

Progress report

Report by the Secretariat

1. In May 2013, the Sixty-sixth World Health Assembly adopted resolution WHA66.22 on follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, through which the Health Assembly endorsed a “strategic workplan to improve monitoring and coordination, and to ensure sustainable funding for health research and development, in line with the global strategy and plan of action on public health, innovation and intellectual property, as a step toward achieving the goal of development and delivery of affordable, effective, safe and quality health products for which existing market mechanisms fail to provide incentives for health research and development ... through the broad engagement of public and private entities, academia and civil society”. The resolution also urged Member States “to strengthen health research and development capacities, increasing investments in health research and development for diseases disproportionately affecting developing countries”.

2. In the resolution the Health Assembly also requested the Director-General to support Member States in their endeavours “to establish or strengthen health research and development capacities and monitor relevant information on health research and development”. More specifically, it requested the Director-General, among other things:

(a) “to establish a global health research and development observatory within the Secretariat in order to monitor and analyse relevant information on health research and development ... with a view to contributing to the identification of gaps and opportunities for health research and development and defining priorities;

(b) to facilitate ... the implementation of a few health research and development demonstration projects to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken;

(c) to review existing mechanisms in order to assess their suitability to perform the coordination function of health research and development;

(d) to explore and evaluate existing mechanisms for contributions to health research and development and, if there is no suitable mechanism, to develop a proposal for effective mechanisms, including pooling resources and voluntary contributions, as well as a plan to monitor their effectiveness independently”.

3. The Director-General was also requested to convene another open-ended meeting of Member States before the Sixty-ninth World Health Assembly in order to assess progress and continue discussions on the remaining issues in relation to monitoring, coordination and financing for health research and development, taking into account all relevant analyses and reports, including analyses included in the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination.¹ This report responds to that request.

GLOBAL OBSERVATORY ON HEALTH RESEARCH AND DEVELOPMENT

4. A demonstration version of the Global Observatory on Health Research and Development was launched at the beginning of 2016. In its first phase, the Observatory integrates available information on funding for health research and development, health products in the pipeline, clinical trials and research publications.² In subsequent phases, the Observatory's functions and remit will be broadened as it receives additional resources, data and analyses. In addition to an online portal,³ a key output of the Observatory will be the development of standard and on-demand analyses of gaps in health research and development, highlighting the main findings of a review of the data collected by the Observatory and contributing to priority-setting mechanisms as part of the coordination function for health research and development. In doing so, it will also support capacity strengthening at regional and national levels in the governance of health research and development and innovation for improved access.

5. Additional activities towards the Observatory's goals and objectives include supporting the publication of a peer-reviewed series on "Informing the establishment of the WHO Global Observatory on Health Research and Development"⁴ and, resources permitting, investing in finding efficient solutions to common problems in the sharing of research and development data, such as inconsistencies in what is reported and in terminologies and methods of data collection, in collaboration with key partners in this field. These activities will also contribute to capacity-building by sharing knowledge and tools and facilitating the development of norms and guidelines for future data collection and sharing.

6. The goals and objectives of the Observatory make it the most suitable option for hosting a broad range of data on health research and development and for meeting the associated information-sharing and capacity-building needs. Using the existing Observatory platform to strengthen and facilitate sharing of information on antimicrobial resistance, emerging diseases likely to cause major epidemics, and other diseases will facilitate global data analysis and comparisons and pave the way for more coordinated approaches to priority setting for health research and development.

HEALTH RESEARCH AND DEVELOPMENT DEMONSTRATION PROJECTS

7. Regional calls for proposals with consultations and broad engagement of relevant stakeholders identified 22 health research and development projects. Pursuant to decision WHA66(12) (2013), the

¹ Document A66/23 (http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_23-en.pdf, accessed 4 April 2016).

² Kiény MP, Viergever RF, Adam T, Boerma T, Røttingen JA. Global platform to inform investments for health R&D. *Lancet*, 2016, 387:1157 (<http://who.int/research-observatory/en/>, accessed 4 April 2016).

³ <http://www.who.int/research-observatory/portal/en/> (accessed 8 April 2016).

⁴ <http://www.health-policy-systems.com/series/GlobalObs> (accessed 8 April 2016).

Director-General convened a global technical consultative meeting of experts in Geneva, 3–5 December 2013)¹ to discuss further the projects in line with the guidance provided by the Health Assembly's decision. The experts reached consensus on eight potential demonstration projects, and recommended the top four for implementation. In light of the recommendations of the meeting, two out of the four projects, both related to leishmaniasis, were merged. In May 2014, the Sixty-seventh World Health Assembly requested the Director-General in decision WHA67(15) to expedite the process of the remaining four projects, in addition to the four already agreed. In August 2014, Brazil hosted a workshop to assist proponents of the remaining four projects in further development of their proposals. The proponents of one decided not to pursue their application but the other three proposals have since been assessed as fulfilling the requirements set for demonstration projects through an evaluation process involving the former Chair and Vice-Chair of the Consultative Expert Working Group and observers from six Member States.

8. The following six demonstration projects were thus finally selected:

- (a) the visceral leishmaniasis global research and development and access initiative (proponents: Drugs for Neglected Diseases initiative and United States Food and Drug Administration)
- (b) exploiting the pathogen box: an international open-source collaboration to accelerate drug development in addressing diseases of poverty (proponent: Medicines for Malaria Venture)
- (c) development of easy to use and affordable biomarkers as diagnostics for Types II and III diseases (proponents: African Network for Drugs and Diagnostics Innovation, China Tropical Diseases Drugs and Diagnostics Innovation Network, et al.)
- (d) development of a vaccine against schistosomiasis based on the recombinant Sm14, a member of the fatty acid-binding protein family: controlling transmission of a disease of poverty (proponent: Oswaldo Cruz Foundation, Brazil)
- (e) multiplexed point-of-care test for acute febrile illness (proponent: Translational Health Science and Technology Institute, India)
- (f) demonstration of the potential of a single-dose malaria cure of artemether-lumefantrine through reformulation in a nano-based drug delivery system (proponent: Council for Science and Industrial Research, South Africa).

9. These projects are at different levels of implementation. An Ad-hoc Technical Committee for the Demonstration Projects/Global Observatory on Health Research and Development² was established to which demonstration projects' proponents submit their project plans and financial requirements. The Committee met in Geneva (19 June 2015), reviewed the technical workplans and budgets proposed for the first year of implementation, and recommended allocation of funding to three projects. Letters of agreement were signed and funds were disbursed. The funding requirements from two more selected projects were reviewed, and financial contributions are awaited from Member States before disbursements can be made.

¹ http://www.who.int/phi/implementation/phi_cewg_meeting/en/index1.html (accessed 8 April 2016).

² http://www.who.int/phi/news/adhoc_committee/en/ (accessed 4 April 2016).

FUNDING FOR DEMONSTRATION PROJECTS AND THE GLOBAL OBSERVATORY ON HEALTH RESEARCH AND DEVELOPMENT

10. As reported by the Director-General to the Sixty-eighth World Health Assembly,¹ a budget line was established outside the WHO's Programme budget in order to finance the strategic workplan agreed by Member States as a result of their analysis of the Consultative Expert Working Group's report. This budget line is managed by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The estimated total financial requirement for implementation of demonstration projects and establishment of the Observatory for four years (2014–2017) is US\$ 85 million, to which Member States have been asked to make a contribution. As at 6 April 2016, a total of US\$ 0.82 million has been contributed by France, Switzerland and the United States of America to the Observatory, and a total of US\$ 7.45 million has been contributed or pledged by Brazil, India, Norway, South Africa and Switzerland to the voluntary fund designated for demonstration projects and the Observatory. Another US\$ 1.02 million was contributed by Switzerland and Norway as matching grants for contributions from developing countries on the basis of half a dollar for each dollar contributed, and US\$ 1.56 million more matching fund was pledged, pending developing country contributions. Funds received have been fully implemented, leaving a financial gap until the end of 2017 of about US\$ 74 million.

EXPLORATION OF FINANCING MECHANISM FOR CONTRIBUTIONS TO HEALTH RESEARCH AND DEVELOPMENT

11. The Sixty-seventh World Health Assembly in 2014 *inter alia* requested the Director-General to further explore with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases the possibility of hosting a pooled fund for voluntary contributions towards research and development for Type III and II diseases and the specific research and development needs of developing countries in relation to Type I diseases, recognizing the following:

- the scope of the diseases should not be limited to Type III diseases but should be in line with the mandate of the global strategy and plan of action on public health, innovation and intellectual property;
- the need for a sustainable financing mechanism for health research and development;
- the role of Member States in the governance of the coordination mechanism.²

12. The above option was further considered and noted by the Sixty-eighth World Health Assembly in 2015.¹ Subsequently, the Special Programme consulted extensively with a wide range of stakeholders from the public and private sectors, including funding agencies, ministries, academe, product development partnerships, industry and civil society.³ Using these inputs, the Special

¹ Document A68/34, noted by Committee B of the Sixty-eighth World Health Assembly, fifth meeting (http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC3/A68_2015_REC3-en.pdf#page=1, pp 310-315, accessed 4 April 2016).

² Decision WHA67(15) (2014).

³ A full report is available outside the meeting and electronically at: http://www.who.int/tdr/news/2016/funding_managing_health_product_R_D/en/ (accessed 4 April 2016). This work was supported by a designated award of SwFr 2 million from the Swiss Agency for Development and Cooperation.

Programme subsequently developed a new tool, Portfolio-to-Impact (P2I),¹ to model the timeline and minimum funding required to develop new medicines, diagnostics and vaccines for populations with limited resources that do not provide a strong incentive for commercial research and development.

13. Using the P2I tool, the Special Programme set out seven implementation scenarios for a new financing mechanism and estimated how many products, either new or re-purposed, might be developed under such a mechanism. The scenarios range from WHO acting primarily as a convener to set priorities to the management by the Special Programme of a pooled fund of various sizes (from US\$ 15 million to US\$ 500 million per annum) to finance product development of needed health products, diagnostics, vaccines and treatments, from promising leads through to the launch of a new product. The P2I is not disease-specific, but has the flexibility to accept the product development needs of developing countries.

14. Finally, the Special Programme explored options for a scientific working group to be responsible for managing the financing mechanism's portfolio, including selection of projects to be funded in line with the identified priorities, monitoring and evaluation of projects as well as financing of selected projects. The expertise required in the members of the scientific working group should include: experience in leading clinical development projects and in making portfolio decisions; field experience in developing country health systems; financing or business development experience; knowledge of infectious diseases; and regulatory agency experience. These core members could be supplemented by experts specific to individual priority disease areas or health interventions. Additional tools to assist the operation of the scientific working group have also to be presented in the report. The scientific working group would use an array of incentive mechanisms from grant-funded push mechanisms and prizes to purchase-commitment-type pull mechanisms in order to provide the best incentives for product developers.

15. Subject to a decision about the creation of a voluntary pooled funding mechanism and the availability of new funding, the Special Programme could adapt its processes and governance mechanisms currently in place to accommodate a new financial mechanism. A WHO-led coordinating mechanism would identify priorities using data from the newly established Global Observatory on Health Research and Development. These priorities would be operationalized by the scientific working group managed by the Special Programme.

COORDINATION OF HEALTH RESEARCH AND DEVELOPMENT

16. In 2010, the Sixty-third World Health Assembly adopted resolution WHA63.21 on WHO's roles and responsibilities in health research, endorsing the WHO strategy on research for health requested in resolution WHA60.15 (2007) and highlighting the need for better coordination of health research globally. The report of the Consultative Expert Working Group also comments that there is no "global" coordination of research and development for major diseases, and that "global health research and innovation system is highly fragmented."² The report concludes that it would be "difficult to create a single, overarching governance structure to coordinate global research and development, owing to the nature of research and development and differences in the structure of the world's

¹ UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (2016) Health product research and development fund: a proposal for financing and operation. http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1 (accessed 8 April 2016).

² http://www.who.int/phi/CEWG_Report_5_April_2012.pdf (accessed 8 April 2016).

economies.” However, it emphasized the role of WHO’s “constitutional mandate for coordination, which might include research and development at global, regional and national levels.” On this basis, the Consultative Expert Working Group recommended the establishment of a new global advisory body. Such a body would be able to build on the data and analyses provided by the Global Observatory and to make recommendations on research priorities.

17. Pursuant to the request in resolution WHA66.22 (2013) on follow up of the report of Consultative Expert Working Group to the Director-General “to review existing mechanisms in order to assess their suitability to perform the coordination function of health research and development;” and “to report on the review of existing coordination mechanisms ... to the Sixty-seventh World Health Assembly, through the Executive Board at its 134th session,”¹ the Director-General submitted document A67/27 to the Health Assembly. In that report, three types of coordination mechanisms were described:

- (a) passive coordination achieved through sharing of information;
- (b) active coordination through networks of researchers agreeing on priorities and collaboration; and
- (c) managed coordination through formal structures to manage the research undertaken and the allocation of resources to support them.

The report further suggested that option (b) would be the most appropriate, and that the Advisory Committee on Health Research could be reconstituted to fulfil this advisory role. Another proposal made in the report was to establish an annual conference of global health research and development stakeholders in order to maintain focus and momentum on these issues. Ideally, this conference would take place in a different region each year and be hosted by a major research institute active in this area.

18. The Advisory Committee on Health Research is a formal expert group with a consultative mandate to support WHO in carrying out its constitutional role of promoting and conducting health research, acting in close cooperation with external institutions pursuing common goals and with the scientific community at large. The committee was established in 1959 as the Advisory Committee on Medical Research and was given the role of advising the Director-General on research issues and formulating “global priorities for health research” in light of policies set by WHO’s governing bodies. All WHO’s regional offices established their own advisory committees on health research. In 2010, a report was published by WHO covering 40 years of work of Advisory Committee on Health Research.² One of the major contributions of the Advisory Committee on Medical Research had been to recommend, in 1974, the establishment of the Special Programme for Research and Training in Tropical Diseases.

19. In its new role as the Global Research and Development Coordination Mechanism, the Advisory Committee on Health Research could review the analyses provided by the Global Observatory on Health Research and Development and the conclusions of the proposed annual conference of global

¹ Resolution WHA66.22 (2013), subparagraphs 4(5) and 4(8), respectively.

² World Health Organization. Research and the World Health Organization: A history of the Advisory Committee on Health Research 1959–1999. Geneva: World Health Organization, 2010 (http://apps.who.int/iris/bitstream/10665/44484/1/9789241564113_eng.pdf, accessed 4 April 2016).

health research and development stakeholders in order to articulate global priorities for research and development. These priorities would be presented to Member States through the statutory annual report of the Advisory Committee on Health Research to WHO's governing bodies. They would be reviewed annually and would form the basis for the work of the scientific working group managed by the Special Programme for Research and Training in Tropical Diseases.

OTHER RELEVANT RESEARCH AND DEVELOPMENT-RELATED ACTIVITIES

20. Two new areas of research and development have emerged more prominently in the work of the Secretariat in the past few years. These are briefly described below.

21. The **research and development blueprint for action to prevent epidemics**. The recent Ebola virus disease epidemic, preceded by the outbreaks of severe acute respiratory syndrome and the Middle East respiratory syndrome and followed by the continuing Zika virus epidemic, has highlighted the need for a robust research and development preparedness for emerging diseases likely to cause severe outbreaks in the near future and for which few or no countermeasures exist. Currently, there is insufficient investment into the development of treatments, vaccines and diagnostics for these severe, emerging epidemic-prone diseases. These diseases are unpredictable, tend to occur in low-resource settings and affect either a limited number of people or populations with low purchasing power. The research and development blueprint addresses the primary issue for which the global strategy and plan of action on public health, innovation and intellectual property was created: ensuring access to affordable, safe and effective health products for which existing market mechanisms fail to provide incentives for health research and development.

22. The blueprint is a global strategy and preparedness plan to ensure that targeted research and development can strengthen the emergency response by bringing medical technologies to populations in need during outbreaks and epidemics. In particular, the blueprint aims to reduce the time between the declaration of a public health emergency of international concern and the availability of effective tests, vaccines and medicines that can be used to save lives and avert crises.

23. As part of the blueprint, an initial prioritized list of severe, emerging, epidemic-prone diseases for urgent research and development was agreed during a meeting of experts convened by WHO (Geneva, 8 and 9 December 2015). This list comprises: Crimean-Congo haemorrhagic fever, filovirus diseases (for instance Ebola virus disease and Marburg haemorrhagic fever), Lassa fever, highly pathogenic emerging coronavirus diseases (severe acute respiratory syndrome and the Middle East respiratory syndrome), Nipah virus disease and Rift Valley fever. Diseases that are considered serious and require action by WHO to promote research and development as soon as possible includes chikungunya, severe fever with thrombocytopenia syndrome, and Zika virus disease. The priority status of the Zika virus disease was raised after the declaration of a public health emergency of international concern by the Director-General on 1 February 2016 because of the ongoing outbreak of Zika virus infection associated with an increase in the number of cases of Guillain-Barré syndrome and microcephaly. Further work by the Secretariat includes defining the current status of basic and applied research for these prioritized epidemic-prone diseases, for incorporation into the work of the Global Observatory on Health Research and Development and to facilitate and coordinate the development of technology road maps to identify how to accelerate research and development for effective diagnostics, vaccines, therapeutics and other medical and information technology for the priority, epidemic-prone diseases. Other important developments concentrate on supporting improved regulatory preparedness for healthcare products epidemic control. The Secretariat is not engaged in research and development as such as part of the blueprint.

24. A research and development response during an epidemic relies on the existence of the right conditions – or an enabling environment – to facilitate timely and efficient action. This means that there must be, for example, a system in place for coordinated action, broad agreement on data and sample sharing, governance of research and development, and standards of care. This constitutes another area of work being covered in the research and development blueprint. Assessment of the effectiveness of the blueprint will rely on evaluating its ability to create such an enabling environment for research and development preparedness in developing countries, and on the impact that research and development plans on availability of medical technologies for the next outbreaks or epidemics.

25. Work is continuing to explore options for adequate and sustainable funding for priority research for severe, emerging, epidemic-prone diseases, for example through aligning and making more efficient use of existing funds and through linking this stream of work with related discussions of the Consultative Expert Working Group. A report on options for strengthening information-sharing on diagnostic, preventive and therapeutic products and for enhancing WHO's capacity to facilitate access to these products, including the establishment of a global database, starting with haemorrhagic fevers, which contains further information on the research and development blueprint, is being submitted to the Sixty-ninth World Health Assembly for consideration.¹

26. **Research and development for new antibiotics as part of WHO's global action plan on antimicrobial resistance.** In May 2015, the Sixty-eighth World Health Assembly adopted the global action plan on antimicrobial resistance in resolution WHA68.7. Because of inappropriate use of antibiotics in human and veterinary medicine and agriculture, pathogens quickly develop resistance. This occurrence is a significant disincentive for the industry to invest in research and development of new antibiotics as the resulting market is expected to be of short duration. As for neglected diseases, investment into the development of new antibiotics is insufficient, resulting in a meagre research and development pipeline. However, contrary to diseases of interest in the global strategy and plan of action on public health, innovation and intellectual property, the antibiotic market remains a commercial market and the diseases caused by resistant bacteria are not Type II and III diseases, but affect all countries. Therefore, the global action plan on antimicrobial resistance, under its Objective 5 on developing the economic case for sustainable development, requests the Director-General to explore options for the establishment of new partnerships to identify research and development priorities, to foster the development of new antibiotics, diagnostics, vaccines and other interventions, to improve the coordination of existing research and development related initiatives, to ensure access and to establish open collaborative research and development models.

27. To implement this part of the global action plan on antimicrobial resistance, the Secretariat and the Drugs for Neglected Diseases initiative have collaborated in the establishment of the Global Antibiotic Research and Development Facility, an independent product development partnership to develop new antibiotic treatments to counter antimicrobial resistance and to promote their responsible use for optimal conservation while ensuring equitable access for all. The Facility will work closely with all stakeholders in the field of antibiotic research and development from countries of all income levels. It will:

- (a) address global public health and specific needs of developing countries, targeting products that industry will not develop owing to lack of profitability;

¹ Document A69/29.

- (b) pilot the use of alternative incentive models that support conservation of and access to new antibiotics based on the experience of the Drugs for Neglected Diseases initiative in implementing alternative research and development models for neglected diseases; and
- (c) ensure that new antibiotics are affordable to all.

The Board of the Drugs for Neglected Diseases initiative approved the role of the initiative as an incubator for the initial start-up phase of this new facility until it becomes an independent entity. The Secretariat will not be directly involved in product research and development activities related to this initiative.¹

Policy coherence in activities related to research and development

28. In the past few months, the Secretariat has set up, or participated in the establishment of, two initiatives to redress insufficient investment into research and development, namely in the areas of emerging infectious diseases with epidemic/pandemic potential (the research and development blueprint) and innovation in antibiotics (the Global Antibiotic Research and Development Facility). The paragraphs below summarize common and divergent features between the agendas driven by implementation of the recommendations of the Consultative Expert Working Group on Research and Development: Financing and Coordination, and those of the two initiatives just mentioned.

29. **Scope of the initiatives.** The Consultative Expert Working Group was tasked with framing its analysis around Type III diseases (those that are overwhelmingly or exclusively incident in developing countries), Type II diseases (those that are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries) and special needs of developing countries concerning Type I diseases (those that are incident in both rich and poor countries, with large numbers of vulnerable populations in each). In the absence of an epidemic, diseases targeted by the research and development blueprint all fall into the category of Type II or Type III diseases. During a large epidemic, these diseases have a potential to qualify as Type I. Many if not all new treatments needed to combat antimicrobial resistance target diseases that can be categorized as Type II and III diseases (for example, multidrug-resistant tuberculosis or neonatal sepsis), while others target Type I diseases.

30. As is the case for diseases of interest in the report of the Consultative Expert Working Group, both the research and development blueprint and the Global Antibiotic Research and Development Facility pay attention to gaps that are not filled by the market-driven research and development system. It is important to note that the reasons for market failure are different for the three areas:

- in spite of a large unfulfilled demand for medical technologies, the market related to diseases targeted by the Consultative Expert Working Group is seen as unattractive because the population in need is poor;
- the demand for medical technologies for emerging epidemic/pandemic infectious diseases is low or inexistent in the absence of an epidemic – vaccines or therapies targeting them are therefore essentially destined to be stockpiled, in relatively limited volumes;

¹ http://www.who.int/phi/implementation/consultation_imnadb/en/ (accessed 5 April 2016).

- similarly, new antibiotics are proposed to be used rationally and essentially reserved for cases where current treatment modalities fail, which means that the demand is likely to be low and therefore a disincentive for the market.

31. The research and development blueprint and the Global Antibiotic Research and Development Facility initiatives have capitalized on the experiences accumulated and mechanisms refined during implementation of the recommendations in the report of the Consultative Expert Working Group, especially in exploration of possible financing models to support biomedical research and development. De-linkage of the market price from research and development costs, use of open knowledge innovation, and use of licensing conditions to favour access, which are the core principles formulated by the Consultative Expert Working Group, are the basic principles of the two initiatives.

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