21Hearing.pdf\)](#)

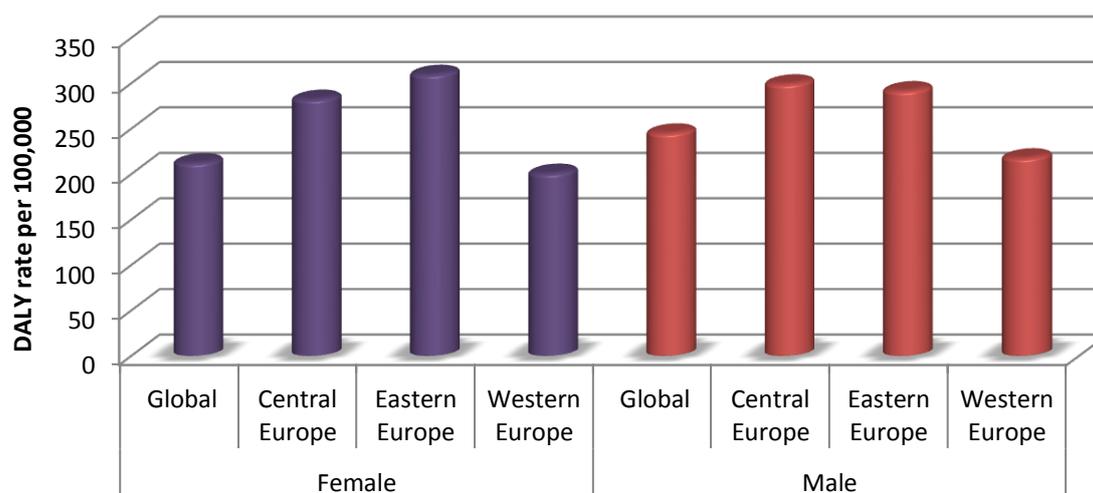
#### *Background*

The ability to hear is critical to understand the world around us and to interact with each other. Hearing impairment is the most frequent sensory deficit in human populations and affects newborns, children, adults, and the elderly.<sup>1</sup>

Hearing impairment can be caused by a number of factors including: measles, mumps, and meningitis; chronic otitis media; exposure to excessive or prolonged noise; head and neck injuries; the use of ototoxic medications including certain types of chemotherapies and antibiotics; industrial solvents; congenital abnormalities and infections and perinatal problems; certain nutritional deficiencies; genetic disorders; and ageing.

In 2008, the WHO estimated that over 360 million people (5.3% of the global population) have disabling hearing loss – 80% of them in low- or middle-income countries. These figures are expected to rise substantially in the future due to ageing of the global population.

Figure 6.21.1: DALY rates caused by hearing loss by sex and region



Source: 2010 Global Burden of Disease Study. *The Lancet*, December 2012.

Despite the high global burden of hearing impairment, there is a lack of statistics and epidemiological surveys in both high- and low-income countries due to poor diagnosis and reporting.<sup>23</sup> The need for standardized procedures when collecting and reporting epidemiological data on hearing loss is essential. Only a few countries, even in Europe, have implemented population-wide screening programmes.

Hearing loss is an important public health concern with substantial economic costs and social consequences. In infants and children hearing impairment retards developmental language and educational progress. In adults, it causes difficulties in both professional and social life as well as stigmatization. Medical costs (for hearing aids, for example) account for only a small percentage of the overall cost. In Europe, untreated hearing loss is estimated to cost €213 billion a year.<sup>4,5</sup>

A number of key measures are needed to help reduce the burden of disease. They include: prevention of excessive exposure to noise; prevention of infectious diseases through vaccination; hearing screening programmes; raising awareness among users of the risks of ototoxic medications; genetic counseling (for some inherited causes of hearing loss); raising awareness among decision makers of the need to monitor the incidence and prevalence of hearing loss in the entire population, ranging from infants to the elderly. Hearing aids and cochlear implants are currently the only available

means to help people partially recover their hearing and communication skills. However, these devices can be very expensive and are not always affordable.<sup>5,6</sup>

### *Developments since 2004*

Several European initiatives are supporting research through different projects on hearing aids and cochlear implants. Meanwhile, recent rapid advances in bioscience and technology make it realistic to envisage a pharmacological treatment for hearing loss related to hair cells caused by different factors. The approaches used are broad, ranging from a search for new pharmacological compounds, gene therapy, RNA silencing, and stem cells, to the discovery of new delivery routes for pharmacotherapy. Up until now, most of the research has been performed in academic research settings. However, pharmaceutical companies are now just starting to be interested by the potential market for new products for hearing loss.

Public-private partnerships to develop new approaches for hearing loss are likely to be created in the near future.

### *Remaining challenges*

Consortia of top-level European research and industrial partners will need to act together and contribute to strengthen the EU's leadership on research into the pharmacological prevention and treatment of hearing loss. As the prevalence of hearing impairment in the world is very high this opens huge potential markets for pharmacological interventions.

### *Research needs*

Research needs include:

- The development and use of large epidemiological surveys across age groups from neonates to the elderly, as well as the use of standardized methods of evaluation and reporting.
- Intensified efforts to develop protective pharmacological agents for hair cells and to research the use of stem cells and hair cells precursors. The highly promising results of research carried out over the past five years make it realistic to envisage a pharmacological treatment for hearing loss.
- More research on new, safer delivery routes for the administration of pharmacological agents into the inner ear.

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## 6.22 Pneumonia

[See Background Paper 6.22 \(BP6\\_22Pneumo.pdf\)](#)

### *Background*

Pneumonia is an acute infection of the lungs. When an individual has pneumonia, the alveoli in the lungs are filled with pus and fluid, which makes breathing painful and limits oxygen intake. Pneumonia has many possible causes, but the most common are bacteria and viruses. The most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and respiratory syncytial virus (RSV). *S. pneumoniae* is the most common cause of bacterial pneumonia in children under five years in the developing world.<sup>1</sup> The second most common cause of bacterial pneumonia in children is Hib, followed by RSV - the most common cause of viral pneumonia in children under two years. The populations most at risk for pneumonia are children under five years, people aged 65 or over, and people with pre-existing health problems.

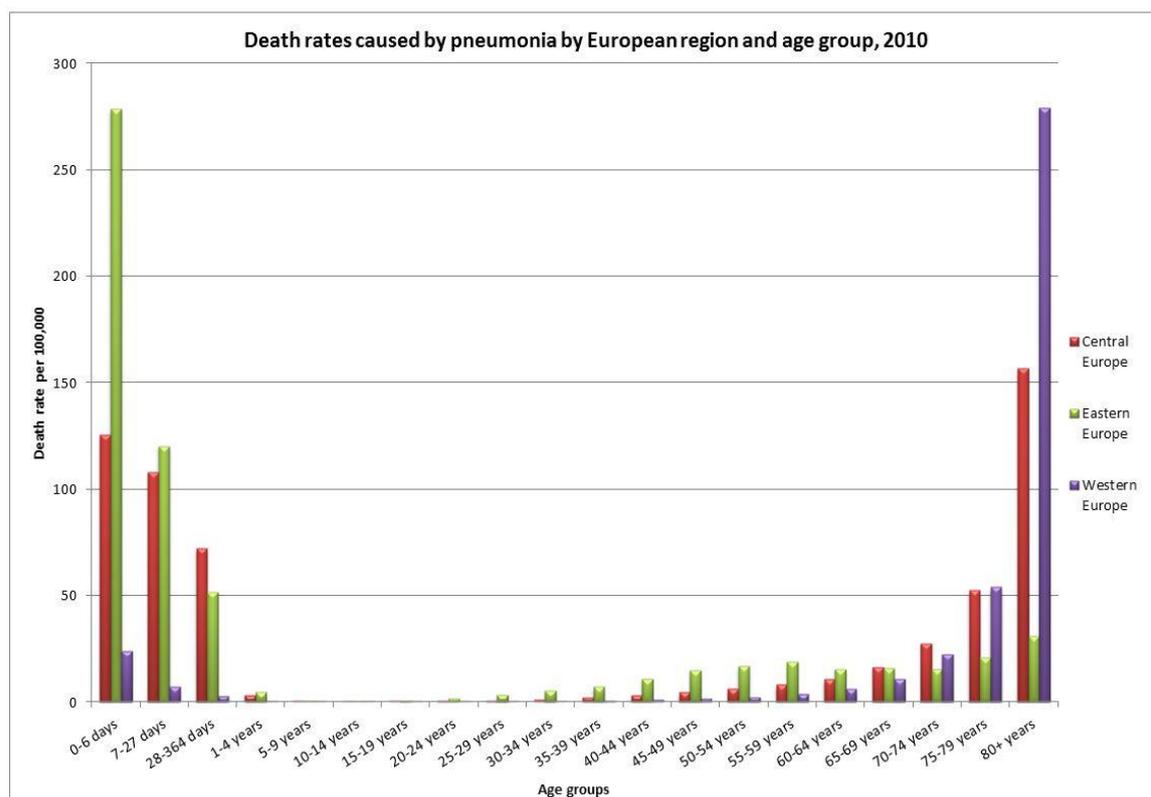
Pneumonia remains the leading cause of death in children under five worldwide. It accounts for about 1.6 million deaths a year in this age group - 18% of all deaths among children under five.<sup>1,2</sup> More than 99% of all pneumonia deaths occur in low- and middle-income countries.<sup>3</sup> South Asia and sub-Saharan Africa bear the burden of more than half of the total number of cases of suspected pneumonia among children under five worldwide. Children in low-income countries are nearly 18 times more likely to die before the age of five than children in high-income countries, due mainly to pneumonia and other acute infections.<sup>2</sup> For both European regions and the world, the disease burden for pneumonia (caused by pneumococcus, Hib, and RSV) is highest in children aged under one year. About 434 779 pneumonia deaths occur in this age group - over 74% of all pneumonia deaths in children aged under five.<sup>4</sup>

In Europe, mortality rates for pneumonia are substantially higher in children up to the age of four and in adults aged 75 and over than in most other age groups. In Western

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Europe the highest mortality rates for pneumonia are in elderly people aged 80 and over (279 deaths per 100 000 people), while in Eastern Europe similar mortality rates for pneumonia exist in infants aged 0 to 6 days (278 deaths per 100 000). See Figure 6.22.1.

**Figure 6.22.1: Death rates caused by pneumonia by European region and age group, 2010**



Source: *Institute of Health Metrics and Evaluation (IHME)*, 2013

Many effective treatments are available for bacterial pneumonia in children and adults. Analysis of recent studies on effective antibiotic treatments showed comparable efficacy between the various antibiotics currently used in clinical practice.<sup>5</sup> However, antibiotics are only effective in treating bacterial pneumonia and cannot treat viral pneumonias such as RSV that mainly occurs in infants. Malaria is an infectious disease that manifests similar symptoms to that of pneumonia, and these symptoms often overlap, making it difficult to identify the cause. However, a rapid diagnostic test (RDT) is available for malaria to help ensure that a definitive diagnosis can be made and correct treatment given, even in resource-poor health settings. There are currently no available rapid point-of-care diagnostics to differentiate between bacterial and viral pneumonia. This is a key gap in monitoring the spread of both bacterial and viral pneumonia and in providing appropriate treatment.

Pneumococcal vaccines, such as Hib, conjugate vaccines and polysaccharide vaccines are highly effective in preventing most bacterial pneumonias.<sup>2, 6</sup> Pneumococcal conjugate vaccines (PCV) are available for use in children and adults, and pneumococcal polysaccharide vaccines (PPV) for adults. Three conjugate vaccines – PCV7, PCV10 and PCV13 – are widely recommended for use in children. Each vaccine protects against different serotypes of the pneumococcus. Children in the developing world are exposed to different serotypes from those that affect children in industrialized countries and this is reflected in the appropriate choice of vaccine.<sup>6</sup>

### *Remaining challenges*

Pneumococcal conjugate vaccines have been shown to have greater immunogenicity against the most prevalent paediatric serotypes and PCV is the current vaccine of choice to protect against *S. pneumonia*, the leading cause of bacterial pneumonia.<sup>7</sup> The ideal vaccine would be a pneumococcal vaccine that can generate an immune response against all pneumococcal pathogens, regardless of their serotype. Development of PCV with additional serotypes or vaccines containing protein antigens is underway. For adults, PPV is used in high- and low-income countries throughout the world. This vaccine prevents invasive pneumococcal disease, most notably in younger, healthier adults, although it was shown to prevent bacterial pneumonia, in a study of nursing home residents.<sup>8</sup>

### *Research needs*

In order to reduce the high global burden of pneumonia, research is needed into the development of point-of-care rapid diagnostic tests for pneumonia and vaccines that can protect against viral pneumonia. The availability of improved rapid diagnostic tests at point-of-care, together with the appropriate use of effective antibiotic treatments would help prevent deaths, while widespread use of pneumococcal vaccines, especially among the elderly, would help lower the incidence of pneumonia worldwide. Research is needed to understand the low uptake of PPV in the elderly so that vaccination rates can be increased. In addition, there is a need to reformulate currently recommended antibiotics into small dosage and injectable forms, in order to ensure better uptake in children and newborns.

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### 6.23 Neonatal conditions

[See Background Paper 6.23 \(BP6\\_23Neonatal.pdf\)](#)

#### *Background*

The neonatal period is only the first 28 days of life and yet accounts for 40% of all deaths in children under five.<sup>1</sup> Even within the neonatal period there is wide variation in mortality rates, with 75% of all neonatal deaths occurring in the first week of life – including 25% to 45% in the first 24 hours after birth.<sup>2</sup> In 2010, neonatal conditions accounted for 3 072 000 deaths worldwide.<sup>1</sup> Among the many neonatal conditions, the three major contributors to the global burden of disease are (in order of magnitude) premature birth, birth asphyxia, and neonatal infections.<sup>3,4</sup>

Premature birth is defined as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period. Complications of premature birth are the single largest contributor to neonatal mortality, due to the lack of necessary physical development. The survivors of premature birth may suffer life-long effects. Neonatal sepsis is a blood infection that can be caused by a number of different bacteria. Neonatal sepsis can have an early-onset (within 24 hours of birth) or late-onset (after eight days of life). Birth asphyxia is defined as the failure to establish breathing or perfusion at birth.

Neonatal conditions exert a heavy burden on families, society, and the health system. Because they occur in the first few weeks of life, neonatal conditions are major

contributors to the global toll of DALYs (having the most potential Years Lived with Disability (YLD) and Years of Life Lost (YLL)).

### *Developments since 2004*

Although a regional survival gaps exist, depending on where a baby is born, neonatal conditions are an issue of global concern. All regions have seen slower reductions in neonatal deaths compared to overall deaths for children under five. This has resulted in an increased share of neonatal deaths among the under-five deaths – up from 36% of under-five deaths in 1990 to 43% in 2011, a trend that is expected to continue.<sup>5</sup> Within Europe, Eastern Europe has consistently higher mortality rates and DALY burden for all three high-burden neonatal conditions (particularly neonatal sepsis and birth asphyxia-related neonatal encephalopathy) than Western and Central Europe.

### *Remaining challenges*

At present, preventive methods, diagnostic tools, and treatments for neonatal conditions remain limited, due to the complex causes of these conditions. Many of the current preventive approaches focus on maternal health prior to the birth (for example, maternal immunization and efforts to ensure a healthy pregnancy). Furthermore, encouraging results and promising safety profiles are emerging from preliminary studies of maternal immunization with pneumococcal polysaccharide conjugate vaccines.<sup>6</sup> Alternative non-pharmaceutical prevention methods for pre-term birth include: birth spacing; optimizing pre-pregnancy weight; promoting healthy nutrition; promoting vaccination of children and adolescents; preventing sexually transmitted infections (STIs), and promoting cessation of tobacco use.<sup>7</sup> Several treatments exist for neonatal conditions that can lower the risk of maternal and neonatal mortality. However, these treatments are still not ideal, due to their formulation, packaging, and/or accessibility (Table 6.23.1).<sup>8,9,10</sup>

**Table 6.23.1: Pharmaceutical gaps of existing treatments for neonatal conditions**

<b>Treatment</b>	<b>Condition treated</b>	<b>Gaps</b>
Tocolytics	Inhibit pre-term labour	- Associated with adverse effects to both mother and newborn
Corticosteroid	Foetal lung maturation	- Associated with increased risk of infection to both mother and newborn
Antibiotics	Treat neonatal sepsis	- Non-ideal formulation and packaging for neonatal use - Require a trained health worker to administer
Surfactant preparations	Treat respiratory distress syndrome	- Expensive to produce

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Several tocolytics (for example, oxytocin antagonists, betamimetics, calcium channel blockers, and magnesium sulfate) are available and are effective in suppressing labour to allow enough time for antenatal corticosteroid treatment for foetal lung maturation prior to delivery and/or to transfer mother and baby to a higher-level facility where appropriate care may be available.<sup>7,11</sup> However, the effects on neonatal outcomes and foetal/maternal side-effects have not been shown to improve the perinatal outcome.

Within the European Union, following the requirements of the Paediatric Regulation, the EMA produces a yearly updated "priority list" of medicines in need for children.<sup>12,13</sup> Neonates are included in these pan-European efforts. These Paediatric Regulations require that any new drug, whatever its main target, should also be considered for potential paediatric use which forces all pharmaceutical companies to think strategically in terms of paediatric medicines.

The 2012 Report of the UN Commission on Life-saving Commodities for Women and Children recommended simple potential product innovations that need further research, particularly for the administration of gentamicin to treat neonatal infections (including fixed-dose presentations for needles and syringes, auto-disable syringes, and micro-needle patch technology for administering gentamicin).<sup>10</sup>

A variety of surfactant preparations have been developed and tested, including synthetic surfactants derived from animal sources, for treatment and prevention in infants at risk of respiratory distress syndrome. Although both surfactant preparations are effective, comparative reviews indicate that natural surfactants may have greater efficacy. However, these are expensive to produce and supplies are limited.<sup>10</sup>

Meanwhile, the lack of rapid diagnostic tests often results in inappropriate use of antibiotics, thereby increasing the risk of the development of antimicrobial resistance. The symptoms of neonatal sepsis are often very similar to other life-threatening diseases (such as necrotizing enterocolitis and perinatal asphyxia), making it difficult to accurately diagnose and treat.<sup>14</sup> Even with the few diagnostic tools that exist, pathogenic organisms remain difficult to identify. The bacterial load in neonates may be low because the mother is being treated with antibiotics and/or because only small amounts of blood can be taken from newborns.<sup>15</sup> In addition, the results of these diagnostic tests take up to 48 hours, which is often too long to wait as the condition of a neonate with neonatal sepsis can deteriorate rapidly.<sup>7</sup>

### *Research needs*

In order to reduce neonatal mortality rates, there is a need to boost the number of innovative products in the R&D pipeline – especially new rapid diagnostic tools and appropriate treatments. More specifically, pharmaceutical gaps that offer research opportunities include:

### Pre-term birth:

- Development of a more simplified dosing regimen and single dose packaging of tocolytics to prevent or delay premature labour.
- Development of tocolytics with fewer side-effects in mothers and newborns.
- Evidence-based protocols for the use of injectable antenatal corticosteroids to prevent respiratory distress syndrome.
- Clearly labeled, pre-packaged or pre-filled delivery systems for antenatal corticosteroid products.

### Sepsis:

- Rapid diagnostics for neonatal sepsis to prevent late or inadequate administration of necessary antibiotics.
- Appropriate product formulation and packaging for treating neonatal sepsis, especially low-dose injectable gentamicin.
- Development of shorter course antibiotics, oral antibiotics, and antibiotics with fewer side-effects for newborns.
- Development of diagnostic tools for neonatal conditions, which can help reduce the inappropriate use of antibiotics.
- Development of new and effective antibiotics to treat bacterial infections that are or will soon become resistant to current antibiotics ([see Chapter 6.1](#)).

### Birth asphyxia:

- Development of effective and lower-cost synthetic surfactants to treat respiratory distress syndrome in newborns.
- Development of a more stable oral surfactant.

Efforts to address neonatal conditions need to be prioritized in order to help achieve the Millennium Development Goal 4 of reducing under-five mortality by two-thirds by 2015. This could have a major impact in reducing the global burden of disease as these conditions have the most potential YLL and YLD. Although the burden of neonatal disease is largest in developing countries, the proportion of neonatal deaths in under-five deaths is highest in developed countries, making this an issue of global concern. The development of innovative and more affordable pharmaceuticals and diagnostics for neonatal conditions require substantive investment and long-term support.

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### 6.24 Low back pain

[See Background Paper 6.24 \(BP6 24LBP.pdf\)](#)

#### *Background*

Low back pain is a very common health problem worldwide and a major cause of disability - affecting performance at work and general well-being. Low back pain can be acute, sub-acute, or chronic. Though several risk factors have been identified (including occupational posture, depressive moods, obesity, body height and age), the causes of the onset of low back pain remain obscure and diagnosis difficult to make.

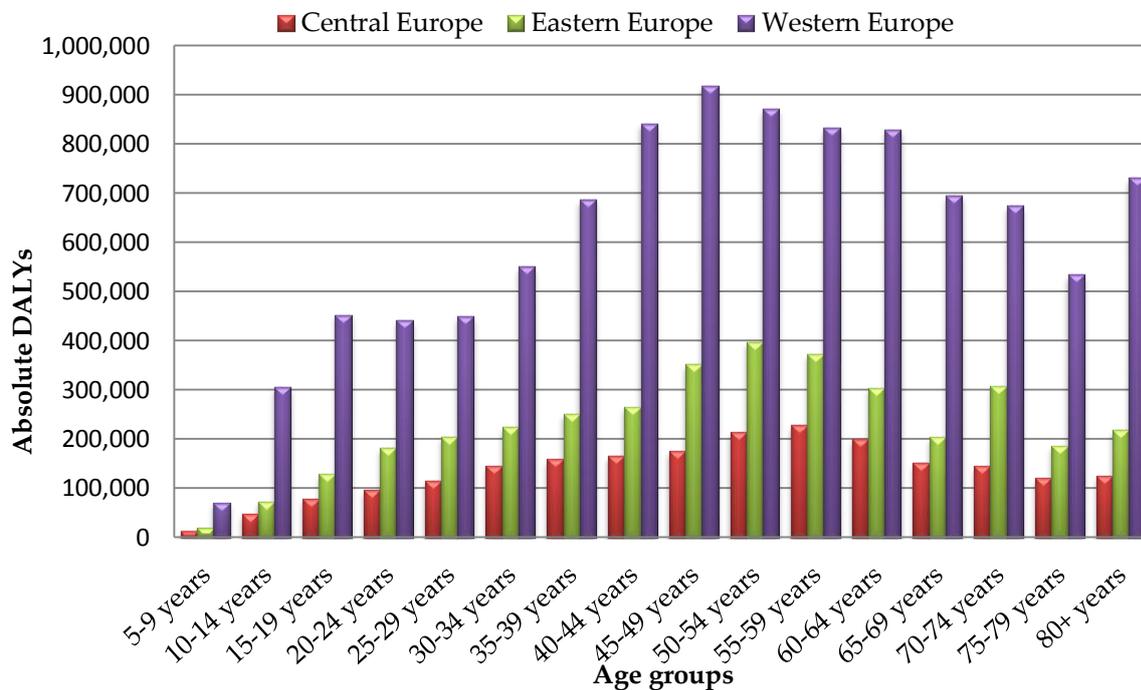
Back pain is not a disease but a constellation of symptoms. In most cases, the origins remain unknown.

Low back pain affects people of all ages, from children to the elderly, and is a very frequent reason for medical consultations. The 2010 Global Burden of Disease Study estimated that low back pain is among the top 10 diseases and injuries that account for the highest number of DALYs worldwide.<sup>1</sup> It is difficult to estimate the incidence of low back pain as the incidence of first-ever episodes of low back pain is already high by early adulthood and symptoms tend to recur over time. The lifetime prevalence of non-specific (common) low back pain is estimated at 60% to 70% in industrialized countries (one-year prevalence 15% to 45%, adult incidence 5% per year). The prevalence rate for children and adolescents is lower than that seen in adults but is rising.<sup>2,3</sup> Prevalence increases and peaks between the ages of 35 and 55.<sup>4</sup> As the world population ages, low back pain will increase substantially due to the deterioration of the intervertebral discs in older people.

Low back pain is the leading cause of activity limitation and work absence throughout much of the world, imposing a high economic burden on individuals, families, communities, industry, and governments.<sup>2,4</sup> Several studies have been performed in Europe to evaluate the social and economic impact of low back pain. In the United Kingdom, low back pain was identified as the most common cause of disability in young adults, with more than 100 million workdays lost per year.<sup>5</sup> In Sweden, a survey suggested that low back pain accounted for a quadrupling of the number of work days lost from 7 million in 1980 to 28 million by 1987. However, the authors state that the existence of social compensation systems in Sweden might account for some of this increase.<sup>5</sup> In the United States, an estimated 149 million work days are lost every year because of low back pain,<sup>6</sup> with total costs estimated to be US\$ 100 to 200 billion a year (of which two-thirds is due to lost wages and lower productivity).<sup>7,8</sup>

At present low back pain is treated mainly with analgesics. The causes of lower back pain are rarely addressed. Alternative treatments include physical therapy, rehabilitation and spinal manipulation. Disc surgery remains the last option when all other strategies have failed, but the outcomes are disappointing.<sup>9</sup>

**Figure 6.24.1: Absolute DALYs caused by low back pain by age group and European region**



Source: Institute of Health Metrics and Evaluation (IHME)

<http://ghdx.healthmetricsandevaluation.org>

### *Developments since 2004*

European guidelines for the management of chronic non-specific low back pain have been developed by experts in the field and provide guidance for diagnosis and treatment. The European Commission is also funding the project Genodisc to identify risks factors, biomarkers, and improve diagnosis of low back pain.<sup>10</sup>

Research performed over recent years on biomaterials, growth factors or stem cells in the intra-vertebral disc space brings new hope for delaying the time before surgery is required. The development of 3-dimensional imaging and more resistant biomaterials should help in addressing the issue of disc prosthesis for low back pain.

### *Research needs*

Future areas for public sector research include:

- the establishment of biomarkers
- the search for anthropometric risk factors and adapted rehabilitation
- the development of biomaterials for disc replacement therapies
- stem cell research to restore discs and the intervertebral space.

There is a still long way to go to improve diagnosis and identify other potential risk factors. As the world population ages, the disease burden of low back pain will increase substantially. If surgery and disc replacement therapies are currently the last option to relieve back pain when all other strategies have failed, new developments in 3D imaging, biomaterials and disc renutrition or stem cell therapies may bring new hope for the treatment of low back pain.

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## 7. Cross-cutting themes

### 7.0 Introduction

This chapter reports on a number of issues which apply to all diseases and therapeutic approaches. The themes include the particular needs of special groups and the development of stratified medicine. The special groups highlighted in this chapter are the same as those covered in the 2004 Priority Medicines Report: children, women and the elderly. Although progress has been made in some areas, special attention for these populations is still warranted. Each of these groups have specific pharmaceutical needs due to their changing physiology, the spectrum of diseases they face, and the fact that these needs are under-represented in the pharmaceutical development process. While similar issues exist for these groups, particular needs have been identified and will be discussed below. An important cross-cutting theme that has been identified throughout this chapter is the need for better use of existing data (electronic health records) to provide insight into, and assess the implications of medicines use in these special patient groups ([see also Chapter 8.4](#)).

Stratified medicine is expected to play an increasingly important role in clinical treatment in the coming decades. Stratified medicine can be summarized as an approach targeting treatment specifically to subpopulations of patients who are more likely to benefit from, or less likely to be harmed by a particular treatment. Many different strata exist, including the special populations addressed in this chapter. New elements in stratified medicine, such as pharmacogenomics and other new technologies are rapidly evolving. Up until now, despite all the projected benefits of this approach, clinical implementation in health care systems has been limited, and various gaps remain at the level of basic research, translational studies and the establishment of societal and regulatory frameworks.

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### 7.1 Priority medicines for children

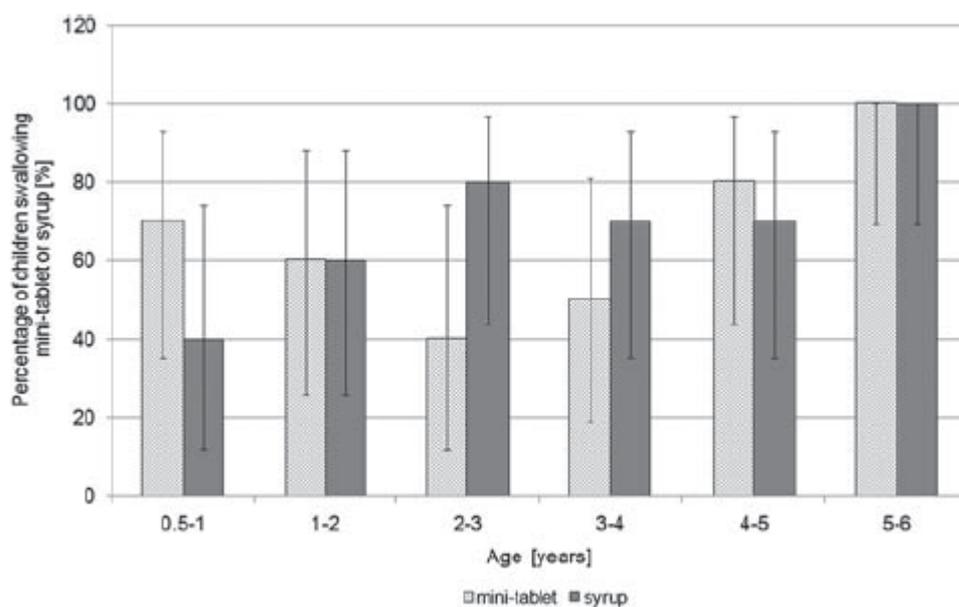
[See Background Paper 7.1 \(BP7\\_1Children.pdf\)](#)

Children are entitled to safe, efficacious and age-appropriate medicines. However, the provision of optimal medicines for children is limited by the lack of commercial incentives, a dearth of clinical trials on children's medicines, delays in licensing medicines for children and the absence of suitable formulations for children. Children are not small adults. They are a vulnerable population with specific needs as a result of changing physiology, and with a range of diseases and patterns of disease that differ

from those in adults. Unmet public health needs of children include, among others, paediatric oncology, pain, and neonatal morbidity. There is currently very little data on the appropriate delivery and use of medicines in children.

The 2004 Priority Medicines Report called for public investments to reverse the insufficient funding for research on children-specific medicine formulations. Such formulations need to take into account children's body development, medicine related toxicity and children's taste preference. In recent years, much progress has been made in the development of age-appropriate novel oral formulations with dose flexibility (mini-tablets, chewable and orodispersible tablets for younger children, and dosage forms dispersible into liquids or mixed with food). This development is in line with the global shift towards the use of solid oral dosage forms for children, as proposed by a WHO expert forum in 2008.<sup>1</sup> Following recent studies on mini-tablets (see Figure 7.1.1),<sup>2,3</sup> the age at which young children can safely swallow orally administered solid forms is decreasing.<sup>4</sup> With the development of orally disintegrating mini-tablets, there are more promising results for infants younger than two years of age.<sup>5</sup>

**Figure 7.1.1: Children's ability to completely swallow mini-tablets and glucose syrup (n=10 children per age group; mean±95% CI).**



Source: Spomer N *et al.* Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Child*, 2012

Despite the (ongoing) development of various innovative oral solid dosage forms and devices for use in children, there are continued research and development (R&D) gaps and further investments are needed. The research on children's ability to swallow medicines needs to be accompanied by studies on children's preferences and adherence to different dosage forms. In addition, alternative routes of administration

(such as oral-transmucosal (buccal strips), intra-nasal and transdermal routes) are ripe for future R&D efforts. For all formulations, methodologically sound data are needed on the impact of new technologies on patient-related outcomes such as clinical efficacy, side effects and administration errors. In view of the concerns about the toxicity of some excipients in formulations for children,<sup>6</sup> more research is needed into the development of safe alternatives for children. An additional concern is the limited marketing of many newly developed drug delivery devices for children. Studies are needed on the implications of price and the need to improve access to innovative products that have tangible therapeutic benefit.

Another key recommendation of the 2004 Priority Medicines Report was the need to include more children in clinical trials. Progress since then includes the adoption by the European Union of the Paediatric Regulation in 2007, thereby combining requirements for paediatric drug development (Paediatric Investigation Plans – PIPs) with incentives for the pharmaceutical industry to, at least partly, cover the additional investment for testing new medicines in children.<sup>7</sup>

From 2007 to 2011, the number of clinical trials with a paediatric population (based on information from the EU clinical trials database, EudraCT) was relatively stable, with an average of 350 trials a year, while the proportion of paediatric trials among all trials increased from 7.4% to 9.9% (see Background Paper 7.1, Table 7.1.6).<sup>8</sup> Of these paediatric trials, 109 were part of an agreed PIP. One effect was the inclusion of younger children in clinical trials for cholesterol-lowering and anti-hypertensive medicines, juvenile idiopathic arthritis, diabetes mellitus and haemophilia A and B. The Regulation may aid in preventing unnecessary trials since protocol-related information is made publicly available through EudraCT.<sup>8</sup>

Since 2008, approximately 70% of all PIPs proposed or required the development of indications for the whole or subsets of the paediatric population. This indicates an increase in the development of medicines for children, as only approximately 30% of medicines applied for and obtained a paediatric indication before the EU Paediatric regulation came into force.<sup>8</sup> Nevertheless, paediatric therapeutic areas addressed by the industry since 2007 seem more aligned with adult drug development than with the indicated unmet public health needs of children. The question as to whether the requirements and incentives system of the Regulation delivered what was expected needs to be answered. In addition, the awarding of SPC extensions to paediatric medicines may increase public expenditures for health care and have cost implications for public payers. Such effects have to be identified and studied.

Based on an EMA survey published in 2010, 45% to 60% of all medicines used in children in the EU27 countries were used outside their marketing authorization (off-label), especially in neonates, patients with serious conditions and in intensive care units.<sup>9</sup> Preterm neonates were the most vulnerable patient group, exposed to high numbers of medicines (up to 90% unlicensed or off-label use), at higher risk of adverse drug reactions and with no information on safety and efficacy available in the Summary of Product Characteristics.<sup>10</sup> Despite the risk of potential harm, off-label use

of medicines has become an accepted practice in health care for children. Off-label drug use can be medically appropriate if the benefits outweigh the potential risks, which calls for a systematic consideration of evidence for safety and efficacy. A priority list of studies into off-patent paediatric medicines has been produced by the EMA to serve as a basis for EU public sector research funding.<sup>11</sup> In the absence of evidence obtained from robust clinical trials, other accessible data sources should be explored, such as existing electronic anonymized patient-level databases. The expanded availability and use of electronic medical records could allow researchers to link clinical treatments and outcomes with prescribing trends in off-label medication and better assess the implications of their use in children ([see also Chapter 8.4](#)).

Such data would also help facilitate other much needed research linked to medicines use in children. The collection of data on the use of medicines at country level could enable intercountry comparisons to be made over time in order to better understand the burden of childhood diseases within the EU and set priorities. The main challenges for a complete and comprehensive evaluation are the lack of systematic and continuous monitoring in all EU countries and the disparity between studies. To counter this, the methodological quality of data collection should be improved, and more multinational collaborative studies should be performed with EU support. Other essential studies include those that assess the effectiveness of interventions to improve treatment, and those that evaluate the impact of adherence-promoting interventions in children.<sup>12</sup>

In summary, to further improve the development and use of medicines in children, investments are needed to: stimulate additional research into the development of age-appropriate medicines; study the impact of formulations development and paediatric regulations on patient and public health outcomes; increase the efficiency of the Regulation with a focus on genuine paediatric needs; facilitate the collection, linkage and use of data on medicines use in children Europe-wide; and improve (information on) the rational use of medicines in children.

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## 7.2 Priority medicines for women

[See Background Paper 7.2 \(BP7\\_2Women.pdf\)](#)

Over recent decades, female health, and especially maternal health, has been one of the top priorities for both health care decision makers and health researchers. Women have particular medicine needs. Not only do they use specific medicines related to reproduction and pregnancy, but they also differ from men in their overall medicines use, pharmacokinetics and pharmacodynamics. The 2004 Priority Medicines Report identified a number of key priorities for R&D in order to meet the particular medicine needs of women. They included the need for: the inclusion of more women in clinical trials; appropriate risk management strategies to monitor the long-term effects of female medicine therapies; and the global collection of data on birth defects and on women's exposure to medicines during pregnancy.<sup>1</sup>

Some improvements in these areas have been observed over recent years. The most recent data (2007 to 2009) from the United States Food and Drug Administration (FDA) show that the participation of women in late-phase clinical trials was on average 44%.<sup>2</sup> Of the new drug applications, 74% included exploratory or confirmative gender-specific efficacy and safety analyses. In early-phase clinical trials the participation of women was slightly lower.<sup>3</sup> The need for gender-specific analyses was recently underlined when the FDA announced a recommendation to lower the dose for women of a medicine that had been on the market for decades.<sup>4</sup> According to an EMA review, the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) do address gender. In particular, ICH guidelines M4E and E3 require adequate demographic (including gender) characterization, analysis and assessment of the patient population.<sup>5</sup> The results of reviews and experience argue against stronger regulations and requirements for additional clinical trials, such as a separate ICH guideline on women as a special population in clinical trials. A better solution to obtain the necessary data would be to use existing (prescription or dispensing) data, especially since in many cases the need for knowledge relates to “old” medicines ([see Chapter 8.4](#)).

Therefore, use of existing data and the development of (innovative) methodological approaches for better use of existing data should be further explored. These data should be able to provide more insight into both the gender-specific benefit-risk profiles of medicines (also related to dosing), and the gender-specific underutilization of medicines. While the latter issue is of concern, with gender differences occurring, these are not consistently biased towards women.<sup>6,7</sup>

Many pregnancy registries have been set up in addition to the already existing birth defect registries. These registries should be further strengthened and collaboration encouraged between registries (for example, in a research network) in order to harmonize strategies and definitions and thereby enhance the pooling of data. Particular attention should be paid to: the potential effect on children of paternal medicines use; the potential long-term effects on children (such as fertility and behavioural problems) of maternal medicines use during pregnancy; the effects of medicines use on fertility and very early spontaneous abortion in women; and opportunities to collect data on medicines use during lactation.

The World Bank estimates that contraceptive use worldwide increased from 58.1% in 1990 to 62.2% in 2010.<sup>8</sup> In Europe, the two most popular forms of contraception among women are oral contraceptives (28%) and the male condom as a single method (17%), with the copper intrauterine device (5%) and other forms of hormonal contraception (such as implants and patches) being less popular.<sup>9</sup> Access to (emergency) contraceptives is a major challenge in many parts of the world, but this issue is beyond the scope of this report. Another major challenge is the need to strengthen informed decision making among women. Women, but also doctors and pharmacists, need to be better informed about (emergency) contraceptive measures. Improving knowledge and attitudes towards contraceptives requires better patient counselling and aids, especially for young women and women with comorbidities. Strategies need to be

developed and evaluated for their impact, not only on the level of knowledge but also on important health outcomes such as unintended pregnancy rates.

In summary, the main recommendations to improve medicines use in women are:

- Use existing (real-life) data to their full potential ([see Chapter 8.4](#)) to provide better insight into: the gender-specific benefit-risk profiles; underutilization of medicines; and (through the use of pregnancy registries) the effects on children of parenteral medicines use. These pregnancy registries should be further strengthened and collaboration encouraged between these registries (for example, in a research network).
- Strengthen informed decision making among women, especially related to (emergency) contraception, by improving knowledge and attitudes and development and evaluation of better patient counselling and aids.

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### 7.3 Priority medicines for the elderly

[See Background Paper 7.3 \(BP7\\_3Elderly.pdf\)](#)

People aged 60 years and older are a growing part of both European and global communities (see also Chapter 5 Figures 5.2.1 and 5.2.2). The proportion of the global population aged 60 years and over is projected to increase from 11% in 2010 to more than 16% in 2030.<sup>1</sup> In Europe, the growth of the elderly population is more pronounced, with an estimated proportion of 29% aged 60 and over by 2030. This rise poses challenges to health and social care systems. The incidence of diseases such as dementia, cancer and osteoporosis is increasing and the use of multiple medicines (polypharmacy) is common, often leading to medicine-related problems. In addition, the elderly reside in different care settings depending on the level of care needed – a trend that underlines the need for integration of care and for better self-management of medication. As with children, many medicines are prescribed off-label to the elderly. All of these issues require careful attention and analysis to guide future decision-making.

It is clear that the elderly often have difficulties with taking their medication, including opening packages, swallowing oral medication and/or reading leaflet information. For example, approximately 9% of people aged 65 years and up to 28% of people aged 85 years or over have problems with swallowing.<sup>2</sup> Since many of the difficulties that the elderly have with medicine formulations are similar to the problems seen in children (e.g. swallowing medication), alignment is needed with the development of formulations for children, taking into account the differences between the two populations. When adapted formulations are developed in the near future, it will be necessary to evaluate these to determine whether these products have indeed led to better health in the elderly.

The elderly are still underrepresented in randomized clinical trials (RCTs), with age and (perceived) frailty being the predominant reasons for exclusion. A recent systematic review showed that in 38.5% of RCTs, people aged 65 years and over were excluded and in 81.3% of the RCTs people with comorbidities were also excluded.<sup>3</sup> Furthermore, age and comorbidities were frequently categorized as poorly justified exclusion criteria (78.4% and 64.8%, respectively). There is a need to develop a consensus definition for frailty and tools to evaluate frailty, because these may enable the selection and inclusion of the elderly in RCTs as well as guide therapeutic decisions. Novel initiatives to increase the participation of the elderly in RCTs include the EU-funded development of a Charter in order to promote participation,<sup>4</sup> and the launch by the European Medicines Agency (EMA) of a geriatric medicines strategy<sup>5</sup> and the establishment of a Geriatric Expert Group. The geriatric medicines strategy promotes discussion concerning the anticipated effects of a medicine in geriatric patients, based on pharmacokinetics and other characteristics of the medicine. Investigation of population pharmacokinetics or specific pharmacokinetic studies (including those involving the very elderly) should be performed in order to recommend dose regimens

and identify patients at risk.<sup>6</sup> For these studies, modelling and simulation might be useful methods. The strategy recognizes the elderly as the main users of medicines and seeks to ensure that the development and evaluation of new medicines take into account specific safety and efficacy aspects related to ageing. In line with the recommendations for children and women, new approaches such as better use of electronic health records may be valuable in obtaining better data on medicine safety and effectiveness in the elderly ([see also Chapter 8.4](#)).

In addition, the strategy acknowledges the need to improve the availability of information for patients and prescribers on the use of medicines in the elderly.<sup>5</sup> A recent study demonstrated that, while important information is often available in the European Public Assessment Reports (EPARs), this information is not sufficiently reflected in the Summary of Product Characteristics (SPC). For 53 new medicines, a maximum of 19 items derived from the ICH E7 guideline for studies involving geriatric populations were scored per new medicine. Of these items, 79% were included in the EPAR compared with only 56% in the SPC.<sup>7</sup> Treatment guidelines appear to be more disease-driven than patient-centered, and specific guidance on the treatment of elderly patients is frequently lacking.<sup>8</sup> This may not only cause overuse but also underuse of medicines in this population. Approaches to translate age-specific information on the benefits and risks of medicines into practical recommendations, in the SPC and/or treatment guidelines, should be further explored. Research should also focus on how physicians obtain the information needed to adequately treat elderly in daily practice, and how this information is updated on a regular basis.

Polypharmacy is very common in the elderly and inappropriate prescribing is often related to this. Medication reviewing, e.g. by pharmacists, is a structured evaluation and reconciliation of a patient's medication and has become common practice in some countries. Although interventions to improve the appropriate use of polypharmacy lead to more appropriate prescribing and fewer medication-related problems, observed effects on important clinical outcomes such as hospital admissions or mortality are conflicting.<sup>9,10</sup> This may at least partly be explained by methodological challenges. Due to a lack of robust research in this area, the cost-effectiveness of medication reviewing has not yet been established.<sup>11</sup>

In order to facilitate appropriate prescribing and conduct medication reviewing more efficiently, there is a need to improve the supporting role of electronic health records. A computerized decision support system (CDSS) can be incorporated into a computerized physician order entry. When combined with other data such as laboratory values, this system can generate more advanced advice to provide clinical guidance that is based on clinical rules and aligned with treatment guidelines. These electronic solutions could make reviewing less time-consuming and help the reviewer to systematically select those patients who might benefit most from a review. In a hospital pharmacy in the Netherlands, the implementation of an alert system for adverse events involving medicines, with about 121 clinical rules, resulted in the selection of different patients and additional interventions performed by the pharmacist, compared with those of the conventional medication surveillance

method.<sup>12</sup> The hospital setting, with more shared data between health care professionals, could serve as an example for primary care. In addition, the added value of fast and extensive data sharing with the aid of computerized systems needs to be established.

Finally, the integration and continuity of care in elderly patients is essential, especially when an elderly patient is living with several co-existing diseases, as many are. A Cochrane Review of follow-up studies involving older patients admitted to hospital who underwent a comprehensive geriatric assessment (a multidimensional interdisciplinary approach), indicated that they were more likely to be alive and to live at home, and less likely to live in residential care, to experience deterioration or to die.<sup>13</sup> Similar approaches in other settings should be further explored. The elderly live in different care settings and each transfer introduces potential risks, such as the unintentional discontinuation of medicines or the re-prescribing of medication that was recently stopped. More extensive sharing of data could play a crucial role in preventing such errors. In addition, while effort is put into ensuring accurate medication taking (for example, through medication reviews), little effort is invested in ensuring effective communication between first and second-line care.<sup>14</sup> Better interface management, both at a policy level and the health care professional level, is therefore needed.

There is a current trend for the elderly to live independently for a longer period of time. However, medication management becomes more complex as they age. Many elderly people have cognitive, physical and/or visual difficulties that may hamper accurate medication management.<sup>15</sup> Tools have been developed to assess their ability to manage their medication at home, but further evaluation of these is needed.

In summary, improvement in the development and use of medicines in the elderly needs investments in:

- The development and evaluation of adapted formulations and packaging for the elderly and alignment with formulations for children where appropriate;
- Better use of electronic health records to obtain data on safety and effectiveness in the elderly, and approaches to translate age-specific information on the benefits and risks of medicines into practical age-specific recommendations;
- Evaluation of the (cost-)effectiveness of interventions to increase appropriate prescribing and use with a focus on important clinical outcomes;
- Approaches that support further integration of care, sharing of information and communication between health care professionals, and the role of electronic solutions, and other tools to assess and improve medication self-management among elderly people living independently in the community.

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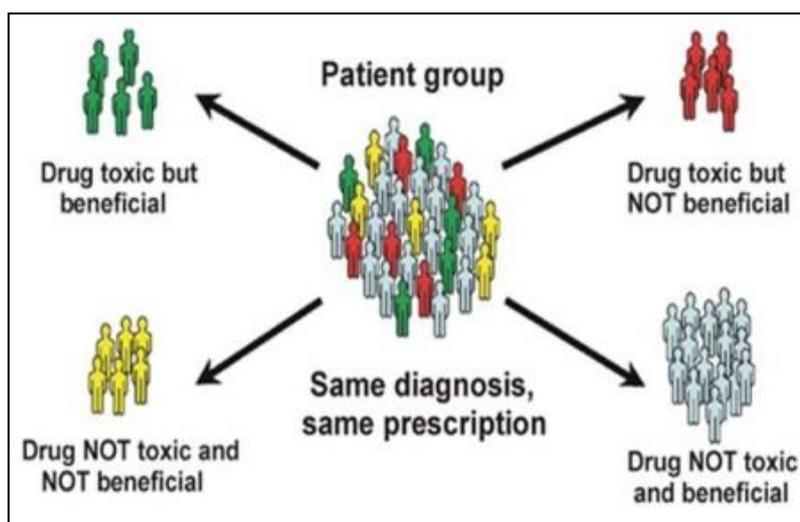
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## 7.4 Stratified medicine and pharmacogenomics

[See Background Paper 7.4 \(BP7\\_4Stratified.pdf\)](#)

Stratified medicine is a rapidly developing field that is likely to have an important impact on clinical practice in the coming decades. Personalized medicine has been defined as *'a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention'*.<sup>1</sup> However the term 'stratified medicine' is more accurate than the still popular term 'personalized medicine'. The term 'stratified medicine' reflects the realistic effects of medicines at population level, while the term 'personalized medicine' reflects the possibly overambitious promise of individualized unique drug targeting and development. The population approach aligns with the public health approach of this cross-cutting chapter and with the overall aim of the Priority Medicines Report.

Figure 7.4.1: The concept of stratified medicine.<sup>2</sup>



Source: <http://www.pharmainfo.net/reviews/role-pharmacogenomics-drug-development>.

Historically, human disease has been treated on a 'one-size-fits-all' basis. One medicine should suit all patients, and the choice of a medicine has been guided by evidence-based information, professional guidelines and a 'trial-and-error' approach. Without applying the concept of stratified medicine, a particular treatment is targeted to the whole patient group, without being able to predict the treatment response in patients. When a patient does not respond adequately to a prescribed medicine or shows substantial adverse drug reactions, the dosage can be adjusted or the medicine may be replaced by another medicine. The availability of genomic and non-genomic biomarkers and other characteristics may enable physicians to increasingly target treatment specifically to sub-populations of patients who are more likely to benefit

from a particular treatment or less likely to develop adverse drug reactions (see Figure 7.4.1). In this way, the benefit-risk profile of the medicine can be assessed per population stratum, and unnecessary (in case of non-response) or harmful (in case of toxic effects) use of medicines may be prevented. In this sense the other cross-cutting themes in this chapter (children, women and the elderly) are also examples of stratified medicine.

Pharmacogenomics study the influence of genomic variation on treatment response. Two successful pharmacogenomics examples include *HLA-B\*5701* genotyping and the risk of hypersensitivity to the antiretroviral treatment abacavir and HER2 testing in breast tumour biopsies and clinical response to the antineoplastic agent trastuzumab.

The first example illustrates the importance of stratified medicine for the safer use of existing medicines. Abacavir was approved in the late 1990s by regulatory authorities. It was well tolerated in the majority of patients, but caused a life-threatening hypersensitivity reaction in a small group of patients (5% to 8%). From 2001 onwards, there was increasing evidence for the relation between a genetic variation in the *HLA-B\*5701* gene and the risk of hypersensitivity to abacavir. Sales of abacavir-containing medicines subsequently declined. A shift took place after the development of a genetic test that was shown to be valid across patient populations (different regions and genetic ancestry) and have a very high negative predictive value, and the development of a skin patch test to immunologically confirm the genetic test. *HLA-B\*5701* testing was rapidly adopted by HIV practitioners and the test was incorporated in clinical guidelines.<sup>3</sup> Genetic testing of *HLA-B\*5701* kept abacavir on the market because it is now possible to target the drug to a patient population with almost no risk for developing the severe hypersensitivity reaction.

The second example is related to medicines effectiveness. Trastuzumab is used to block human epidermal growth factor receptor 2 (HER2). This protein is encoded by the *ERBB2* gene and the gene is overexpressed in approximately 15% to 30% of patients with breast cancer. Only patients with high levels of HER2 are likely to respond to trastuzumab.<sup>4</sup> Regulatory agencies have approved trastuzumab for the treatment of HER2 overexpressing breast cancer (and in other HER2-overexpressing carcinoma) and HER2 testing has been imbedded in clinical guidelines. The classic example of trastuzumab and HER2 highlights the potential of stratified medicine in the targeted use of expensive medicines, thus ensuring that (public) expenditures are not wasted on ineffective pharmaceutical care.

Despite these and similar examples, clinical implementation of stratified medicine has been limited. However, it holds promise for better and safer use of existing medicines in all settings, as well as for the identification of new medicines, drug targets and the development of innovative diagnostic tools. Science is shifting from monogenic (assessing one single gene, e.g. many orphan diseases) to polygenic (assessing multiple genes at the same time, e.g. many chronic diseases such as diabetes mellitus, cancer and depression) diseases and approaches. Pharmacogenomics is only one of the many -omics technologies that have emerged. All of these technologies (e.g. transcriptomics,

proteomics and metabonomics) hold promise, to a greater or lesser extent, to improve the prediction of the incidence and course of disease, phenotyping of disease and prediction of drug response.<sup>5</sup> This chapter focuses mainly on the role of pharmacogenomics in stratified medicine as this particular field has been most successfully translated into clinical practice in comparison to the other -omics fields. Although technologies develop rapidly and collaborations emerge, there remain major gaps related to the development, translation and implementation of this new knowledge.

Currently, stratified medicine mainly focuses on the development of new medicines, drug targets and diagnostics. This is also reflected in the guidelines of the different regulatory agencies on the use of pharmacogenetic methodologies in assessing drug pharmacokinetics, which primarily concentrate on medicines that are currently under development.<sup>6</sup> In addition, pharmaceutical companies may be less interested in assessing stratified medicine post-approval, due to pricing inflexibility and possible loss of market share.<sup>7</sup> Several genomics initiatives are emerging in low-resource settings, but stratified medicine approaches are still rare and should be encouraged.<sup>8</sup> In countries where resources are limited, stratified medicine could be very successful in ensuring that limited health care resources are used as efficiently as possible. In addition, efforts should be made to stimulate the use of stratified medicine in vulnerable groups. Research should be funded to allow biomarker-based prescribing during pregnancy and childhood.

It should be acknowledged that a large part of variability in treatment response cannot be explained by genomic variations.<sup>9</sup> Patient characteristics (such as age, gender, severity of disease), gene-environment interactions, patient compliance, and also epigenomic regulation and protein modification may also play an important role and should not be underestimated. Therefore, the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters should be stimulated.

Several scientific limitations currently hamper efforts to exploit the full potential of stratified medicine. For example, the lack of standardization of response outcomes, including adverse drug reactions complicates the comparability of studies.<sup>10</sup> Successful replication is generally low, and there is as yet no global or European pharmacogenomic database with a thorough inventory of available knowledge and biological specimens. A European catalogue of pharmacogenomic datasets and a harmonization programme should therefore be established. To validate pharmacogenomic findings, there is a need for replication studies in different cohorts and for harmonization of outcome measures. An electronic platform that will enable data sharing is therefore essential. Finally, a funded EU research network could function as a partner for the European Union in identifying opportunities in research, strengthening collaborations within Europe, contributing to standardization processes, and organizing educational and scientific conferences.

Ideally, medicines and diagnostics should be developed simultaneously and stratification of patients should be taken into account during the drug development process, market authorization and reimbursement procedures. However, in the EU introducing stratification prior to registration has been complicated due to the different regulatory frameworks for diagnostics and therapeutics. The EC recently submitted a proposal for a new regulation to replace the current Directive 98/79/EC on in vitro medical devices, which includes clinical genetic tests.<sup>11</sup> However, other regulatory guidelines and reimbursement procedures might need to be adapted. There is a need to align regulatory processes between different regulatory agencies, but also on the evidence required to assess clinical utility. A randomized clinical trial might not always be feasible because of ethical reasons, lack of resources or small populations. Clear guidelines are needed to assess when a randomized clinical trial is necessary in order to test a stratified medicine approach. Furthermore, an adaptive trial design, which enables the researcher to implement prior knowledge to optimize the remainder of the trial might be a cheaper and faster alternative to test observational findings.<sup>12</sup> Assessment of the added clinical value of a test or a marker calls for the development of a framework in which clinical utility and cost-effectiveness are assessed and compared to current clinical practice.

There is a need for a well-organized technology infrastructure, professional training and an internationally aligned ethical, legal and regulatory framework. At present, only a low proportion of health care providers have received training in stratified medicine and pharmacogenomics.<sup>13</sup> They should be better prepared for clinical decision making by having adequate knowledge about the medicines for which patients should be tested and how test outcomes should be interpreted and acted upon. Patients and the public need to be informed about stratified medicine in order to understand the possibilities and limitations of this approach. The new genomic era brings with it new ethical and social issues such as genomic data sharing, consent, ownership and liability.<sup>14</sup> These issues should be further studied in order to guide the implementation of stratified medicine in global health.

In summary, this chapter recommends investments in the following areas to further strengthen research in and knowledge of stratified medicine and pharmacogenomics:

- Stimulate pharmacogenomic approaches to existing drugs, with a particular emphasis on the use of stratified medicine approaches for vulnerable groups.
- Stimulate the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters.
- Establish a European research network and establish a European catalogue of pharmacogenomic datasets with a harmonization programme.
- Adapt regulatory guidelines and pricing and reimbursement procedures. For pricing and reimbursement, develop a framework in which clinical utility and the cost-effectiveness of new approaches are assessed and compared to current clinical practice (clinical added value) and, where needed, refined.
- Develop and evaluate harmonized training and education programmes, not only for researchers, but also for clinical specialists, pharmacists and the public.

- Investigate the ethical, legal, economic and social implications of stratified medicine.

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## 8. New approaches to promoting innovation

### 8.0 Introduction

Chapter 8 aims to provide an overview of the main tools that can stimulate pharmaceutical innovation with a focus on achieving public health objectives. The focus is in particular on those topics addressed in Chapter 8 of the 2004 Report (then titled “New Approaches to Promoting Innovation”). All topics from the 2004 Report are covered here, but the structure of this chapter is different and the scope has expanded. More specifically, a new section has been added on patient and citizen participation in priority setting. This topic was not a major part of the previous report, but there have been many developments in this area that warrant a separate section. Additionally, the focus on research priorities has been strengthened compared to the 2004 Report.

The structure of this chapter can be seen as the sequential steps from drug development to use in clinical practice. This approach has been chosen to highlight key developments in the field while not being exhaustive.

Chapter 8.1 focuses on public-private collaborations, a topic that has grown in importance since the previous report and which can assist in priority setting for early stage innovation, development and also systems improvement. Chapter 8.2 addresses the regulatory system related to market authorization and focuses on research priorities that can support current developments in the field. Chapter 8.3 on pricing and reimbursement policies has this same perspective: it identifies research priorities that can fuel current discussions about new tools and methods for setting pricing and reimbursement levels that recognize and incentivize innovation. Chapter 8.4 focuses on the opportunities that exist in the area of electronic health records (EHR) to capture the use of medicines and outcomes in clinical practice. With the increasing use of databases and new tools for analysis, this is an especially promising area that will impact on all areas covered in Chapters 6, 7 and 8.

Finally, Chapter 8.5 addresses the role of patients and citizens in priority setting. Although ways in which patients and citizens can play an optimal role in priority setting are still being explored, the movement towards more patient and citizen involvement is strongly supported. It is, however, still a field in which several research questions need to be answered.

It should be emphasized that there are many cross-links between the sections in Chapter 8 (for example, real-life data plays an increasingly important role in drug development, regulation, and pricing and reimbursement) and other chapters of this report (e.g. different disease areas in Chapter 6). Therefore, they should be viewed in conjunction. In several places these cross-links have been highlighted.

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### 8.1 Public-Private Partnerships and innovation

[See Background Paper 8.1 \(BP8\\_1PPPs.pdf\)](#)

In the 2004 Report, public-private partnerships (PPPs) were identified as a promising solution for addressing challenges in pharmaceutical innovation. Since then, there has been considerable progress in the development of PPPs and in particular in the product development partnerships (PDPs). The current challenges in drug development require the mobilization of significant resources from a wide variety of stakeholders, PPPs can help facilitate this process and capitalize on the benefits of new approaches such as ‘open innovation’.<sup>1</sup>

Public-private partnership can be defined as any informal or formal arrangement between one or more public sector entities and one or more private sector entities created in order to achieve a public health objective or to produce a health-related product or service for the public good. In a PPP, the partners share certain risks and may exchange intellectual property, financial, in-kind, and/or human resources in any mutually agreed upon proportion.

There are several reasons for establishing PPPs. They include the need to:

- Increase scale: pooling of resources can help to address issues that cannot be addressed by a single entity (for example, because the knowledge or expertise that is needed to answer a question is not available in a single company or institute, or the scale of the activities required is too large).
- Share risk: by sharing risks (for example, through government involvement), projects can become of interest to potential partners who, without a subsidy or support, would be unwilling to get involved. An example of such a project would be the repurposing of existing drugs.<sup>2</sup>
- Focus R&D priorities: by defining a strategic research agenda, in consultation with stakeholders, resources can be focused on issues of particular public health interest.
- Optimize the use of available knowledge and resources: in order to make progress in many areas, there is a need to bring together data or expertise that resides with different parties. In addition, PPPs can be used to create a research infrastructure for future work (networks, biobanks, research databases etc.) Research on the performance of PDPs for neglected diseases showed that industry working alone and public groups working alone performed less effectively overall than public-private collaborations.<sup>3</sup>

- Foster a more competitive private sector to promote economic growth: governments that support PPP research may also aim to support new R&D activities within their region or country. In this way, PPPs can both address a medical need and help generate new forms of economic activity. Therefore, PPPs are an important factor for innovation and business models in the life sciences (such as the 'open innovation' paradigm<sup>4</sup>).
- Address topics that require a neutral/multi-stakeholder environment: to make progress on some issues, a neutral environment has to be created.<sup>1</sup>A partly publicly-funded consortium can be an appropriate vehicle for this. An example would be topics in the regulatory arena in which regulatory authorities (should) play a role, but where input from industry is also needed.

Against this background, different types of PPPs can be identified, based on their focus on different parts of the medicines development pipeline:

**Research partnerships:** supporting (early stage) innovation or creating technology platforms in high priority disease areas. Examples of this type at the EU level are: the Top Institute (TI) Pharma in the Netherlands, which was launched in 2006 with total funding of €260 million and which has used the 2004 Priority Medicines Report as the foundation for its research programme; and the Innovative Medicines Initiative (IMI), which was launched in 2008 with total funding of €2 billion. Both these examples are discussed in more detail in Background Paper 8.1. This type of PPP is a relatively new model for collaboration in the development of medicines. All such partnerships face a challenge in that funding time-lines are often short and it can take a long time (5 to 10 years or more) to see the impact that such research partnerships can have on the development of drugs or diagnostics that reach patients. Efforts will be needed to reconcile the issue of long-term funding commitments if these partnerships are to fulfil their great potential. This means that evaluating intermediate outcomes is of critical importance. For those projects that focus on tools and method development, intermediate outcomes should be identified that fit this goal.

**Product development:** focus product development activities on concrete products, in many cases to address diseases that occur mainly in low- and middle-income countries. Examples in this area are the Medicines for Malaria Venture (MMV), the Foundation for Innovative New Diagnostics (FIND) and the Drugs for Neglected Diseases initiative (DNDi).

Partnerships concentrating on the development of medicines and diagnostics for tuberculosis and neglected tropical diseases (including malaria) have had considerable success. While the 2004 Report warned that these partnerships may face challenges in relation to the sustainability of funding, the current outlook for many of these PDPs is reasonable, despite the impact of the financial crisis.

**Concept development and overall systems strategy:** PPPs can also play an important role in overall discussions and contribute to systems reform. Many broader issues in pricing, market authorization or sustainable models for innovation can only be

addressed in projects that involve all stakeholders. Such 'system innovation' projects, appear promising and should be further monitored and expanded. These kinds of projects could potentially have a broader scope and also involve global players (e.g. the EU, Japan, the United States and emerging market economies).

There are several additional forms of public-private collaboration, such as Public Supply Partnerships. However, these are not discussed here as they fall outside of the scope of this report.

PPPs face a number of challenges, irrespective of their overall goal. These are more prominent for PPPs involved in research partnerships such as the IMI and TI Pharma as experience in this area is more limited.

These challenges include:

- Time-lines and sustainability: PPPs generally receive tranches of funding for a three to five year period. In view of the long time-lines in drug development, this amount of time may be insufficient to achieve the development of new compounds and targets.
- The role of small and medium-sized enterprises (SMEs) and large companies: the need to ensure the appropriate engagement of SMEs is especially important in efforts to achieve economic targets (e.g. nurturing new companies, job creation). The conditions for the participation of SMEs differ from those for large pharmaceutical companies or academic institutions. This aspect of economic development is important to the EU and many other countries.
- Consortium leadership and project management: managing partnerships requires a different set of competences and skills than managing regular research projects. Capacity building for this skill-set is of critical importance for the success of any PPP.
- The role of the central entity: a well-functioning central entity or 'office' is essential for any PPP. This can play a role as a neutral entity, trusted third party or honest broker.<sup>4</sup> An appropriate and balanced role for the central entity is also critical in building and maintaining trust in the PPP from participants and society as a whole.
- Intellectual Property (IP) structure: the goal of many PPPs is to generate innovative insights into diseases and their diagnosis or treatment. This means that the way intellectual property is handled in the consortium is of key importance and provides an important reason for partners to participate or not.
- Performance measurement: one of the major challenges for partnerships is to measure the added value that the partnership provides. This is important for public funders, companies, and academia from the perspective of the efficient and responsible allocation of their different resources.<sup>5, 6</sup> There is currently a requirement for investments in this area.

For future research, there is a need to learn more about what are the most successful models for PPP collaboration. This is an area where industry, governments and academia have much to contribute, in particular by the sharing of information and

experience. Knowledge about what are the most useful indicators (structural, process, output or outcome) of successful partnerships would be beneficial for all those involved.

The growth of knowledge about what constitutes a successful partnership (apart from better prioritization) will help facilitate more realistic assessment of what can be achieved within a given time-frame with the resources invested.

Another area for research is the important issue of stakeholder involvement in PPPs and how patients and citizens can best be involved in the decision-making process. Chapter 8.5 contains a number of research recommendations that are also relevant for PPPs: build models or frameworks for meaningful patient and citizen involvement, research methods for capacity building and assure standard indicators for assessment of initiatives that involve patients and citizens.

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## 8.2 Regulatory structures to support pharmaceutical innovation

[See Background Paper 8.2 \(BP8\\_2regulatory.pdf\)](#)

The regulatory system for market authorization is a critical factor in the development of new medicines. This system has to take into consideration the protection of public health while, at the same time, ensuring that patients have timely access to medicines including those that address unmet medical needs. Overall, the system has been successful in ensuring that many valuable medicines with a positive benefit-risk profile have reached the market. However, there are important challenges to be met if the

regulatory system is to ensure a continuous flow of the new medicines most needed by society.

In order to function optimally the regulatory system has to find the right balance in three key areas:

- Cautiousness: It can be overly or insufficiently cautious, for example, by not granting marketing approval for a medicine with a favourable benefit-risk profile or by allowing unsafe or ineffective medicines on the market).
- Incentive structure: It can lack incentives for pharmaceutical innovation, or incentivize innovations that do not address public health needs.
- Comprehensiveness: It can add undue regulatory burden through redundant regulation or have regulatory gaps.

This search for the right balance is especially pertinent in the 'adaptive' approaches to marketing authorization that have been proposed and discussed since the 2004 Report. Such approaches are known under various names (including staggered approval, adaptive approval, progressive authorization and adaptive licensing) and have been proposed by key opinion leaders in the EU and the United States.<sup>1,2</sup> These adaptive approaches are all based on the premise that knowledge about medicines is not binary but continues to evolve over time. The proposal is to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation. The use of adaptive approaches, which also incorporate elements of existing pathways, should be seen as a holistic option in the future regulatory system.

Although the concept of adaptive approaches is attractive, these approaches face a number of challenges. For example, when medicines are initially approved for a restricted population (based on specific evidence for this subpopulation), the process of appropriately defining, targeting and learning from this population during the initial phases would require efforts to monitor the utilization of medicines as well as interventions to ensure their appropriate use, including patient adherence. These actions would need to be strong enough to influence the behaviour of actors such as patients, pharmacists and physicians, and provide sufficient information for policy makers.

The 2004 Report emphasized that *"every aspect of the regulatory process should be re-examined" and that "the evidence base for regulatory practices should be critically analysed using modern methodologies."*<sup>3</sup> Over recent years, numerous studies have been conducted on different elements of the regulatory system such as evidence generation for initial marketing approval and the benefit-risk assessment. In addition, various new trial designs and analysis techniques are being piloted. Meanwhile, initiatives such as NEWDIGS<sup>4</sup>, CASMI<sup>5</sup> and The Escher Project<sup>6</sup> have created networks for analysis of regulatory practices and information sharing in Europe (see Background Paper 8.2).

Another issue that was highlighted in the 2004 Report was the need for communication between stakeholders. An overview of recent discussions shows that this field has

progressed considerably in recent years. For example, there is now widespread interest in how regulators and industry can further improve communication and most productively engage in an early dialogue in the drug development process and in how changes in regulations impact on product development.

The 2004 Report highlighted two weaknesses in the regulatory process: the critical role of patients and the need for an increased focus on post-marketing activities. Various regulatory authorities now accept the changing role of patients and that they should be involved in the regulatory process. However, more information is needed about what patients can add at the different stages of decision making. In addition, the optimal tools for patient involvement have not yet been identified (see Chapter 8.5 and the related Background Paper). With regard to post-marketing activities, the strengthening of the pharmacovigilance legislation and discussion about adaptive licensing are important drivers for an increasing role for post-marketing studies. While 10 years ago it was not uncommon for important policy documents to exclude the post-marketing phase, today this is rarely seen, and the role of post-marketing (safety) surveillance is well entrenched. Nevertheless, there are still important challenges, such as the post-marketing surveillance for medicines used exclusively in low- and middle-income countries (e.g. antiretroviral medicines for children or new antimalarials). Less well established is the role of post-marketing effectiveness evaluation. As such, the appropriate use of real-life data ([see Chapter 8.4](#)) is critical for the future.

Although these changes are welcome, a number of key priorities for research have been identified. In particular, tools are needed to: enable regulators to release medicines on to the market with confidence, including in cases where more limited evidence is available than is customary at the market authorization stage; and to collect and analyse evidence proactively over time after release. In an adaptive approach, a medicine's regulatory status (authorization and indication) is likely to change over time. This could have implications for pricing and reimbursement decisions, especially when value-based pricing is fully implemented.

In line with this, when the 2004 Report was published, the traditional randomized controlled trial was still seen as the gold standard for measuring efficacy. In 2013, this is increasingly being challenged, based on the need to move from efficacy based on limited clinical trials to real-world effectiveness, with broadening of indications, repurposing of medicines and demands for comparative effectiveness data. There is a clear need for more research in this area.

### *Research priorities*

Four research priorities have been identified:

#### **Continue to develop and pilot new methods for evidence generation and benefit-risk assessment**

Additional research is needed on alternative instruments (such as the use of surrogate and other clinical outcome measures and adaptive study designs) to optimize regulatory requirements for initial marketing approval. In addition, the increased use of post-marketing observational studies for effectiveness and safety should be explored. In line with the adaptive licensing proposals, effectiveness studies would also be needed to make better assessments for the (future) real-world effectiveness of medicines under development based on trial efficacy. Improving this kind of learning could help to achieve an adequate level of (safety and efficacy) knowledge while requiring less data to be collected before the medicines are approved.

In addition, various collaborative initiatives have been proposed in order to develop more structured benefit-risk assessments, based on qualitative and quantitative instruments. The aim is to increase the consistency and transparency of benefit-risk assessments and thereby the predictability of the marketing authorization procedure. Examples of collaborative initiatives are the Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative of the Centre for Innovation in Regulatory Science (CIRS),<sup>7</sup> the IMI PROTECT work package on benefit-risk integration and representation<sup>8</sup> and EMA's Benefit Risk Methodology Project.<sup>9</sup> However, as with the proposals for adaptive evidence requirements, introducing structured qualitative and quantitative instruments for benefit-risk assessment requires substantial changes in a regulator's way of decision-making and in the way companies prepare submission documents. At present, little evidence exists as to how quantitative instruments affect the quality of regulatory decision-making or public health. Additional field studies should identify practical limitations and test optimal ways of data visualization. In addition, these field studies of quantitative benefit-risk instruments could gain insight into uncertainties in benefit-risk assessments and demonstrate how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real-world data would affect the balance.

#### **Clearly identify expectations and key performance indicators for new regulations and set up prospective studies**

Measuring the success and cost (-effectiveness) of regulatory policies is often difficult. In order to evaluate and improve existing regulations and to base new incentives on best practices, expectations should be made explicit and performance indicators should be defined and reported on.

European Union regulatory incentives for pharmaceutical innovation for special disease areas, special populations and special products may not always take into account all the factors involved in successfully bringing a medicine to the market. In

the case of the orphan drug regulation the market exclusivity incentive has, without doubt, yielded an increase in the number of potential drug candidates for rare diseases. However, some instruments, such as free protocol assistance, may not be a key driver for generating more innovative medicines. Other incentives, such as the significant investments by governments in research into rare diseases, or the market exclusivity period may play a far more important role. The paediatric regulation could be looked at in a similar manner. Future research could establish which incentives provide added value from a societal perspective and help to achieve public health goals.

The 2012 EU pharmacovigilance legislation will enforce post-marketing obligations and complement the current conditional approval regulation. In implementing the newly established pharmacovigilance legislation, European regulators explicitly defined measures of impact such as change of behaviour in prescribing, dispensing and consumption and outcomes such as mortality, morbidity and quality of life. Formulating expectations by qualitative and quantitative performance indicators, and monitoring them through carefully designed studies could stimulate timely adjustments in the regulations and provide evidence for new policies. For this purpose, the effective use of electronic health record (EHR) databases and real-life data is of critical importance ([see also Chapter 8.4](#)).

### **Establish constructive collaborations and dialogues with key actors**

Many actors are involved in the marketing authorization of medicines. Collaboration and dialogue between all these parties is essential for an effective regulatory process and should be supported at multiple levels. Creating such dialogues and collaborations is not easy. Often, it is not part of the tradition of the parties involved. As a result, different actors speak different languages.

First, both regulators and pharmaceutical companies should be encouraged to have a dialogue at an early stage of drug development (e.g. in the preclinical phase or during Phase I), especially for those products using innovative approaches for development. Scientific advice is one of the key tools for this.

Second, involving Health Technology Assessment and Pricing and Reimbursement bodies in such a scientific dialogue is important to harmonize requirements and post-marketing authorization obligations.

Third, involving patients and prescribers could better adjust benefit-risk assessment to their preferences or risk perceptions. Although networks of patients have been established (e.g. in the EMA Patients and Consumers Working Party), there is a need to determine how patients can most effectively contribute to decision making. At present, little is known about how best to involve patients in decision making and at what stage they can most effectively contribute ([see Chapter 8.5](#)).

### Invest in sharing and analysis of regulatory datasets for system evaluation

In order to support evidence-based improvements of the regulatory system and to test and explore new methods for drug development and regulatory decision-making, close collaboration is needed between regulatory agencies and academia, as well as input from companies.<sup>10</sup> For the purpose of regulatory science, regulatory databases should be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper.

The EMA publishes the European Assessment Reports of approved, non-approved and withdrawn products on its web site. Although to some extent this offers the opportunity to evaluate previous marketing authorization procedures, certain informative documents that could add to the learning process, such as the objections made during the marketing authorization procedure, also provide insight into the priorities and perspectives of the regulator. More detailed data on outcome measures and confidence intervals are also needed in order to validate quantitative benefit-risk instruments.

Regulations play a critical role in balancing people's expectations for new medicines to address unmet medical needs against the need to ensure that medicines are efficacious and have a positive benefit-risk ratio. For regulators and companies to adapt to a changing world, research on the regulatory process is needed.

In conclusion, there has been real progress since 2004, which has created controversies and challenges, but regulators have shown willingness to be involved in stimulating innovation. Regulatory science has not been a research priority, but many forms of drug innovation need to be supported by research in regulatory science in order to be able to move forward in the most effective way.

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### 8.3 Pricing and reimbursement

[See Background Paper 8.3 \(BP8\\_3Pricing.pdf\)](#)

Many European countries share the health policy objectives of sustainability, equity and quality of care<sup>1</sup>, but the way in which these are handled can differ substantially between countries.<sup>2</sup> Pricing and reimbursement policies used in the EU include: external price referencing (international price benchmarking); internal reference pricing; decision making based on Health Technology Assessment (HTA) and economic evaluations; value-based pricing; caps and co-payments; taxes; price-volume agreements; fixed margins in distribution channels; and tendering. The impact of these policies on the price of medicines, the availability of and access to medicines, and pharmaceutical expenditure vary. In some cases, these policies can have adverse effects, such as creating shortages or inappropriate incentives. In other cases, more efficient allocation of resources can create “headroom for innovation” by allowing budget savings elsewhere to be invested in innovative medicines that address medical needs. Although an individual European country’s pricing and reimbursement policies may not have a major influence on the global pharmaceutical industry, the combined European pharmaceutical market ranks second only to that of the United States. Therefore, the joint or shared policies of European countries help shape the global landscape for pharmaceutical R&D. However, it is important to note that the balance is shifting rapidly. Between 2011 and 2016 the combined market of Brazil, China, India and Russia will, for the first time, overtake the traditional EU5 markets (France, Germany, Italy, Spain and the United Kingdom).<sup>3</sup>

In most OECD countries, the government has the main role in decision-making regarding the pricing and reimbursement of medicines. Within the EU, pricing and reimbursement decisions are prerogatives of the Member States. However, rules and regulations at the EU level (mainly regarding transparency and the free movement of goods) also influence pricing and reimbursement policies at the Member State level. In

general, three key strategies are open to governments to control costs and reward innovation for marketed medicines: managing price; determining which products will be reimbursed; and managing volumes (as determined by prescribing and dispensing). Policies of the EU and Member States have to address a number of interacting and sometimes conflicting elements that are inherent in the health care system. These include:

### *Incentives for innovation - controlling costs*

Pharmaceutical companies are provided with a period of market exclusivity (mostly due to patent protection and in EU also due to data exclusivity) whereby R&D investments can be recouped and additional profit made, which in turn can be reinvested in the development of future medicines. Coverage and reimbursement policies are critical factors in the reward of innovation.<sup>4</sup> At the same time, increases in health care expenditures often exceed economic growth in the EU and need to be managed to avoid becoming unsustainable.<sup>5</sup> What constitutes a fair 'premium price' for a new medicine, therefore, is a crucial element in any pricing policy that seeks to reward innovation.

### *Role of the EU - role of Member States*

The EU Transparency Directive, for which the European Commission proposed a revision in 2012, provides a common procedural framework for pricing and reimbursement decisions, notably with regard to the time-frame for decision-making and how decisions should be communicated. The Transparency Directive explicitly states that the decision-making process itself is and shall remain a responsibility of the Member States. At the same time, a number of European countries cooperate through networks such as the EU-supported EUnetHTA and increasingly exchange knowledge and information regarding the assessment of data that can inform reimbursement decision-making. For example, EUnetHTA is currently exploring a common 'Core Model' for the assessment of new medicines seeking reimbursement in EU Member States.

### *Medicinal products – health care services*

The way in which medicines are priced and reimbursed can influence the use of medicines and the uptake of innovations. Furthermore, in many cases the incomes of health care providers (in particular pharmacists) are linked to discounts, rebates and dispensing fees. This can have a positive impact, by creating the right incentives for rational use of medicines, but it can also have adverse effects by creating a stimulus for inappropriate use of medicines, or create a threat to the economic sustainability of health care providers (e.g. if incomes are linked to certain margins on products, and these margins are excessively reduced).

### *Influence of policies on other Member States*

Policies in one Member State can influence those in another. For example, pricing policies in one country can have an impact on parallel trade or external price referencing (see Background Paper 8.3).

### *Current trends*

The 2004 Priority Medicines Report highlighted differential pricing as a key policy for the future and also put a strong emphasis on pharmacoeconomics as a tool to value new medicines. Since then, more European countries have incorporated HTA and economic evaluations in their reimbursement and sometimes in their pricing policies.<sup>6</sup>

However, in most of Europe external price referencing remains the predominant pricing policy, being used by 24 out of 27 Member States (although the exact implementation and the basket of reference countries varies). An alternative to external price referencing is value-based pricing, in which the price of a new medicine is determined by the (added) value it generates, using cost-effectiveness as the main criterion to determine the price. At present, this pricing policy is only used in Sweden according to the narrow definition of value-based pricing used in the corresponding background paper to this chapter, though other countries do include cost-effectiveness in the price negotiation process. The United Kingdom is planning to implement value-based pricing for new medicines in 2014, and many countries have already implemented 'value-based' elements in their decision-making.

In recent years, European countries have implemented a number of measures to capture the potential value, in terms of cost savings, created by patent expiration leading to the subsequent market entry of generic medicines stimulating their appropriate use. Yet, in many European countries opportunities still exist to either speed up generic entry, increase generic consumption and/or lower the prices of generic medicines, as substantial differences remain in generic entry, uptake and prices, compared, for example, with the United States.<sup>7</sup> Savings could create "headroom for innovation" and partly be used to facilitate uptake of, or rewards for, innovative medicines. But explicitly linking generic uptake to rewards for innovation in policy practice can be challenging.

Another important development since the publication of the 2004 Report is the increasing role played by networks such as EUnetHTA, Competent Authorities on Pricing and Reimbursement (CAPR) and Pharmaceutical Pricing and Reimbursement Information (PPRI) in informing and collaborating in the discussions between Member States about methods used for pricing and reimbursement decision-making and exchanging information. In addition, little information is available about various aspects of health care systems, such as prices in hospitals; these areas are still a "black box" from a research perspective. Furthermore, discounts and rebates of medicine prices are widespread and are often held to be confidential.<sup>8</sup> As a result, the list prices of medicines in most EU countries do not reflect the actual prices. Although

confidential discounts and rebates hinder the potential for savings through external price referencing, they are the only tool through which lower-income countries can negotiate lower *actual* prices. Due to the existence of parallel trade within Europe and the widespread use of external price referencing, there is limited incentive for companies to offer lower prices to lower-income countries when this would subsequently decrease prices (through external price referencing) or lost sales (through parallel trade) in other European markets. Companies frequently offer confidential discounts or rebates to get around this issue.

In order to align the health policy objectives of sustainability, equity, and quality of care with the continued reward for pharmaceutical innovation, countries have tended to move towards pricing and reimbursement practices that are adapted to three distinct categories of medicines:

- Patent-protected medicines, primarily those with high volumes: value-based pricing, possibly with (confidential) discounts and rebates for differential pricing and/or with price-volume agreements;
- Low-volume medicines (including patented and off patent medicines and medicines for rare diseases as well as stratified disease medicines): price-volume agreements that reward innovation, possibly with (confidential) discounts and rebates for differential pricing;
- Generics: competition (including tenders) with price transparency. When tenders are used, sustaining a competitive market with multiple players should be a focus. However, this principle may not be applicable for all off-patent medicines (e.g. biosimilars).

### *Research priorities*

The research priorities identified include studies that focus on the broader environment of pricing and reimbursement policies and the specific 'tools' that are used. In addition, in order to conduct these studies there is a critical need for cross-country learning, co-development of methodology and exchange of information and experiences. To achieve these objectives, it is essential to build an appropriate research infrastructure, including a research network.

Priority research is recommended in the following areas:

### *Policy environment:*

- The meaning of innovation for pricing and reimbursement authorities: what do the various stakeholders perceive as innovation? A particular topic for research is how this relates to (cross-country) willingness to pay to reward innovation.
- The impact of the current financial crisis in Europe on issues such as access and availability; consumption volumes (particularly generics use) and the price of medicines; tax levels; co-payments; and coverage decisions.

- The effects of newly implemented pricing and reimbursement policies and regulations (such as an updated Transparency Directive) and, in particular, the effects that they have on time to market entry for medicines and on innovation.
- Issues surrounding delays to entry should also be seen in the light of potential market entry strategies by pharmaceutical companies due to external price referencing. The interaction between price referencing policies and marketing strategies of companies (and impact on patient access) should be studied.
- The extent to which pricing and availability issues are related at the global level. In particular, information is needed about the differences between public and private sector channels and the different price components. Creating high quality longitudinal datasets in this area could help to study trends and the impact of policy.

### *Methods and tools:*

- The effects of external price referencing (EPR) and the effects of parallel trade. Although EPR is still a widely used method, little is known about the potential adverse effects of these policies in Europe and at the global level (such as how it relates to equity, access and possibilities for differential pricing in Europe). Some studies indicate, for example, that EPR may have negative effects for 'low price' countries.<sup>9</sup> The results of any ongoing study should be taken into account. Value-based pricing: evaluate experiences, compare methods, share experiences, assess resource requirements and how societal values can be included. Further studies should focus on how experiments in value-based pricing interact with other aspects of pricing practices (such as parallel trade or external reference pricing).
- Differential pricing mechanisms and policies. At present, the pricing of medicines at a 'formal' level (official list prices) does not reflect differential pricing achieved through rebates and discounts. Case studies may be needed to further elucidate the actual end user prices between and within countries.
- The impact of policies including generic entry and managed entry practices. At present, experiments are taking place with various generic policies such as tendering and price-volume agreements. In many instances, these policies have been successful in driving down prices. However, these policies can also have adverse effects on availability as well as on pharmacies and dispensers (for example, shortages are threatening the economic viability of pharmacies).
- Pricing and reimbursement policies in areas with small volumes, such as orphan diseases and stratified medicines (see Background Paper 7.4). Although tools such as value-based pricing could also be used in this field, the special conditions on the market (high medical needs, small volumes) require specific policies and tools. As orphan and stratified medicines will become more prominent in coming years, further research in this area (e.g. on experiences and best practices) will be needed.
- How patients can best be involved in pricing and reimbursement decision-making (see Chapter 8.5 and the related Background Paper for additional research priorities). Where patients are already involved the impact needs to be assessed (e.g. in Malta and the United Kingdom).

### *Research network:*

For the above recommendations to be successful, it is critical to build and support a research infrastructure that is able to create a research network that links all stakeholders and existing networks such as EUnetHTA, CAPR and PPRI with international organizations such as Health Action International (HAI), the WHO and the World Bank (especially for networks between the EU and low- and middle-income countries). Existing networks such as EUnetHTA and the PPRI network could also provide a basis for future networks (e.g. by adding a more explicit academic component), and make important contributions to the development of methodology, such as generalizability and transferability of economic evaluations. While such networks may appear costly they build on the strengths of the European Union to share and develop knowledge.

In conclusion, one of the major challenges in government policies relating to medicines is how to align the need to control health care expenditures, with creating incentives for innovation that addresses public health needs. In recent years, there have been a large number of developments in this area. For the coming years, this will require efforts to carefully weigh and evaluate the different tools that are available, refine methodologies and assess the impact on medicine use and innovation. This will require significant investments and the involvement of all stakeholders. Sometimes this will lead to the discovery of uncomfortable truths and a need to accommodate strongly divergent points of view. However, the development and implementation of policies that can make an innovative and sustainable pharmaceutical market a reality will bring substantial benefits for patients, governments, companies and payers.

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### 8.4 Real-life data and learning from practice to advance innovation

[See Background Paper 8.4 \(BP8\\_4Data.pdf\)](#)

The costs of pharmaceutical R&D are high, with clinical trials being a major component of these development costs. At the same time, there is an urgent need to address therapeutic gaps in order to be able to respond to unmet medical needs. To help resolve this problem, there is a need to increase efficiency and to bridge bench and clinical research with real-world practice. Data obtained from health information systems can be used to support innovation, detect safety problems and assess the real-world effectiveness of medicines. These data are now more widely available than ever before and offer new opportunities for research and health systems development. Policy initiatives such as adaptive licensing, value-based pricing and comparative effectiveness studies are critically dependent on the efficient use of electronic health record (EHR) data. However, the resources available in Europe are fragmented, and good quality data are often only available for limited disease areas or geographic regions.

In the 2004 Priority Medicines Report, the use of electronic health records was highlighted as an area of high importance. It was suggested as “*a way of creating post-marketing ‘randomized epidemiology’ studies to better understand comparative effectiveness and cost-effectiveness.*”<sup>1</sup> Although progress has been made since then the potential is still largely unfulfilled.

Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings. Clinical trials are typically conducted according to a well-defined set of regulations, guidelines and ethical criteria. As a result, strict inclusion/exclusion criteria exist, based on age, gender, comorbidity and geographical location. This con-

trasts with medicine use in the 'real world'. Here, the patient mix may differ greatly from the clinical trial population. For example, the main trials for selective COX-2 inhibitors such as rofecoxib and celecoxib were on patients with severe osteoarthritis or rheumatoid arthritis and aimed at long-term use (six to nine months). However, the majority of patients who were prescribed these medicines in clinical practice did not have these diseases. In addition, the duration of use was shorter and the daily doses were about one-third of those used in the clinical trial setting.<sup>2</sup>

Meanwhile, various aspects that are not included in the trial setting play an important role in the real world. One of the key influences on real-life effectiveness is adherence and persistence. For example, in the pivotal trial of alendronate for treating osteoporosis, 89% of study participants were still using the medicine after three years.<sup>3</sup> However, in a real life setting, after the same period only about 35% of patients were still using the medicine.<sup>4</sup> These realities raise important questions about the external validity of trial results, and account for what is described as the gap between 'efficacy' (the trial effects of medicines) and 'effectiveness' (the real-world effects of medicines).

### *Potential value of electronic health records (EHRs)*

Today, electronic health records (EHRs) are an increasingly important source of information to capture the real-world setting. Electronic health records can be defined as a "longitudinal collection of electronic health information about individual patients and populations."<sup>5</sup> This includes information about diagnosis (e.g. laboratory tests), treatment (e.g. dispensing of medicines) and outcomes of patients (e.g. hospitalization and mortality). For some research purposes, these data can be linked to other non-health datasets (e.g. data about employment or socio-economic information) to generate a comprehensive picture.

Real-life data on medicine use at the patient level first became available during the 1980s when administrative information about medicine use and health system activities was first stored at a significant level. Over recent decades, innovation in information technology (IT) infrastructure and capabilities and methodological refinements have played an important role in the increasing capabilities and potential of using real-life data to answer questions relevant for innovation.

Historically, EHR databases have played a key role in evaluating drug safety. A more recent development in this area is the increasing use of EHR databases for pharmacogenetic research. This could, for instance, assist in the development of a stratified medicine approach by identifying populations at highest risk for adverse effects.<sup>6</sup> EHR databases can also be used for finding novel relationships between diseases, re-evaluating medicine usage and discovering phenotype-genotype associations. As EHR databases and related methodology become more refined, this will be of increasing importance for drug discovery and development (e.g. by facilitating adaptive licensing and other approaches to speed up drug development).<sup>7</sup> Adaptive licensing is being considered as a model that allows step-wise authorization of medicines, with iterative phases of data gathering and regulatory evaluation. More

focused pre-authorization studies could be followed by larger point-of-care trials that collect outcomes which can be routinely obtained using EHRs.

EHR databases are routinely used to measure the uptake and outcomes of medicine use. In various studies using different data sources and in different health care settings, the lost opportunity from non-adherence is well described (see also alendronate example described above).<sup>8</sup> EHRs can help identify where problems are located and thus can provide leads for innovation (e.g. for new dosing forms and formulations) and can fuel powerful tools to predict long-term risk of disease. An example is the QRISK score, which predicts the 10-year risk of cardiovascular disease.<sup>9</sup> Risk scores such as these can be implemented in treatment guidelines (as is done in the United Kingdom for statins).

Another major potential of EHR databases lies in facilitating research in the area of comparative effectiveness or relative effectiveness, defined as *“the extent to which an intervention does more good than harm compared to one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice.”*<sup>10</sup> EHR methods can provide valuable and extremely cost-effective tools to assess relative effectiveness. A properly performed trial using real-life data may provide a far better estimate of actual effectiveness than efficacy derived from pre-approval clinical trials, especially when these trials lack statistical power (e.g. due to low sample size). For example, in such as trial using real-life data patients would be recruited at the point of care, randomized among routinely available interventions, and followed up using the EHR data. An illustration is the randomization of patients between atorvastatin or simvastatin with monitoring of major clinical outcomes with the EHR.<sup>11</sup> Data from such studies could be used as the basis for value-based pricing.

Also, the impact of pharmaceutical policy interventions and prioritization of research needs can be studied in detail using EHRs. An example of policy evaluation is the measurement of the impact of a discontinuation of reimbursement of oral contraceptives.<sup>12</sup> An example of priority setting would be off-label medicines use in children.<sup>13</sup> In all these areas EHRs provide the potential to test policy interventions and to identify or fill knowledge gaps about how medicines are used in clinical practice. Therefore, effective models for EHR data use and sharing would also facilitate R&D within an ‘open innovation’ paradigm, which is one of a number of new business models being proposed for the pharmaceutical industry.<sup>14</sup>

### **Challenges**

Since the 2004 Priority Medicines Report many initiatives have been taken to move forward the development of EHRs. However, translating the vision presented above into feasible and sustainable models that are applicable independent of country or health care setting is a major challenge. In order to develop EHRs to their full potential, three critical aspects have to be taken into consideration:

- Structural (e.g. ‘ownership of data’, incentives for health care professionals to participate and collaborate).

- Technical (e.g. quality of data, IT, methods of record linkage).
- Legal/ethical (e.g. data confidentiality, privacy protection).

There are currently over 300 EHR databases in 45 countries.<sup>15</sup> The content of these EHR databases varies greatly as information is being collected for different reasons and using different software and coding systems. In this report, five major issues that need to be resolved are highlighted in light of the three aspects mentioned above:

- Not all EHR databases may be of sufficient quality for research. Three dimensions of data quality may be fundamental and need to be addressed: correctness (are the data valid?); completeness (is the 'whole truth' known about a patient? Can information captured be used in different systems?); and currency (what is the time lag between an 'event' and the update of the EHR?). The conventional answer to the challenge of completeness is to ensure interoperability. However, this is extremely hard to do in practice. Many countries have spent substantial resources on this, with only limited success.
- Evaluations of rare adverse events, comparisons of individual products or the heterogeneity of drug effects in different sub-groups of patients often cannot be done in a single database. Therefore, there is a need to perform studies across different EHR systems and across different countries and find ways to integrate the different datasets to generate results.
- Another challenge for observation research is "confounding." Confounding means that observed differences between comparison groups are not caused by the exposure of interest but by unevenly distributed risk factors. Confounding can play an important role, especially when comparing interventions.
- Research that uses EHR data can be based on strictly a-priori defined criteria or on data dredging and post-hoc changing of study definitions. There are now several examples of studies, within the same EHR database, but with different protocols that reached opposite conclusions. External access to protocols will ensure that deviations from the protocol are transparent and subject to peer review.
- The right of data privacy is crucial and high standards of data protection are essential for any EHR database. Analyses using EHR databases often use anonymized data. In many countries, anonymized EHR data do not require the informed consent of the patients. Some EHR databases use an opt-out system in which patients can refuse that their data is transmitted to the research database. Other EHR databases require an opt-in system in which patients have to provide consent to research use. This topic, and the merit of the different approaches, is also being discussed in new European legislation. The critical question is whether the right of data privacy trumps all other rights and duties or whether there is a balance between different considerations. For example, in an adaptive licensing system the balance between the individual's right to 'control' the use of his or her personal information and public health may put more emphasis on the latter.

### *Research recommendations*

To unlock the full value of EHR databases, investment is needed at the European level to create a good infrastructure for research and innovation. The development and appropriate use of EHR databases is essential, especially for the success of new policy initiatives such as adaptive licensing and various pricing schemes. Efforts to strengthen the capabilities of Europe in this area and to build on existing infrastructure are of key importance. Furthermore, from a public health perspective, data that are gathered as part of (publicly funded) health care practice should be available to a broad audience, if the data is of appropriate quality. The key activities to be supported are:

- **Establish a funded European research network for comparative effectiveness and health policy evaluation:** In contrast to the situation in the United States,<sup>16</sup> there is no funded European research network on comparative effectiveness and health care policy evaluations. Such a network could build on existing strengths and fund the development of the research infrastructure. The key focus for this would be methodology development, and collectively addressing the challenges described above (data quality, integration or at least interoperability of datasets, confounding, protocol publication and privacy). This network could also help to facilitate a dialogue about the availability and use of real-life data.
- **Focus on the development of new statistical models for the systematic measurement of data quality:** Information in EHR databases can change substantially over time. In view of the multitude of EHR databases, their varying content and possible changes in recording methods over time, there is a need to develop and implement statistical models of data quality. The ideal would be to have models that regularly evaluate the quality of the EHR database for the information that is at a minimum required for a certain study.
- **Development of methods to predict long-term risks through the use of EHR databases:** A multitude of advanced statistical models are being applied to large datasets including EHR databases. The objective of these analyses is to improve the prediction of risks of adverse outcomes. But the methods of comparing different statistical models for risk prediction are not yet fully developed. The further development of risk prediction with EHR databases can support clinicians in identifying patients who require medical review.
- **Create a European database to make explicit the uncertainties in routinely used interventions and to help prioritize new research:** For appropriate priority setting, researchers and health care professionals need to be aware of uncertainties about the effects of treatments. In the United Kingdom, a Database of Uncertainties about the Effects of Treatments (United Kingdom DUETs) publishes treatment uncertainties from patients, carers, clinicians and from research

recommendations, covering a wide variety of health problems. Several sources are used to identify uncertainties about the effects of treatments, including questions from the patients, carers and clinicians about the effects of treatment, research recommendations in reports of systematic reviews and ongoing research.<sup>17</sup>

Addressing these research questions would ensure that progress is made on the structural, technical and legal/ethical aspects and help to unlock the full potential value in EHR databases. The European pharmaceutical industry, regulators, pricing and reimbursement authorities and patients would all benefit from having interoperable, quality-assured EHR databases available and accessible. Such a pan-European resource would be a major competitive advantage for Europe.

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### 8.5 Patient and citizen involvement

[See Background Paper 8.5 \(BP8\\_5Stakeholder.pdf\)](#)

At the time of the 2004 Report, patient and citizen participation in priority setting was uncommon and knowledge about and experience of the impact of such participation was limited. Today, the involvement of patients and citizens in health research and policy is supported by legal and regulatory requirements. Moreover, there is a substantial body of literature on the topic and much work has been done to realize patient and citizen involvement. This progress indicates that the need for patient and citizen involvement is widely acknowledged by stakeholders. A variety of underlying motivations drive the efforts to involve patients and citizens in priority setting for pharmaceutical innovation.

First there are political reasons, based on the desire to promote democratic ideals of legitimacy, transparency and accountability. In the year 2000, The Council of Europe declared that the right of the public to be involved in the decision-making processes affecting health care is a basic and essential part of any democratic society.<sup>1</sup> This democratic right is echoed in government reports, legislation and in statements from patient and citizen groups. Setting (research) priorities affects the use of limited public resources, and research demonstrates that values and ethical considerations play a role in recommendations on, for example, guideline development. Therefore, societal values should be considered and decisions should be informed by input from patients and citizens since they are affected by the decisions.<sup>2</sup>

Second, the promotion of patient and citizen involvement can be driven by arguments of transparency and trust. For example, an analysis of the benefits of patient involvement by the EMA led the agency to conclude that: *“participation of patients in the scientific committees leads to increased transparency and trust in regulatory processes and develops mutual respect between regulators and the community of patients.”*<sup>3</sup>

A third category is health-related motivation that stems from the need to better align pharmaceutical innovation with the real, unmet needs of patients. Pharmaceutical innovations do not always meet the needs of patients effectively. Biases within the health research system may tend to favour certain research and topics over others. This could result, for example, in a lack of interdisciplinary and integral approaches and little attention paid to recovery of patient function.<sup>4</sup> In addition, important questions may be overlooked because of an emphasis on chronic but not acute conditions, severe but not common health problems, and disease-specific but not cross-cutting issues, such as social care, improved surgery, and anaesthesia.<sup>5</sup> Evidence shows that health professionals' research priorities differ from those of patients.<sup>6</sup>

Another health-related motivation focuses on the actual contribution which especially patients can make to the decision-making process, and thus to the rationality of the process and the quality of its direct or long-term outcome. Patients not only have a right to engage in discussions on decision making about priorities (the political stance), their input is also needed because they have a specific, relevant type of knowledge: their 'experiential knowledge'.<sup>7,8</sup>

These motivations provide a strong justification for efforts to further develop patient and citizen involvement in priority setting. A next step is to create an evidence base for meaningful models of involvement. At present, there is a lack of an overview of various initiatives undertaken and several knowledge gaps exist; together these are hampering efforts to evaluate and further develop patient and citizen involvement in priority setting.

### *Perspectives of patients and citizens*

One of the first questions to be asked is: how should patients and citizens be distinguished between? While there is widespread belief that values for health states differ between patients and the general public, there is a long-standing debate among health economists about the evidence to support this belief. Research findings suggest that patient and population preferences can both be used to set priorities for pharmaceutical innovation,<sup>9</sup> although there is evidence that patients may give higher valuations to certain health states compared to members of the general public.<sup>10</sup> In general, it seems that patient and citizen involvement can be captured by the term 'public involvement' in many but not all cases. For a start, patients and citizens may have competing or contrasting interests in priority setting for pharmaceutical innovation. Second, there are circumstances that call for a more specific use of experience. This is the case when involvement is sought with the explicit aim of seeking to use the experiential knowledge of a patient, or a well-described group of patients or care takers.

### *Models for involvement and their impact*

The rich variety of structures for involvement that have been employed in the field of health policy and research is a sign of a developing field of expertise and experience. In

general, the literature on roles of patients and citizens in health policy and research appears to reflect a joint search for models for involvement that not only yield a patient or citizen perspective, but also allow real influence on the decisions made. However, one aspect of patient and citizen involvement seems to lag behind in this process: developing good understanding of the expertise and the contribution of patients and citizens at different levels of involvement (i.e. consultation, collaboration or control) and in a variety of models.

Assessment of the impact of patient and citizen involvement is complicated by the way experiences are reported in the literature. In general, these descriptions are brief and provide limited evidence of impact. Concepts like consultation, representation, and expertise have been used interchangeably, with patient and citizen involvement variably defined and often poorly described. Longer qualitative descriptions often provide a better insight into impact. However, while such descriptions can be very valuable, they provide no indication of the extent of impact, its magnitude or how it compares across different areas of impact.<sup>11</sup>

### *Validity and representativeness*

One of the main arguments for patient involvement concerns the contribution that patients could make to the relevance and quality of biomedical research based on their 'experiential knowledge'. However, the validity of patients' experiential knowledge in the context of biomedical research processes raises questions: To what extent is the experienced perception of a patient representative credible? And how can this specific experiential knowledge be absorbed into the scientific process? The same questions may also occur in citizen involvement: (How) can one representative account for the perspectives of citizens with a variety of social and cultural backgrounds? And how can a lay perspective be preserved when citizens (or patients) are educated to participate in the scientific process?<sup>12</sup> What methods can be used to enhance the credibility of the contribution of patients and citizens to the decision making?

A second problem for validity and representativeness is the potential for conflict of interest. Many patient and consumer groups accept pharmaceutical industry funding to support their activities. Some of them see this as a necessity to achieve their aims and argue that patient groups are able to defend their independence from the influence of any sponsor.<sup>13</sup> Other patient organizations refuse drug industry funding in order to maintain their autonomy.<sup>14</sup> With the rise of patient and citizen involvement, the focus of attention on conflicts of interest has also grown. Accepting funding from the pharmaceutical industry clearly puts patient organizations in a position of potential conflict of interest. As with conflict of interest among professionals, the response of most regulatory authorities is to request transparency. The EMA, for example, formulated criteria to be met by patients' and consumers' organizations involved in EMA activities.<sup>15</sup> Problems may arise when information about funding sources is not disclosed, or if the relationship between the funding sources and activities of patient organizations is not appropriately addressed. This may lead to diminished trust in patient organizations and additional problems of validity and representativeness.

Therefore, relationships with sponsors and common policies to maintain independence should be discussed transparently in order to avoid these problems.

Questions of validity need to be addressed since they limit acceptance of non-expert involvement.<sup>16</sup> While patient and citizen organizations struggle to demonstrate credibility, their position may be undermined by ambiguity in their roles and the goals of their involvement in priority-setting and decision making.

### *Recommendations for research*

Priority research on patient and citizen involvement is recommended in the following areas:

- **Framework for patient and citizen involvement:** Although the wide variety of approaches for patient and citizen involvement has helped in the accumulation of experience, this has not yet resulted in a widely accepted model or a framework for meaningful involvement. Such a framework is needed to ground patient and citizen involvement in an evidence base and to optimize its practice. The Background Paper lists different 'toolkits' in this area that have been developed over the years, such as the Value+, G-I-N, INVOLVE and the Participatory Methods Toolkit. To help facilitate further improvement in frameworks and to create a needed consensus, more research is needed on models for patient and citizen involvement, based on a combination of five variables. These variables or key questions are: what is the goal of the involvement of patient and citizen organizations in priority setting and decision-making; who should be involved; what is the role or expertise of the patient or representative involved; what level of involvement is pursued; and what is the most suitable structure for involvement.
- **Research on capacity building:** In the absence of people who are willing and able to realize the full potential of this kind of stakeholder involvement, it will remain a paper tiger, weak and indecisive. What is needed now is research on methods for capacity building to help ensure the meaningful involvement of patients and citizens in priority setting for pharmaceutical innovation. In addition to the framework development discussed above, other research efforts are needed to identify and establish best practices, mainly in education and training. All stakeholders need to be prepared for decision making on priorities that involve patients and citizens. This requires the empowerment of patients and citizens and education and training for all the parties involved. Initiatives such as the IMI supported European Patients' Academy on Therapeutic Innovation (EUPATI) will play an important role in this capacity building.
- **Outcome assessment:** A third research recommendation is to assure structured outcome assessment of initiatives to involve patients and citizens. This will not only strengthen the evidence for patient and citizen involvement, it is also needed to justify policy making and the expenditures required to facilitate this

involvement. Critical scrutiny of initiatives would not only involve description and effect measurement, but also a cost-benefit assessment.

Patient and citizen involvement can strengthen the quality and legitimacy of the decision-making process. Its potential is currently widely acknowledged and much experience has been gained over the past decade. Thus, patient and citizen involvement is here to stay. However, to fully capture the value offered by such involvement, there is a need to invest in research in this area.

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# 9. Summary of observations, discussion, conclusion and recommendations

## 9.1 Introduction

The 2004 Report *Priority Medicines for Europe and the World* determined the priority needs for pharmaceutical innovation from a public health perspective and made policy and research recommendations to address these needs. Within this public health context, a key objective throughout the 2004 Report has been the need to identify common areas of interest between Europe and the world as a whole, particularly in the area of discovering and developing new and improved medicines to combat diseases and conditions which pose a current or future threat to public health. This updated 2013 Report has the same objectives. It is important to acknowledge that medicines are of course not the only intervention to prevent, treat and diagnose diseases. In this report, vaccines and diagnostics have therefore also been identified as potential priority areas.

The objectives of this report must be set against a backdrop of the key demographic changes that are transforming the global disease burden (Chapter 5). Low- and middle-income countries are currently facing a shift in their disease burden from one that is dominated by communicable diseases towards one dominated by chronic noncommunicable diseases (NCDs). This change has profound implications for health care systems and the development of innovative medicines. These changing disease burdens are entirely predictable. The key drivers are both demographic and epidemiological and include factors such as the ageing population and changes in risk factors such as tobacco and alcohol use as well as obesity which are leading to the increasing prevalence of chronic NCDs. As a result, health systems in many low- and middle-income countries will face a double burden of disease, as NCDs add to the existing burden of communicable diseases and reproductive health problems addressed in the Millennium Development Goals 4, 5 and 6.

While the first part of the report, Chapters 1 to 6, identifies high-burden diseases and substantial risk factors for which pharmaceutical gaps exist, Chapter 7 takes a more holistic approach and looks at common themes around children, women, the elderly and the new concept of stratified medicine. Chapter 8 builds on work done in the 2004 Report to identify incentive systems for pharmaceutical innovation in Europe, that increase efficiency and equity and involve patients and citizens in key decisions that affect them. The chapter suggests multiple approaches for addressing identified pharmaceutical gaps, including through proposed incentives for the pharmaceutical industry.

### 9.2 Methods used in the updated 2013 Report

The methods used in the updated 2013 Report are similar, but not identical, to those used in the 2004 Priority Medicines Report (see Chapter 4 and the related Background Paper). Several key criteria were used to define a preliminary list of diseases which would be reviewed in depth. To this end the WHO Global Burden of Disease dataset was used to determine the highest disease burdens in Europe and the world, with the explicit inclusion of critical risk factors (tobacco and alcohol use and obesity). In addition, the concept of social solidarity (rare diseases, neglected tropical diseases), and public health projections (pandemic influenza and increasing antimicrobial resistance) were used as additional criteria, as in the 2004 Report. However, in contrast to the 2004 Report, the pharmaceutical gaps were not investigated via a Cochrane analysis prior to writing full reviews. Such investigations were included as part of the background papers (Chapter 6.1- 6.24) and are presented in the background papers. Authors of the reviews identified research topics which would be the most beneficial from a public health point of view.

Data sources were expanded from the original WHO 2004 Global Burden of Disease dataset to include the WHO projections for both Disability Adjusted Life Years (DALYs) and mortality for 2008 as well as data from the 2010 Global Burden of Disease Study (GBD 2010 Study) as published in *The Lancet* in December 2012. However, the GBD 2010 Study used a different methodology and different geographical regions, making it challenging to compare the burden of disease results between the WHO projections and the GBD 2010 Study. All previously reviewed diseases from the 2004 Report were again included in the final list of detailed reviews in the 2013 Report. In addition, some new topics that emerged as relevant in the top 20 diseases in the GBD 2010 study were included. This resulted in the addition of six new diseases and risk factors due to their high disease burden: obesity, diarrhoeal diseases, hearing loss, pneumonia, neonatal conditions and low back pain.

Under cross-cutting themes (Chapter 7), a new section is included on stratified medicine because of its potential impact on clinical practice over the next decade. In the chapter on incentive systems for innovation (Chapter 8), new sections have been added on the use of real-world data through the availability of electronic health records (EHR) to support innovation and on the role of patients and citizens in priority setting for pharmaceutical innovation.

### 9.3 Priority medicines and pharmaceutical gaps

“Priority medicines” as defined in this report are medicines which are needed to meet the future priority health care needs of the population. They are needed because a treatment gap exists for a number of high-burden diseases and conditions. Different types of treatment gaps include:

- Gap 1:** Treatment(s) exist but will soon become ineffective;
- Gap 2:** Treatment(s) exist but the pharmaceutical delivery mechanism or formulation is not appropriate for the target population;
- Gap 3:** Treatment does not exist OR is not sufficiently effective.

The three categories are non-exclusive. For example, malaria could be placed in Gap 1 (medicines will become ineffective due to AMR) or Gap 3 (no medicines or vaccine exists) as no malaria vaccine is available. Similarly, HIV might be placed in Gap 2 (treatment is available but there is a need for paediatric formulations) or Gap 1 (the current treatment might become ineffective) or Gap 3 (no vaccine exists).

While the focus of this report is on pharmaceuticals needed to fill treatment gaps, the importance of prevention cannot be overemphasized. For many conditions prevention is of paramount importance and remains underutilized for conditions and risk factors such as chronic obstructive pulmonary disease (COPD), liver cirrhosis, type 2 diabetes, tobacco use, alcohol consumption and obesity. A fourth category has therefore been created (Gap 4) to address the problem of key risk factors for disease (obesity, tobacco use, alcohol use).

A brief summary and recommendations are provided below for each of the diseases, conditions and risk factors identified. More information on these conditions can be found in the individual sections of Chapter 6 and in the background papers.

### 9.4 Gap 1: Treatment(s) will soon become ineffective

#### *Antibacterial resistance*

Antimicrobial resistance remains a serious threat to global health, with an increase in the spread of new highly-resistant organisms, including many Gram-negative bacteria and those causing tuberculosis (TB) and malaria. Some progress has been made since 2004 with increased funding from the Innovative Medicines Initiative (IMI) for research into AMR. Continued surveillance is needed both in Europe and worldwide as well as close cooperation between countries in order to combat the threat of AMR. There also remains a need for new and rapid diagnostics, for new business and R&D models, and for alternatives to the use of antibacterials, such as substances to modify host/pathogen interactions or vaccination for primary prevention of infection. As stressed by the European Commission and public health authorities, vaccination can and should be play a key complementary role in anti-microbial resistance programmes.

#### *Pandemic influenza*

Since 2004, an influenza pandemic has occurred, stimulating the development and mass production of new types of vaccines. In the current inter-pandemic period, various gaps exist in therapy and access to vaccines. Among these challenges are: the low uptake of inter-pandemic seasonal immunization, which limits production

capacity and restricts the world's surge capacity in times of a pandemic; rapidly mutating viruses that require new vaccines (including adjuvanted vaccines); and the need for more antiviral compounds. More sensitive rapid diagnostic tests for influenza are needed in order to detect and distinguish between influenza virus subtypes. New antiviral agents are needed with broad reactivity against all virus strains and sub-types.

### **9.5 Gap 2: Treatments exist but the delivery mechanism or formulation needs improvement**

#### *Ischaemic heart disease*

Despite ongoing research, no new 'breakthrough' medication has been developed with the potential to improve on the existing generally effective treatment used by patients with established ischaemic heart disease (IHD). The focus here is therefore on better use of existing medicines, particularly in high-risk individuals who have already had a heart attack or stroke. This includes the potential use of a "polypill" of four effective generic medicines for the secondary prevention of ischaemic heart disease (IHD) as already recommended for study in the 2004 Report. This combination product is now available but needs to be evaluated with a large-scale trial to demonstrate its impact on mortality rates and on prevention of repeat heart attacks or strokes in survivors of first events. There is also a need to identify barriers to improving the prevention and treatment of CVDs and strategies to overcome these barriers.

#### *HIV/AIDS*

HIV/AIDS continues to be one of the deadliest epidemics of our time. There has been a reduction in the rate of new infections worldwide, in part due to increased roll-out of treatment with antiretrovirals. However, there is still a need for approved formulations for children as well as paediatric diagnostic tests. Not all the viral targets have been explored and new modalities of treatment are still possible. Funding and research for the development of an HIV vaccine should be maintained.

#### *Cancer*

Since 2004, there have been a number of major therapeutic breakthroughs resulting from a better understanding of the biology of cancer and the identification of tumour-specific biomarkers. However, targeted therapies are needed that improve survival, together with a concerted effort to address cancer in children. In addition, the major disparities in cancer care and epidemiology between high-income and low- and middle-income countries should be addressed. The affordability of cancer therapeutics is also of great concern, but this is difficult to address without changes in the way health care systems are organized.

### *Depression*

Treatment gaps for depression persist. Too many antidepressants have serious adverse effects and for that reason about half of the patients discontinue treatment within the first six months. Research is needed to better understand the link between genetic factors and the efficacy and safety of treatment. Safer treatment alternatives for adolescents are required and many health system barriers to treatment remain to be addressed. Work is also needed on the development of biomarkers and new delivery methods.

### *Diabetes*

Diabetes and diabetes-related illnesses place an enormous burden on the health care systems of most countries throughout the world. There is an alarming increase in the incidence of type 1 diabetes (currently incurable) and an increase in the prevalence of type 2 diabetes, especially in low- and middle-income countries. It is estimated that about half of all cases are undiagnosed. There is a continuing need for the development of a heat-stable version of insulin (mainly for use in developing countries), and new treatments are needed that mimic the bodily response to glucose. An effective solution is needed to counter the progressive loss of beta-cells in those with type 2 diabetes, which accounts for the vast majority of people with diabetes. In addition, a pharmacological strategy is required to reduce the problems associated with polypharmacy for patients with several risk factors for diabetes, such as the development of single drugs or fixed-dose combinations with multiple targets that affect several risk factors such as dyslipidemia, hypertension and obesity.

### *Pneumonia, diarrhoeal diseases and neonatal diseases and conditions*

Effective treatments for bacterial pneumonia exist but there is a need for better and more rapid diagnostic tests with the ability to distinguish between viral and bacterial pneumonia, and for new formulations of antibiotics for use in infants and newborns. Further R&D is vital in order to bring promising vaccine candidates for pneumonia and diarrhoea on to the market. Neonatal conditions account for a high proportion of the global burden of disease. Research is needed to develop new therapies to address the problem of preterm births, neonatal sepsis and birth asphyxia. With regard to preterm birth there is a need for the development of tocolytics with fewer side-effects in mothers and newborns and for clearly labeled, pre-packaged or pre-filled delivery systems for antenatal corticosteroid products. For neonatal sepsis there is a need for the development of shorter course antibiotics, oral antibiotics, and antibiotics with fewer side-effects for newborns; rapid diagnostic tools for neonatal conditions in order to avoid the inappropriate use of antibiotics (thereby lowering the risk of AMR); and appropriate smaller dosage forms for newborns. To prevent birth asphyxia, research efforts should include the development of effective and lower-cost synthetic surfactants and a more stable oral surfactant.

### *Malaria*

Since 2004, there has been a substantial decline in the incidence of malaria combined with better access to effective medicines (artemisinin combination therapy) and insecticide-impregnated bednets. This is largely due to an unprecedented financial commitment by global donors over the past decade. In addition, the widespread and reliable use of rapid diagnostic tests has helped ensure that malaria, and not other conditions, are treated with antimalarials. Although there are several promising antimalarial therapeutic candidates in the development pipeline, resistance will remain a threat until an effective vaccine is available to prevent the disease. Continued support is needed for research on the development of vaccines, new medicines and rapid diagnostic tests for use in low-prevalence settings.

### *Tuberculosis*

Tuberculosis (TB) remains mainly a disease of poverty with a high burden in low- and middle-income countries and in countries with high HIV prevalence. Today, new funders are investing in R&D for TB. Rapid diagnostic tests are now available, but there is a need to improve existing diagnostic tests for use at various levels in the health care system, in diverse patient groups and in high-burden settings. Although the TB medicine pipeline is growing, more effective and safer treatments are still needed due to the development of multi-drug resistance. The development of fixed-dose combinations of the new regimens and more suitable formulations for children would be a major advance. Meanwhile, research is ongoing to find a new, more effective vaccine.

### *Neglected tropical diseases*

Of the 1 556 new drugs approved in Europe and the United States between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and TB. Although there is more commitment now and a promising pipeline of products, more effective diagnostics and treatments are still needed, particularly for leishmaniasis, trypanosomiasis and dengue. Some medicines are inappropriate for tropical environments and need to be re-formulated. Meanwhile specific formulations for children and neonates are still needed for many diseases.

### *Postpartum haemorrhage and maternal mortality*

Postpartum haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. As a result of the 2004 Report, successful research was undertaken to understand the thermal stability of oxytocin. However these findings need to be applied to help accelerate the development of heat-stable oxytocin in a single-dose system which can be used by midwives to actively manage the third stage of delivery.

### 9.6 Gap 3: Treatment does not yet exist or is insufficiently effective

As in 2004, stroke, osteoarthritis, COPD, and Alzheimer disease and other dementias were identified as high-burden diseases with very limited therapeutic options. In addition, hearing loss and lower back pain are now added to the list. Some progress has occurred in identifying biomarkers of disease onset or progression, for instance in Alzheimer disease and osteoarthritis, but these biomarkers lack the sensitivity required for diagnosis and clinical trials. For these and other diseases, the development of diagnostic measures (including the use of biomarkers) and new treatments remain the priority.

#### *Acute stroke*

The current treatment of acute stroke is unsatisfactory, and investment is needed for basic and clinical research to develop new treatments. Most agents are not sufficiently effective and some are associated with an increased risk of adverse events. Progress in the fields of neuroprotection and stem cell research are badly needed. Some progress has occurred in establishing biomarkers to identify or measure progress, but none are fully validated for use in drug development or to evaluate clinical impact. The development of diagnostic measures, including the use of biomarkers, remains the first priority. Barriers to effective secondary prevention need to be identified.

#### *Osteoarthritis*

Osteoarthritis is the single most common cause of disability in older adults. There are currently no medicines that can cure, reverse, or even halt the progression of the disease. The available diagnostic tools have low sensitivity and specificity. The lack of valid biomarkers limits pharmaceutical development and clinical monitoring. Some progress has occurred in identifying biomarkers that could be used to identify or measure progression of the disease, but none are fully validated for use in drug development or to evaluate clinical impact. The first priority is therefore the development of diagnostic measures, including the use of biomarkers.

#### *Alzheimer disease and other dementias*

With the ageing of the population both in Europe and worldwide, managing Alzheimer disease and other dementias is becoming a major concern as governments are poorly prepared to face the magnitude of the situation unless effective treatment becomes available. In 2012, the World Health Organization published a report identifying dementia to be a public health priority. There are currently no specific tests that can positively confirm a diagnosis of Alzheimer disease, and no treatment can delay its onset or affect the course of the illness. Some progress has occurred in identifying biomarkers that could measure progress but none are fully validated for use in drug development or for evaluating clinical impact. The development of diagnostic measures, including the use of biomarkers, therefore remains the priority.

These markers are essential as they can provide new pathways for research and pave the way towards better understanding of the onset of the disease. The development of existing bio-banks including tissues, blood, urine and cerebrospinal fluid from patients and healthy volunteers should help identify such markers.

### *Chronic obstructive pulmonary disease*

The burden of COPD is increasing, but there is a general lack of public awareness of the disease. For this condition prevention through tobacco use cessation is critical. Currently there is no effective cure for COPD and medicines are needed to halt or slow down the progression of the disease, not just to control the symptoms. An effective diagnostic test and effective COPD anti-inflammatory treatments are required. New information on the inflammatory progress and surrogate biomarkers is also needed.

### *Hearing loss*

At present, the use of cochlear implants and hearing aids is the only way to partly recover hearing and communication skills. However, these devices can be very expensive and are therefore not always affordable. A cure for hearing loss, which is associated with ageing, would be a tremendous advance in public health. More progress is therefore needed in pharmaceutical research to treat or prevent hearing loss. Primary prevention of hearing loss in low- and middle-income countries through immunization against measles, rubella and *Haemophilus influenzae* type b (Hib) has been successful. There is a need to assess the potential health benefits and economic impact of vaccines targeting other pathogens that impair hearing. Consortia of European research and industrial partners could contribute to strengthening the EU's leadership on research into the pharmacological prevention and treatment of this frequent disorder, which has received little attention so far.

### *Low back pain*

Low back pain affects people of all ages, from children to the elderly, and is a common reason for medical consultations. As the world population ages, low back pain will increase substantially. At present there are no pharmaceutical interventions that can cure back pain, and only palliative care is possible. There is also a need for validated biomarkers for low back pain. Meanwhile, three-dimensional imaging should be further investigated to help to diagnose and monitor progression and design disc prostheses.

### *Rare (including orphan) diseases*

In the EU, a disease is considered "rare" when the number of people affected is less than 5 per 10 000. The causes of many rare diseases are unknown and this can result in a missed or delayed diagnosis. There has been considerable progress since 2004 in developing disease-specific products but often at high prices. Gaps in clinical evaluation call for an internationally recognized rare disease classification system

which would help in generating reliable epidemiological data. A public database should be created, underlying an infrastructure of earlier epidemiological surveillance. There is a need to develop easier diagnostics, biomarkers and site-specific delivery systems. Continued support for networks remains important for such infrequent cases.

### 9.7 Gap 4: Global risk factors with no or insufficient pharmaceutical treatment

This report also addresses the leading risk factors for disease that might be amenable to pharmaceutical solution(s). Such solution(s), if found and made available, should be used in concert with other preventative interventions related to personal and societal factors.

#### *Tobacco use cessation*

Tobacco use continues to be the leading cause of preventable deaths, despite aggressive national educational campaigns and fiscal policies. Smoking cessation products are rarely reimbursed by health or insurance schemes. More effective safe medicines are needed to achieve long-term abstinence. Research is also needed on the cost-effectiveness of pharmacotherapy for smoking cessation in low- and middle-income countries to inform decision makers about the need for the development of lower-cost therapeutic options for their countries. Some new treatment options are available and various smoking antagonists are in the pipeline. However, it is necessary to determine the safety, efficacy and effectiveness of existing and new therapeutic modalities for specific patient groups (including adolescents and pregnant women), as well as a better definition of the criteria for using some of the therapeutic modalities in combination.

#### *Obesity*

Only very limited pharmacotherapeutic treatment options exist for obesity. Only one product is available in most European countries (orlistat) and no current pharmacotherapy can produce clinically significant long-term weight loss (at least 5% to 10% weight loss) in a large proportion of morbidly obese patients. Safety concerns (mainly due to central nervous system and cardiovascular effects) have resulted in the decision by medicines regulatory authorities not to approve or even withdraw marketing approval. Biomarkers are needed to identify those individuals most likely to benefit from available interventions and long-term studies are needed to prove safety. New pharmacotherapeutic options are urgently needed to treat those already affected by morbid obesity. More research is needed on adherence, on regaining body weight after discontinuation of pharmacotherapy, and on the cost-effectiveness of different therapies.

### *Alcohol-related diseases*

The EC has funded research on alcohol use disorders and alcohol-related diseases and some new medicines have shown promise in conjunction with behavioural therapy. There is poor understanding of liver pathogenesis and the treatment for liver cirrhosis has low effectiveness. The outlook is poor in the short- and medium-term for development of new therapies for diseases and conditions related to alcohol abuse. The major need is for translational research to convert basic science advances into products that can be used in clinical trials.

## 9.8 Cross-cutting themes

The following cross-cutting themes apply to all diseases and therapeutic approaches. The two major themes in Chapter 7 include the particular needs of special groups (children, women and the elderly), and the concept of stratified medicine which enables targeting of treatment to sub-populations more likely to respond or less likely to be harmed.

### *Summary of key points and recommendations for cross-cutting themes*

Despite the adoption of new regulations and other initiatives by regulatory authorities, which have led to some progress, children and the elderly are still underrepresented in clinical trials. Important information is often lacking on dosing, effectiveness and safety for children and the elderly and many medicines used in these populations are therefore prescribed “off-label”. Similarly, there is a shortage of gender-specific analysis and data on the use of medicines during pregnancy. However, stronger regulations are not considered as the most appropriate way forward. New approaches, such as better use of existing electronic health records (EHR) ([see also Chapter 8.4](#)), may be more valuable in obtaining the much needed data on safety and effectiveness of medicines in children, (pregnant) women and the elderly. It is also important to translate this age- or gender-specific information into practical recommendations. In addition, existing data could assist in stratified medicine and in identifying populations at highest risk for adverse events (safer use of existing medicines) and treatment responders (targeted use of expensive medicines), thereby leading to more effective pharmaceutical care.

Children and the elderly have several similar difficulties in taking their medication. Adapted, age-appropriate children’s medicines have been developed over the past decade, with especially innovative oral solid dosage forms. Continued R&D investments are required for new routes of administration, safer excipients, responding to patient preferences and patient-related outcomes such as adherence, efficacy and side-effects. For the elderly, alignment is needed with the development of formulations for children, taking into account the differences between the two populations. Moreover, tools to assess and improve medication self-management among elderly people living independently should be further developed and evaluated.

Polypharmacy is very common in the elderly. Although interventions to address polypharmacy can lead to more appropriate prescribing and fewer medication-related problems, it is unclear how this improved practice can be translated into clinical outcomes such as reduced hospital admissions and lower mortality rates. More research in this area is needed to inform policies and practices. The supporting role of EHR needs to be improved, and the added value of fast and extensive data sharing with the aid of computerized systems needs to be established. Sharing of information and communication between health care professionals is also vital for integrated and continuous care, particularly in the elderly patient living with several coexisting diseases. Approaches that support advanced integration of care need further investment.

Clinical implementation of stratified medicine with personalized diagnosis and treatment has been limited until today, but holds the promise of better use of existing medicines in all settings, and of the identification and development of drug targets, new medicines and diagnostic tools. Limitations currently hampering the attainment of the full potential of stratified medicine can be addressed by the following seven strategies: (1) stimulating pharmacogenomic approaches to existing medicines, (2) stimulating the use of multi-dimensional analyses (integration of biomarkers and clinical parameters), (3) establishment of a European research network and a European catalogue of pharmacogenomic datasets with a harmonization programme, (4) adaptation of regulatory guidelines and reimbursement procedures, (5) the development of a framework to assess comparative (cost-)effectiveness, (6) development of harmonized training and education programmes for health care professionals and the public, and (7) research into the ethical, legal, economic and social implications of stratified medicine.

### **9.9 Incentive systems for pharmaceutical innovation**

Pharmaceutical innovation is the key approach to address the gaps described above, and some general barriers to innovation need to be addressed. A pharmaceutical gap can occur when market forces fail to meet public health needs. By identifying incentives for and barriers to pharmaceutical innovation, action can be taken to facilitate the development of new medicines to fill pharmaceutical gaps. Although substantial progress has been seen in some therapeutic areas (e.g. cancer, multiple sclerosis, rheumatoid arthritis), there is still growing concern about the inefficiency of the drug discovery and development process for new medicines for unmet medical needs. Whether this decline in R&D productivity is due to research depletion, too strict regulatory hurdles, or the current pharmaceutical business model remains unanswered.

### *Public-Private Partnerships and Innovation*

Public-private partnerships (PPPs) were mentioned in the 2004 Report as a promising solution for filling the pharmaceutical gap. Since 2004, there has been great progress in the development of PPPs, in particular the Product Development Partnerships (PDPs). Partnerships focusing on TB, malaria and neglected tropical diseases as well as diagnostics for neglected tropical diseases have had considerable success. For example, the Top Institute (TI) Pharma in the Netherlands and the Innovative Medicines Initiative (IMI) have developed into effective partnerships focusing on enabling research. All such partnerships face a challenge in that funding time-lines are often short while drug or diagnostics development takes a long time. Reconciling this tension with long-term funding commitments will be necessary for these partnerships to fulfil their great potential. There is a need to identify the most successful models for PPP collaboration. Knowledge about what are the most useful indicators (structural, process, output or outcome) of successful partnerships would be beneficial for all those involved. Another area for research is stakeholder participation (including patients and citizens) in PPPs and their involvement in the decision-making process. Chapter 8.5 contains a number of research recommendations that are also relevant for PPPs.

### *Regulation and innovation*

Regulation plays an essential role in balancing societal expectations of new medicines addressing unmet medical needs and ensuring a favourable benefit-risk profile for these medicines. The 2004 Report called for a re-examination of the regulatory process and for a critical analysis of the evidence base for regulatory practices using modern methodologies. Since then, networks for analysis and information sharing have been initiated across Europe and numerous studies have been undertaken on different aspects of the regulatory system. However, research methodologies are still under development and should be further refined. Other examples of progress in this area are better communication between stakeholders (regulatory dialogue) and strengthening of the role of post-marketing surveillance.

Despite these developments, challenges remain. Additional research is needed on promising instruments to optimize regulatory requirements for initial marketing approval (e.g. the use of surrogate outcome measures and an adaptive study design) and on quantitative instruments supporting more standardization of benefit-risk assessment. In line with the adaptive licensing proposals, more studies are needed to reduce uncertainty around effectiveness and safety, while measuring and comparing the effects of medicines in real-life settings. Improving this kind of learning could help to achieve an adequate level of safety knowledge while requiring less data to be collected pre-approval.

Measuring the (cost-)effectiveness of regulatory policies is an important challenge. In order to evaluate and improve existing regulations and to base new incentives on best practices, impact measures should be defined explicitly in terms of quantitative and qualitative performance indicators, and monitored in carefully designed studies.

Collaboration and dialogue between all actors, including the involvement of patients and citizens in the regulatory system, should be supported at multiple levels ([see Chapter 8.5](#) for priorities on patient involvement in decision making).

Close collaboration is also needed between regulatory agencies, industry and academia to test and explore new methods for drug development and regulatory decision making. The new field of regulatory science, studying the performance of the system as a whole, would benefit from investments in sharing and analysing existing and future regulatory datasets.

### *Pricing, reimbursement and innovation*

Many European countries share the implicit or explicit health policy objectives of sustainability, equity and quality of care, but the way in which these are handled can differ substantially between countries. Pricing and reimbursement policies used in the EU include external price referencing, internal reference pricing, decision-making based on Health Technology Assessment (HTA) and economic evaluations, value-based pricing, caps and co-payments, taxes, price-volume agreements, fixed margins in distribution channels and tendering. The 2004 Priority Medicines Report highlighted differential pricing as a key policy for the future and also put a strong emphasis on pharmacoeconomics as a tool to value new medicines. Since then, more European countries have incorporated HTA and economic evaluations in their reimbursement and sometimes pricing policies. In most of Europe, however, external price referencing remains the predominant pricing method. An alternative to external price referencing is value-based pricing, in which the price of a new medicine is determined by the (added) value it generates. These policies are now (being) implemented in a few countries.

The 2013 Report identifies three different broader topics for future research. Firstly, research priorities that focus on the broader environment of pricing and reimbursement policies: studying the meaning of innovation for pricing and reimbursement authorities, the impact of the financial crisis, evaluation of new regulations and the link between pricing and availability at a global level.

Secondly, a set of research priorities focus on some of the main methods used for pricing and reimbursement policies: the effects of external price referencing (both beneficial and adverse effects), the experience with the implementation of value-based pricing policies, differential pricing mechanisms and policies (especially official list prices and informal discounts and rebates), volume control (generic policies and practices, managed-entry schemes), models for small volumes (medicines targeting rare diseases and stratified medicines), and patient involvement ([see Chapter 8.5](#)). Thirdly, for all these studies, cross-national learning, co-development of methodology and exchange of information and experiences are critical. To achieve these objectives, it is therefore essential to build an appropriate research infrastructure.

### *Use of real-world data to support innovation*

Data obtained from health systems is critical to support innovation as this information plays a vital role in closing the gap between clinical research and clinical practice, thereby improving the whole medicine development chain including regulation, pricing, reimbursement and treatment decisions. Electronic health records (EHR) are currently the most important source of information to capture the real-world setting, and should be used to assess the effectiveness (real-world effects) and safety of medicines, especially in populations that are not sufficiently included in clinical trials. The use of EHR databases for research into stratified medicine is a more recent development. Other important new uses have also been identified, including: use for better understanding of diseases; identifying adherence failure; predicting risk; and comparing effectiveness. Moreover, policy initiatives such as adaptive licensing, value-based pricing, policy evaluations and priority setting are critically dependent on optimal use of EHR data.

Current challenges are the fragmentation of the resources available in Europe and the limited availability of good quality data, often limited to a specific disease area or geographic region. Many important research questions call for larger databases, highlighting the need for performing studies across different EHR systems and countries and finding ways to integrate the results. To foster pharmaceutical innovation, a European research network should be established for comparative effectiveness and health policy evaluations using EHR data. New statistical models are needed for the systematic measurement of EHR data quality, new methods are needed to predict long-term risks through the use of EHR databases, and a European EHR database should be established to make explicit the uncertainties in routinely used interventions.

### *Patient and citizen involvement in innovation*

The final section in Chapter 8 addresses patient and citizen participation in priority setting for pharmaceutical innovation, which was only briefly mentioned in the 2004 Report. Since then, patient involvement has received substantial attention from patient organizations, policy makers, governments and researchers. The number and variety of initiatives, models and frameworks that have been developed reflect the broad acknowledgement of the value and importance of patient and citizen involvement. However, these initiatives have not yet resulted in a widely accepted model or a framework for meaningful involvement. Such a framework is needed to ground patient and citizen involvement in an evidence base and to optimize its practice.

Although a framework is essential, it will remain weak and indecisive in the absence of people and organizations willing and able to realize the potential of patient and citizen involvement. Hence, capacity building is needed to realize meaningful involvement. In addition, other research efforts are needed to establish best practices for patient and citizen involvement (e.g. identification of barriers to meaningful involvement, design and evaluation of measures to overcome these barriers, and the development of

strategies to ensure the primacy of the interests of patients and society). Another important research recommendation is to ensure that effective assessments of initiatives to involve patients and citizens are undertaken and published. Critical scrutiny of initiatives would include cost-benefit assessments in addition to regular effect measurements.

### 9.10 The role of the European Commission in supporting research for health

It should be recognized that much of the progress that has occurred since the 2004 Report has been as a result of activities undertaken by the European Commission, particularly DG Research. These activities are well documented on the Community Research and Development Information Service CORDIS ([http://cordis.europa.eu/home\\_en.html](http://cordis.europa.eu/home_en.html)). However, while CORDIS reports call for research and awards when the awards are made, information on project outputs and outcomes may be delayed and the project web site is often shut down when project funding is completed. This information asymmetry in CORDIS is similar to that of the United States National Institutes of Health (NIH) which has established an Office of Portfolio Analysis to address this and related issues. It is recommended that the EC establishes an open archive for the web pages of these projects which should be uploaded at the time of project completion.

### 9.11 Final comments

This 2013 Report *Priority Medicines for Europe and the World* identifies key areas of priority research for pharmaceutical innovation to meet public health needs. In providing an update to the 2004 Report, the present report has been able to highlight areas where important progress has been made and those where additional investment is needed.

To improve the health of the people of Europe and the world will require innovation to develop new and better medicines, vaccines and diagnostics that can be used efficiently and equitably in existing health systems with sustainable financing. The European Union has done much to ensure that this vision continues to be fulfilled.

