A report to the Director-General of WHO

The Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox

Geneva, Switzerland

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Executive summary

Purpose

The purpose of the meeting was to provide guidance to the WHO Director-General on the public health implications of synthetic biology technology as it relates to public health measures for smallpox preparedness and control. The public health implications are for countries and for WHO, and include diagnostics, vaccines and medicines and research related to the variola virus.

Background

At the Sixty-seventh World Health Assembly in May 2014, WHO was requested to undertake a consultation on the use and potential impact of technologies for synthetic biology on smallpox preparedness and control, in order to further inform the World Health Assembly in its discussions on the timing of the destruction of existing variola virus stocks. As part of this consultative process a group of experts, the Independent Advisory Group (IAG) on Public Health Implications of Synthetic Biology Technology Related to Smallpox, was convened at the end of June 2015 in order to provide an assessment to the Director-General.

Prior to the meeting of the IAG, a Scientific Working Group (SWG) on Synthetic Biology and Variola Virus and Smallpox was convened on 16–17 April 2015 to review the evidence and inform the deliberations of the IAG. The SWG addressed relevant scientific and technical questions around the re-creation of variola virus; the risks and benefits of synthetic biology for variola virus research; and the guidance required from WHO regarding distribution and handling of live variola virus maintained at the two designated WHO collaborating centres that are authorized repositories of variola virus. The conclusions of the SWG were as follows:

> *"With the rapid advances in synthetic biology, there is now the capability to recreate the variola virus, the causative agent of smallpox. While recreating variola is quite complex, it is increasingly possible due to the availability of genetic material and of machines for complex assembly, as well as increasing know-how among a broad array of persons. Furthermore, the rapid rise in availability of genetic material from commercial sources and the so-called "grey market" is driving the cost of this material down, making recreation possible by multiple institutions and persons, including those with malicious intent. The "WHO Recommendations concerning the distribution, handling and synthesis of variola virus DNA" should be revised. Consideration should be given to adding a component or separate document on guidance to commercial DNA providers for screening requests for DNA fragments.*
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> *With the development of these technologies, public health agencies have to be aware that henceforth there will always be the potential to recreate variola virus, and therefore the risk of smallpox re-emerging can never be fully eradicated."*

Methodology

A scenario approach was chosen to foster discussion and debate on the implications of synthetic biology among the members of the IAG. They were expected neither to comment on the likelihood of occurrence of the scenarios nor to provide solutions or recommendations for them; rather the aim was to have illustrative events to frame and guide the discussions.

The four scenarios described the following situations and were followed by discussions on the question of the impact of synthetic biology on controlling the emergence of smallpox disease.

- Scenario 1: the emergence of smallpox-like disease in a remote area in a developing country.
- Scenario 2: the emergence of smallpox-like disease in a densely populated city.
- Scenario 3: the emergence of smallpox-like disease following a laboratory accident.
- Scenario 4: a situation in which a group of individuals inject themselves with synthesized variola virus.

Implications

Before synthetic biology was possible, two potential situations for re-emergence existed: (1) natural re-emergence (e.g. by mutation of another poxvirus), and/or (2) a laboratory release (deliberate or accidental) from one of the two WHO variola virus repositories or from unknown locations.

Therefore, the risk of re-emergence is not new. However, it has increased as synthetic biology technologies to recreate, and even modify, the virus continue to become cheaper and more easily accessible. Even if the live virus stocks are destroyed, the act of destruction is not irrevocable.

Given that the risk has changed, the key questions facing the world now are:

- Is the world prepared for this additional risk? If not, what should be done to become sufficiently prepared?
- What are the implications for (1) public health preparedness for re-emergence and (2) research around this new risk?
- Does the new, additional risk change the parameters of the discussion for the destruction of the variola virus in the two repositories?

Based on recent reviews of the public health responses to the H1N1 pandemic and to the Ebola outbreak, there is recognition of fundamental gaps in several areas of preparedness for any emerging disease outbreak, including smallpox. Risk reduction strategies and preparedness need to be adapted to take into account this new risk from synthetic biology in addition to the core capacities already required under the International Health Regulations 2005 (IHR 2005), including:

- **Increased capacity for early detection and diagnostics:** clinical capacity to recognize and treat smallpox; laboratory capacity, particularly at local level; development of simple diagnostic tests.
- **Increased capacity for disease control:** anticipation and preparedness of requirements for public health countermeasures such as vaccines and antivirals; supplies and quantities of vaccines and drugs needed for different scenarios; global expertise in specific epidemic diseases such as smallpox.
- **Increased biosecurity:** revised regulations for research on DNA fragments of variola virus and synthesis of variola virus DNA by new technologic approaches;; increased biosafety and biosecurity in laboratories, including stock inventories; strengthened regulatory frameworks and their implementation; coordination between sectors including health, judiciary, law enforcement and customs.
- **More effective risk communication:** acknowledgement of risk in the context of other infectious risks; transparency regarding dangers and measures to prevent and avoid them; avoidance of attempts to mislead the public; tracking of and responding to rumours; community engagement to detect and manage disease and to assist in information sharing.

Synthetic biology goes beyond smallpox and should be considered in relation to the elimination and eradication of other infectious diseases as well.

1. Background

1.1 Objectives and process of the consultation

The Independent Advisory Group (IAG) on Public Health Implications of Synthetic Biology Technology Related to Smallpox met at WHO headquarters on 29–30 June 2015. The purpose of the meeting was to provide guidance to WHO's Director-General on the public health implications of synthetic biology technology, as related to public health smallpox preparedness and control. The implications reviewed were for countries and for WHO, including diagnostics, vaccines and medicines and research related to the variola virus. The agenda of the meeting is contained in Annex 1. A list of the members of the Independent Advisory Group and of the resource persons who attended the meeting is contained in Annex 2.

The meeting was opened by Dr Keiji Fukuda who welcomed the participants. Dr Fukuda stressed the importance of the meeting, noting that the matters to be discussed would be significant not only for smallpox but also for other issues. Although the disease smallpox had been eradicated, Dr Fukuda noted that the virus still exists in research laboratories. In addition, with the development of synthetic biology the recreation of variola virus has become a possibility. He pointed out that the issue of the timing of the destruction of the variola virus is a matter for discussion by WHO Member States.

The topic was being addressed because the World Health Assembly in 2014 had asked about the significance of synthetic virology in relation to smallpox. The Director-General would respond to the Health Assembly's question and the meeting of the Independent Advisory Group would be a major part of preparing that response. The Director-General would consider the advice given by the IAG and would decide how to disseminate the report.

The meeting was attended by members of the IAG as well as four internationally renowned experts on variola virus and smallpox. All participants were asked to treat the discussions as confidential.

1.2 Overview of smallpox

Dr Sylvie Briand gave an introduction to smallpox disease which has been a cause of fear for centuries and for which the first ever vaccine was developed in 1796. WHO's smallpox eradication programme was started in 1966, and the last natural case of the disease was reported in 1977 in Somalia. The World Health Assembly declared smallpox eradicated in 1980. However, the variola virus has not been eradicated, as it was decided at that time to maintain stocks in the Soviet Union and the United States. The live virus is today maintained at two WHO Collaborating Centres: the Centres for Disease Control and Prevention, Atlanta, USA (CDC), and the State Research Centre of Virology and Biotechnology, Novosibirsk, Russian Federation (VECTOR).

Humans were the only reservoir for the disease. The disease course has a long incubation period of 7–17 days. People are infectious only from the onset of rash and remain infectious until disappearance of the last scab. Transmission is through large and small particle aerosols, and direct contact with body fluids. The disease is also spread by fomites. In its last decades the disease was chiefly spread in households and health-care settings. In a susceptible population the average number of cases of smallpox generated by an infected person is 3–6 (while for measles it is 12–18).

The symptoms of the disease can be confused with other diseases such as monkeypox and even chickenpox. Various vaccines and diagnostics are available, and antivirals are being developed. In addition there is VIG (Vaccinia Immune Globulin) which is made from the blood of individuals who have been vaccinated with the smallpox vaccine. Given the research of recent decades there are more interventions available now than there were in the pre-eradication period.

During the Smallpox Eradication Programme, the vaccine used had serious adverse reactions (5-10 in one million vaccinees), and 1-2 in one million died. However, vaccination was carried out because the risk from the vaccine was less than the risk from the disease. Today the vaccine could not be used in certain populations, such as persons with HIV. Although attenuated, safer vaccines are available, there is uncertainty about their effectiveness and safety in mass campaigns.

It is highly likely that an outbreak of smallpox will lead to similar challenges to those posed by the recent Ebola outbreak in West Africa or MERS-CoV outbreak in the Republic of Korea. Major priorities in such an outbreak would be fear management, risk communication and community engagement to promote compliance with control measures and reduction of stigma. If several countries are infected there will need to be rapid delivery of vaccines, and countries would be expected to want more than they need. The global emergency stockpile of smallpox vaccine is 2.4 million doses in Switzerland, plus 32 million doses donated and available in other countries. The overall quantity of vaccine available is estimated to be around 700 million doses. There is a lack of clarity about the length of immunity after vaccination, and the only certain lifetime protection comes from having already had smallpox once.

The main concern in an outbreak of smallpox would be that no one under 40 years of age (around 3.6 billion people) has been vaccinated, thus leading to an increasingly susceptible population. There would be delays in diagnosis since the disease is unknown by many health workers, and a global panic can be anticipated even with only a small number of cases.

There would be a major economic impact – the 2015 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in the Republic of Korea is estimated to have cost the Korean economy many billions of dollars. .

Meeting participants noted that little is known about potential hidden stocks of variola viruses. At the same time, the development of synthetic biology reduces our confidence in eradication. If the disease were to reappear, whether naturally or due to a synthetic virus, we would have 14 days (maximum incubation period) to vaccinate contacts. However, given the intensity of international travel, the disease would potentially spread rapidly and, since health systems in developing countries are often under-resourced, delays in diagnostics can be anticipated.

1.3 Report of the Scientific Working Group

In April 2015 WHO convened a meeting of a Scientific Working Group (SWG) on Synthetic Biology and Variola Virus and Smallpox. The report of the SWG, which was presented to the Independent Advisory Group by Professor Geoffrey Smith, is attached as Annex 3. The aim of the SWG was to provide scientific background information on synthetic biology technology with regard to the variola virus.

The SWG concluded that, with the increasing availability of DNA fragments that can be synthesized from simple chemicals, it would be possible to recreate variola virus, and that this could be done by a skilled laboratory technician or by undergraduate students working with viruses in a relatively simple laboratory. To recreate the variola virus by synthesizing the DNA and then relinking the parts is theoretically possible but is considered to be highly unlikely to happen accidentally since the variola genome is large and complex. It was therefore felt that synthesis would require a deliberate and sustained effort.

Over 45 genomes of the variola virus have been sequenced and the sequence is in the public domain, and other orthopox viruses (which have similar DNA) have been recreated. Recreating variola virus is prohibited by under the World Health Assembly (WHA) resolutions, though anyone trying to do this may not know or care about WHO's rules. Someone recreating the virus could, either by accident or deliberately, introduce elements to enhance its virulence or make it resistant to existing medicines and vaccines.

The SWG noted that, although a recreated variola virus could be useful for research on vaccines and diagnostic tests, there are serious concerns regarding modifications of the virus by institutions or individuals with malicious intent. Members of the SWG concluded that the WHO recommendations concerning the distribution, handling and synthesis of variola virus DNA should be revised. Additionally, consideration should be given to the addition of a component or separate document on guidance to commercial DNA providers regarding screening of requests for DNA fragments. The SWG further concluded that, given the ability to recreate the variola virus using synthetic biology techniques, the destruction of the remaining stocks of variola virus at the two WHO Collaborating Centres would not irrevocably destroy the virus. After destruction of the stocks, the variola virus could still be recreated.