World Health Organization

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Progress reports on technical and health matters

Report by the Secretariat

CONTENTS

A. POLIOMYELITIS: MECHANISM FOR MANAGEMENT OF POTENTIAL RISKS TO ERADICATION (resolution WHA61.1)

1. At an urgent stakeholders consultation of the Global Polio Eradication Initiative in February 2007 participants agreed on a 24-month intensified eradication effort with specific indicators to monitor progress. In May 2008, the Health Assembly in resolution WHA61.1 urged all remaining poliomyelitis-affected Member States to engage all levels of political and civil society to ensure that every child is consistently reached and vaccinated during every supplementary immunization activity against poliomyelitis. It also urged Nigeria to undertake intensified activities to stop rapidly the outbreak of poliomyelitis in the north of the country, and Afghanistan, India and Pakistan to implement large-scale mopping-up activities to interrupt their final chains of poliovirus transmission. The Health Assembly requested the Director-General to assist in mobilizing the financial resources necessary for full implementation of the intensified eradication effort, to undertake the necessary research for managing the long-term risks of reintroduction of poliovirus and re-emergence of poliomyelitis and to develop a new strategy to reinvigorate the fight to eradicate poliomyelitis from the remaining affected countries.

2. In June 2008, the Minister of Health in Nigeria established a high-level task force in order to improve the quality of supplementary immunization activities. Two such activities were urgently undertaken across the northern states in July and August 2008. Although the large outbreak of the disease experienced in 2008 has subsided, monitoring indicates that significant gaps in coverage of these immunization activities persist, with more than 60% of children remaining not fully vaccinated (having received three or fewer doses of oral poliovirus vaccine). Because of a continuing outbreak caused by a type 2 vaccine-derived poliovirus, northern Nigeria is the only area in the world where all three poliovirus serotypes are circulating. Since June 2008, polioviruses originating in northern Nigeria have spread to Benin, Burkina Faso, Chad, Côte d'Ivoire, Ghana, Mali, Niger and Togo.

3. In October 2008, India confirmed that indigenous type 1 poliovirus had not been detected in Uttar Pradesh state for 12 consecutive months, affirming the technical feasibility of poliomyelitis eradication. However, a new outbreak due to type 1 poliovirus in western Uttar Pradesh, following importation of the virus from Bihar state in mid-2008, has highlighted the fragility of progress because of the suboptimal efficacy of oral poliovirus vaccine in this area. Mopping-up activities with monovalent oral poliovirus vaccines continue on average every six weeks in western Uttar Pradesh and central Bihar. New approaches to enhancing vaccine efficacy are being assessed in order to accelerate eradication in northern India. In December 2008, type 1 poliovirus originating in western Uttar Pradesh, was detected in a sewage sample in Cairo.

4. In Pakistan, and to a lesser extent Afghanistan, the number of poliomyelitis cases surged in the second half of 2008 as a deterioration in security resulted in large-scale population movements and outbreaks in poliomyelitis-free areas, particularly in the Punjab province of Pakistan. In late 2008 and early 2009 Pakistan increased the number of nationwide supplementary immunization activities to supplement mopping-up activities in known reservoir areas, such as Sindh province where coverage during supplementary immunization activities was suboptimal. By early 2009 poliomyelitis was largely restricted to areas where insecurity hampers supplementary immunization activities, notably North-West Frontier Province in Pakistan and three of Afghanistan's 34 provinces (all three are in that country's Southern Region). This reality was underscored by the deaths in 2008 of two doctors and their driver on WHO duty for poliomyelitis eradication, in Kandahar province, Afghanistan.

5. Responses to outbreaks are continuing in 16 countries where there are cases associated with the importation of poliovirus in 2008 and early 2009. It is a matter of concern that 12 of these countries have become reinfected since mid-2008, demonstrating that international spread of poliovirus is continuing. Three of the outbreaks have continued for more than 12 months because response activities have been suboptimal:[1] Angola, Chad and Ethiopia and border areas in southern Sudan. Although the risk of poliovirus importation remains high globally, 90 Member States have not maintained certification-standard surveillance for acute flaccid paralysis, as requested for global certification, and 39 have not maintained routine immunization coverage with oral poliovirus vaccine at more than 80%, as recommended in resolution WHA61.1.

6. In order to reduce the risk of international spread of poliovirus, in November 2008 the Advisory Committee on Poliomyelitis Eradication urged WHO to amend its recommendations on immunization against poliomyelitis in *International Travel and Health*,[2] to ensure that all travellers to and from countries affected by poliomyelitis are fully immunized. Travellers who are resident in an area affected by the disease are recommended to receive an additional dose of oral poliovirus vaccine between one and 12 months prior to each international journey.

7. Resource mobilization activities have been enhanced in order to sustain the intensified eradication effort in 2009–2010. In 2008, countries where poliomyelitis was endemic and a range of new and existing donors provided additional funding for eradication activities, with important new multi-year commitments by Rotary International, the Bill & Melinda Gates Foundation and several G8 countries, the latter following a renewed commitment to poliomyelitis eradication by G8 leaders at the 2008 Summit (Hokkaido, Toyako, Japan, 7–9 July 2008). Rigorous resource mobilization activities will continue in order to ensure full funding of the intensified eradication effort. As at 27 February 2009, the Global Polio Eradication Initiative had a global funding gap for the period 2009–2010 of US$ 340 million, against a budget of US$ 1340 million.

8. New research on the management of the long-term risks of reintroduction of poliovirus and re-emergence of poliomyelitis includes: the development, field-testing and introduction of a real-time polymerase chain reaction test for more rapid detection of circulating vaccine-derived polioviruses; eight studies to characterize better the risks of chronic immunodeficiency-associated excretion of vaccine-derived polioviruses in low- and middle-income countries; investigation of the use of adjuvants and strategies to decrease doses and compress vaccination schedules in order to reduce the cost associated with existing inactivated poliovirus vaccines; and, a clinical development project for the production of an inactivated poliovirus vaccine using Sabin-strain polioviruses.

9. As a basis for a renewed fight to eradicate poliomyelitis, the Global Polio Eradication Initiative has developed a new strategic plan for 2009–2013. The plan consolidates the proven eradication strategies and recently-developed tools and tactics (i.e. monovalent oral poliovirus vaccines and their use), with new and country-specific initiatives to respond to the primary challenges in each remaining area affected by poliomyelitis.[2] These new initiatives include the following: development of new vaccines (e.g. bivalent oral poliovirus vaccine); novel use of existing vaccines in areas where the efficacy of oral poliovirus vaccines is compromised (i.e. higher-titre monovalent oral poliovirus vaccine type 1 and inactivated poliovirus vaccines); targeted use of seroprevalence surveys to assess vaccine efficacy and programme effectiveness more accurately; short interval additional dose strategies

[1] With respect to the activities Member States were urged to undertake in resolution WHA59.1.

[2] Conclusions and recommendations of the Advisory Committee on Poliomyelitis Eradication, November 2008. *Weekly Epidemiological Record*, 2009, **84**(3): 17–28.

to deliver extra vaccine doses to communities living in security-compromised areas; ensuring the continuation of annual oral poliovirus vaccine campaigns in areas subject to recurrent importations; and full implementation of the commitments of state governors in northern Nigeria outlined in their communiqué of 2 February 2009 entitled the "Abuja Commitments to Polio Eradication in Nigeria".[1]

10. In October 2008, the Director-General announced the commissioning of an independent evaluation of the intensified eradication effort at its 24-month mark in March 2009. After consultation with stakeholders in the Global Polio Eradication Initiative, the evaluation will focus on the principal affected areas, giving particular attention to the primary challenges identified in each,[2] and will establish a common roadmap for the actions needed in order to achieve the 2009 and 2010 milestones of the Global Polio Eradication Initiative Strategic Plan 2009–2013.

B. SMALLPOX ERADICATION: DESTRUCTION OF VARIOLA STOCKS (resolution WHA60.1)

11. The present document reports on the tenth meeting of the WHO Advisory Committee on Variola Virus Research (Geneva, 19 and 20 November 2008) and on the work of the Secretariat. In resolution WHA60.1, the Health Assembly requested the Director-General to undertake a major review in 2010 of the results of the research undertaken in accordance with the terms of resolution WHA55.15, so that the Sixty-fourth World Health Assembly may reach global consensus on the timing of the destruction of existing variola virus stocks.

12. **Update on research proposals submitted to WHO.** The Advisory Committee received a list of research proposals currently approved by its scientific subcommittee. Overall, 18 work programmes have been approved. For the major review of variola virus research in 2010, research projects that are in progress should be concluded, with an extension being considered only after the review has been finalized; that does not preclude submission of research proposals but it does mean that clear research goals are vital for enabling assessment of such proposals.

13. **Virus strains in the two repositories.**[3] The Committee reviewed data on the variola virus strains and primary isolates held in the two collections. The planned introduction of a new biosafety level 4 laboratory at the Centers for Disease Control and Prevention in the United States of America in 2009 will increase capacity for research. Since the previous report to the Committee,[4] there have been no additions to or withdrawals from the long-term repository, but material was withdrawn from the laboratory stocks for work on agreed research protocols. At the VECTOR centre in the Russian Federation a new repository with high physical security has been created. During the past year, 200 working stocks of non-viable or duplicate material have been destroyed, bringing the total number of vials in the Russian repository to 691.

[1] Accessible online at www.polioeradication.org.

[2] Conclusions and recommendations of the Advisory Committee on Poliomyelitis Eradication, November 2008. *Weekly Epidemiological Record*, 2009, **84**(3): 17–28.

[3] Russian State Centre on Virology and Biotechnology (VECTOR), Koltsovo, Novosibirsk Region, Russian Federation and the Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America.

[4] Document EB122/29 Add.1, section E.

14. **Update on prophylaxis and therapeutics.** The Committee was informed of progress in research into chimeric chimpanzee/human monoclonal antibodies. Combinations of antibodies fully protected mice challenged with vaccinia virus and were also active therapeutically. Recent advances in the development of antiviral agents against orthopoxviruses include the synthesis and testing of a series of compounds for antiviral activity in cell culture against various orthopoxviruses; 74 compounds from three groups proved to be active, and it is planned to extend this research to cowpox virus and ectromelia virus in mice. The orally-administered prodrug of cidofovir, CMX001, and a series of other compounds are currently being investigated. Further pharmacokinetic studies of oral administration of ST-246 have been conducted in order to establish appropriate doses, which have been shown to be effective in the monkeypox primate model. ST-246 was made available for emergency (compassionate) use in 2007 for the treatment of a clinical case of eczema vaccinatum and the manufacturer would consider direct requests in the case of a further requirement for such use.

15. **Update on diagnostic assays.** The Committee was informed of recent developments in diagnostic assays. Two assays, both based on real-time polymerase chain reaction, were designed for field use; one differentiated variola virus from other orthopoxviruses and the other distinguished between variola major and minor. Information on both the assays is in the public domain. Another avenue of research has been the development of protein-based "point-of-care" diagnostic assays for antigen and antibody detection. Pilot studies of a serological assay conducted in field conditions in the Democratic Republic of the Congo confirmed the robustness of the assay. The Committee noted the potential application of these diagnostic systems in the field, as long as they were affordable and available.

16. **Update on animal models.** The Committee was informed of the results of five years of primate model development authorized by WHO to facilitate the evaluation and licensing of antiviral drugs and vaccines using the Animal Efficacy Rule of the Food and Drug Administration in the United States of America. These models simulated human smallpox but could be improved by mimicking more natural routes of exposure. Additional enhancements were described but, although parallels between monkeypox and smallpox exist, the Committee heard conflicting views on the utility of monkeypox as an adequate surrogate for variola. Significant progress has been made, but further refinement of the animal models is desirable.

17. **Update on vaccines and vaccination.** The Committee was told about the results of experiments using live variola virus as the target of plaque-reduction neutralization tests in the evaluation of different vaccination regimens. The data suggest that such tests may be important for evaluating smallpox vaccines. The Committee was also updated about the attenuated vaccinia vaccine LC16m8, which is being stockpiled in Japan and may confer long-lasting protective immunity in humans. The Committee noted several advantages of LC16m8, and it was argued that LC16m8 had not received sufficient attention as a less reactogenic smallpox vaccine.

18. **Regulatory issues.** An overview was given of current strategies to improve the safety of the smallpox vaccine while maintaining its efficacy. In the United States of America, the Food and Drug Administration's Center for Biologics and Research requires that any new candidate vaccine demonstrate efficacy in multiple animal models of smallpox but not necessarily in a model infection with variola virus. Use of live variola virus would, however, be desirable, in terms of expediting the review process, and would be needed for the evaluation of new antiviral agents. It was argued that the usefulness of non-variola animal models should not be underestimated and that they should be fully exploited. Other members stressed that a better understanding of the correlates of immunity or pathogenesis may be required for the evaluation of new candidate vaccines and therapeutics.

19. **Is there a need to stockpile ST-246?** The Secretariat informed the Committee that its previous report had generated interest among Member States, in particular regarding access to antiviral agents. The Committee considered that it would be premature to establish a WHO stockpile of any drug that had so far shown promising activity in animal models of variola but did not yet have approval for use by drug regulatory authorities. An in-depth evaluation of potential epidemiological scenarios would be required to estimate the need for drugs when they were approved. The Secretariat would act as a facilitator between potential users and the company in the case of a requirement for emergency compassionate use of ST-246.

20. **Synthesis of variola virus.** The Committee was given a brief review of the literature which suggested that currently available technology could allow the recreation of a full-length variola virus genome solely by chemical synthesis, as has been done for other larger microorganisms. The Secretariat reminded the Committee that WHO had published guidelines[1] on the use of fragments of variola virus DNA that strictly excluded the synthesis of the virus. Members of the Committee were strongly encouraged to promulgate these guidelines widely, not just in the orthopoxvirus research community but also among policy-makers and other researchers.

21. **Review of research proposals.** The Committee accepted the suggestion that the Scientific Subcommittee should be expanded to seven members, approved its new membership, and agreed to mechanisms for increasing its efficiency.

22. **Review in 2010 and process.** The Committee reviewed the timetable necessary to undertake the major review in 2010 and decided to consider the following steps: (1) a comprehensive review of the literature and of unpublished data concerning live variola virus research to be undertaken by a group of scientists endorsed by the Committee and representing all areas of research and development on orthopoxviruses; (2) the consideration by the Advisory Committee of the above-mentioned reviews; (3) an external review of the above-mentioned reviews to be undertaken by independent experts from outside the field of variola virus research; and (4) the preparation of a report on the major reviews for the final consideration by the Advisory Committee. A report from the Secretariat would be submitted to the Executive Board for consideration at its session in January 2011 and that report and the Board's comments would be further considered by the Sixty-fourth World Health Assembly. The Committee agreed that the state-of-art review should target a broad range of readers and cover the following subjects: the current state of the variola virus stocks and repositories, diagnostics, genomics, vaccines, therapeutic agents, animal models and pathogenesis, and benefits. The final review by the Advisory Committee should also feature policy issues, such as how to respond to and manage outbreaks and the regulation of relevant biologics and drugs, with final conclusions and recommendations about the way forward.

23. **Variola virus diagnostic network.** The Committee discussed the possible need for a WHO informal network of laboratories for smallpox confirmatory diagnostics and considered that such a network would be important; additional details were needed on criteria for membership, quality management, and diagnostic testing. A specific concern was to limit the culturing of potentially infectious material. The Committee also considered how to formalize such a network, in particular verification of smallpox diagnostic capabilities with the involvement of the two WHO Collaborating Centres for smallpox, but no criteria were determined.

[1] *Weekly Epidemiological Record*, 2008, **83**(44): 393.

24. The Executive Board noted the progress report at its 124th session in January 2009.[1]

25. In March 2009 a WHO biosafety team undertook an inspection of the authorized repository in the Centers for Disease Control and Prevention (Atlanta, Georgia, United States of America). The team was impressed with the security and safety arrangements, and made some recommendations, which were to be seen as contributing to a process of continuous improvement. The report of the mission is being finalized and will, as requested in resolution WHA60.1, be made available for public information.

C. MALARIA, INCLUDING PROPOSAL FOR ESTABLISHMENT OF WORLD MALARIA DAY (resolution WHA60.18)

26. WHO convened a panel in January 2008 to examine the technical issues underpinning malaria control and to review the feasibility of eradicating the disease. The achievements of the past few years demonstrate that, with a rapid expansion of effective antimalarial interventions, malaria-related morbidity and mortality can be significantly reduced within a relatively short period of time in all epidemiological situations. However, malaria cannot be eradicated with existing tools. The Secretariat is proposing that a meeting of the WHO Expert Committee on Malaria be convened in 2010 in order to make technical recommendations on malaria control and elimination.

27. WHO has worked at all levels with partners such as UNICEF, the World Bank Global Strategy and Booster Program, the Malaria Initiative of the President of the United States of America, and the Roll Back Malaria Harmonization Working Group in order to support countries prepare applications to Rounds 7 and 8 of the Global Fund to Fight AIDS, Tuberculosis and Malaria. This support had an unprecedented result: some 70% of country applications for funding on malaria control and elimination were successful.

28. The United Nations Secretary-General announced the appointment of Mr Raymond G. Chambers of the United States of America as his Special Envoy for Malaria and issued a call to action on the goal of providing universal coverage of key malaria interventions to Africa by the end of 2010, and to reduce preventable malaria deaths to near zero by 2015.

29. Events took place worldwide to celebrate the first global World Malaria Day on the theme of *Malaria – a disease without borders*, with the support of all WHO regional offices. World Malaria Day was an ideal platform for countries and regions to encourage greater awareness and to ensure that advocacy is sustained in all regions.

30. On 18 September 2008, the Director-General launched the *World malaria report*,[2] which noted an estimated 247 million cases of malaria and 881 000 deaths from the disease in 2006, mostly among children in Africa. A total of 91% of deaths were in Africa and 85% of deaths were in children under five. Yet the report provided strong evidence that a renewed global assault on malaria, under way since the turn of the millennium, has been accelerating in the past few years. Further integration of existing strategies will help to achieve the goals.

[1] See document EB124/2009/REC/2, summary record of the twelfth meeting, section 4.

[2] *World malaria report 2008*. Geneva, World Health Organization, 2008.

31. The Roll Back Malaria Partnership launched the Global Malaria Action Plan at the 2008 United Nations Millennium Development Goals Malaria Summit.

32. International funding commitments to the Global Malaria Action Plan in 2008 included US$ 1620 million over two years from the Global Fund with a plan to distribute 100 million additional bednets; US$ 1100 million from the World Bank; US$ 168.7 million from the Bill & Melinda Gates Foundation for vaccine research; and £40 million from the United Kingdom of Great Britain and Northern Ireland, which includes support for artemisinin combination therapy.

33. The following major constraints on resources and capacity continue to require attention.

- Inadequate funding for malaria control remains an issue in some countries where there is a lack of domestic funds or a failure to appropriately manage the available funds.
- In countries where malaria is endemic, more human resources are required to ensure that national malaria control programmes have the necessary managerial and technical capacities to deliver interventions.
- Requests for technical support are increasing but are not matched by sufficient funding. As a result, WHO and its partners are facing the crucial challenge of maintaining adequate human resources to respond to countries' needs.
- A major effort to increase the capacity of health systems should be extended beyond the health facility level in order to empower communities to achieve treatment and prevention goals.
- With malaria incidence and deaths decreasing in many places, there is an additional demand on surveillance systems to monitor progress.
- Resources are required to support research into improved formulations of artemisinin-based combination treatments, particularly those for children, and into new combination medicines.

34. The Executive Board at its 124th session noted the progress report.

D. IMPLEMENTATION BY WHO OF THE RECOMMENDATIONS OF THE GLOBAL TASK TEAM ON IMPROVING AIDS COORDINATION AMONG