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Progress reports

Report by the Secretariat

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B. SMALLPOX ERADICATION: DESTRUCTION OF VARIOLA STOCKS

1. 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.

2. **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.

3. **Virus strains in the two repositories.**[1] 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to the Committee,[2] there have been no additions to or withdrawals from the long-term repository, but material was withdrawn from the laboratory stocks for work on agreed research protocols.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.

4. **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.

5. **Update on diagnostic assays.** The Committee was informed of recent developments in diagnostic assays. Two assays designed for field use that were based on real-time polymerase chain reaction; 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

[1] 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.

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

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.

6. **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.

7. **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.

8. **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.

9. **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 showed 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.

10. **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

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

strongly encouraged to promulgate these guidelines widely, not just in the orthopoxvirus research community but also among policy-makers and other researchers.

11. **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.

12. **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.

13. **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.

G. WORKING TOWARDS UNIVERSAL COVERAGE OF MATERNAL, NEWBORN AND CHILD HEALTH INTERVENTIONS

14. Maternal, newborn and child health interventions have helped to decrease under-five deaths from 10.3 million in 2004 to 9.5 million in 2006. Measles deaths alone fell from 757 000 in 2000 to 242 000 in 2006. Maternal mortality remained stable between 1990 and 2005, although no region achieved the necessary 5.5% annual decline to meet Millennium Development Goal 5. In sub-Saharan Africa annual rates in decline in maternal and under-five mortality are especially low, at 0.1% and 1%, respectively.

Current levels of coverage

15. Coverage of effective interventions remains limited and large inequities in access have been noted within and between countries. The proportion of women wishing to delay or stop childbearing but who do not have access to contraception varied between 10% and 24% across regions, according to data reported in 2007. The consequence is high fertility rates, with adolescents particularly vulnerable to unwanted pregnancy. Although 75% of pregnant women in low-income countries

received one antenatal visit, only around 50% received four or more. The proportion of births attended by a skilled health worker in low-income countries showed an 8% increase between 2006 and 2008. The greatest increases in coverage of child health interventions over a three-year period from 2000 (for countries with two data points), were observed for distribution of insecticide-treated nets in selected countries (7%) and for neonatal tetanus protection (5%). Interventions requiring 24-hour services, such as managing childhood illnesses, increased by 1% between 2006 and 2008. Immunization coverage with three doses of diphtheria/pertussis/tetanus vaccine increased from 73% in 2000 to 81% in 2007, and measles vaccination coverage increased from 72% to 82%. Table 1 illustrates coverage levels in 68 high-burden countries between 2000 and 2006.

16. Low-intervention coverage is naturally associated with health-system deficiencies. Workforce density in 54 of the 68 countries fell below the threshold required to deliver primary health care interventions. In 60 countries, the proportion of payments made by households to point-of-use health services was more than 15%, a level that can lead to hardship and impoverishment.

Action to improve coverage

17. WHO monitors progress in reproductive, maternal, newborn and child health and nutrition with partners – including through participation in the Countdown to 2015 initiative to track progress towards achievement of the United Nations Millennium Development Goals. Immunization coverage is reported annually by 95% of countries. WHO also has produced country profiles for maternal health and supported countries in adoption of indicators to assess reproductive health. An assessment of key national policies for maternal, newborn and child health was completed in 2008 and showed that the domain required further strengthening.

18. WHO, UNICEF, UNFPA and the World Bank agreed in July 2008 on a framework on coordinated country action to reduce maternal and newborn deaths. WHO also worked through the International Health Partnership, the Global Campaign for Health, and the Partnership for Maternal, Newborn and Child Health to improve standardization. WHO played a leading role in organizing the Women Deliver Initiative and Conference for Global Advocacy (London, 18–20 October 2007).

19. The Secretariat has worked with Member States to formulate strategies and action plans for reproductive, maternal, newborn and child health, and to introduce updated guidelines. It also has promoted policies that increase coverage and quality of care, including authorizing midwives to perform life-saving tasks and community health workers to manage common childhood illnesses.

20. Organizationally, the Secretariat is working on guidelines for integrated services, including integrated management of childhood illness and integrated management of pregnancy and childbirth. For instance, immunization contacts are used to distribute vitamin A capsules, insecticide-treated nets, and medicines for de-worming. Prevention of mother-to-child transmission of HIV is included in antenatal and postnatal care. Linkages are promoted between services for sexual and reproductive health and HIV/AIDS. WHO created three regional networks of experts on malaria in pregnancy in 2004. A fourth network is being set up in Asia.

21. WHO is evaluating the effectiveness of approaches to increasing access to services, such as abolishing user fees for maternal and child health services, contracting out of reproductive health services and performance-based payment schemes, including collaboration with the private sector and civil society.

22. The need to increase investment in maternal, newborn and child health was stressed in the Toyako Framework for Action, drawn up at the G8 Summit in 2008 (Toyako, Japan, 7–9 July 2008), and in multiple forums, such as Countdown to 2015 and Women Deliver conferences, and in the Director-General's roundtable with women leaders at the United Nations General High Level Event on the Millennium Development Goals (25 September 2008). WHO supports the GAVI Alliance in its allocation of funds for health-system strengthening, and builds capacity in countries in order to maximize use of the Global Fund to Fight AIDS, Tuberculosis and Malaria and strengthen reproductive, maternal and child health services.

Table 1.

Key indicators of intervention coverage for reproductive, maternal, newborn and child health[1]				
			Range	
Number of countries		**Median (%)**	**Low (%)**	**High (%)**
Nutrition				
63	Proportion of infants < six months old who were exclusively breastfed	28	1	88
63	Proportion of infants 6–9 months old who received complementary foods and continued breastfeeding	62	10	91
55	Proportion of under-fives who received two doses of Vitamin A supplementation in the last 12 months	78	0	99

[1] The data were compiled for 68 countries that account for 97% of maternal and child deaths. "Number of countries" indicates the countries for which comparable data were available in the period 2000–2006. The latest data point was included in the analysis. "Median" lists the median coverage level among the countries with relevant data, but masks the inequities between and within countries. "Range" reflects the lowest and highest coverage levels. Indicators marked * reflect interventions applicable to the 45 (out of 68) countries that have endemic malaria. Sources of data: Multiple Indicator Cluster Surveys, Demographic and Health Surveys, interagency global monitoring of immunization coverage and of Vitamin A coverage. More details can be found in the Countdown Report 2008 at www.countdown2015mnch.org.

Key indicators of intervention coverage for reproductive, maternal, newborn and child health[1]				
			Range	
Number of countries		**Median (%)**	**Low (%)**	**High (%)**
Child health				
68	Proportion of infants who were immunized against measles	80	23	99
68	Proportion of infants less than one year old who had received the third dose with diphtheria, tetanus and pertussis vaccine	81	20	99
57	Proportion of children less than five years old with diarrhoea who received oral rehydration therapy, or increased fluid with continued feeding	38	7	76
35	Proportion of children less than five years old who slept under an insecticide-treated net in the last 24 hours*	7	0	49
34	Proportion of children less than five years of age with fever in the last two weeks who received antimalarial treatment*	40	0	63
60	Proportion of children less than five years old with suspected pneumonia who sought care from a qualified health provider	48	12	93
19	Proportion of children less than five years old with pneumonia who received treatment with an antibiotic	32	3	82
Reproductive, maternal and newborn health				
64	Proportion of women of reproductive age (15–49) who are using (or whose partner is using) a contraceptive method, at a particular point in time	29	3	87
40	Unmet need for family planning	23	9	41
39	Proportion of women who had four or more antenatal care contacts during their last pregnancy in the five years prior to the most recent survey	49	12	87
64	Proportion of pregnant women who received two doses of tetanus vaccine	81	31	94
22	Proportion of pregnant women who received at least one dose of intermittent preventive treatment for malaria*	7	0	61
66	Proportion of births attended by a skilled health worker	53	6	100
47	Proportion of infants who initiated breastfeeding within one hour of birth	43	23	78

ACTION BY THE EXECUTIVE BOARD

23. The Board is invited to note these reports.

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