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Advances in science and technology: impact on response to infectious disease outbreaks and relevance to Article VII

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Summary

This working paper considers recent developments in science and technology relevant to Article VII of the BTWC, with particular examples emerging from the response to the Ebola Virus Disease outbreak in West Africa. Advances in surveillance, detection and diagnostics, and in vaccines and therapeutics have been considered also under the standing agenda item on science and technology in BTWC meetings; these may contribute to global efforts to respond to infectious disease outbreaks whether of natural, accidental or deliberate origin. Information sharing will be a key factor for future progress. The BTWC process for review of scientific and technological advances needs the flexibility to address emerging issues relevant to particular provisions; this should be addressed by the Eighth Review Conference in deciding the structure and role of the future programme.

Introduction

1. Amongst the lessons identified by assessments of the international response to the Ebola Virus Disease (EVD) outbreak in West Africa is the need to expand investment in research and development on diagnostics, drugs and vaccines for neglected diseases with outbreak potential, and to ensure access to such medical countermeasures whenever and wherever they are needed.

2. Many developments relevant to requirements for responding to future infectious disease outbreaks have been reviewed under the standing agenda item on science and technology in the previous years of the current intersessional programme. Specific advances that were made as a direct consequence of the EVD outbreak, particularly in accelerating the development of vaccines, therapeutics and diagnostics are continuing to progress. Any effective results of such research and development will contribute to efforts to prevent, detect and respond to outbreaks of infectious disease, whether natural, accidental or deliberate. Hence, all such scientific and technological advances are of relevance to the strengthening of Article VII, in providing assistance to any State Party exposed to danger as a result of a violation of the Convention. This Working Paper summarises some examples of relevant recent developments.

Surveillance, Detection and Diagnostics

3. Rapid advances in the throughput, resolution, scalability and affordability of high-throughput sequencing (HTS) technologies have facilitated whole genome sequencing and the capability for epidemiological tracking in infectious disease outbreak investigations. HTS has been used during the EVD outbreak to characterize viral genomes and evaluate changes in the virus in real-time. Real-time monitoring of viral evolution is crucial to determine if there is any impact on diagnostic and therapeutic targets, and to help in investigation of the source and transmission of the virus. HTS has also been used in the investigation of the re-emergence of EVD in Liberia, almost two months after it was declared Ebola-free, showing that initial isolates are genetically similar to earlier viruses that circulated in Liberia. This suggests that it is unlikely that the strain implicated was imported from affected neighbouring countries or indicated a new emergence from an animal source.

4. The ability to perform such real-time analysis was enabled by the establishment of in-country genomic surveillance facilities which meant that samples did not have to be sent overseas for analysis.[1] Significant logistical challenges, including provision of an uninterrupted power supply and purified water, had to be overcome, and local scientists trained to ensure long-term sustainment of the capability. The contribution of such capabilities to the EVD outbreak response highlights a need for global sequencing capabilities as part of the first response during future virus outbreaks.

5. Advances in nanopore sequencing have resulted in a promising technology for application in the field. Recent work has shown that a portable, palm-sized gene sequencer that plugs into a laptop via a USB and can read long sequences in rapid timescales is capable of performing at the front lines of an infectious disease outbreak investigation, such as EVD.[2]

6. The challenges of providing effective, reliable and rapid diagnostic capabilities during the EVD outbreak underlined the need for developments in rapid diagnostics, including point-of-care tests. The benefits of developing such capabilities were also highlighted in the 2013 Report of the Meeting of States Parties.[3] A number of rapid lateral flow immunoassay test kits, based on the detection of Ebola virus antigens have been

[1] Kugelman et al (2015) Monitoring of Ebola Virus Makona evolution through establishment of advanced genomic capability in Liberia. Emerging Infectious Diseases 21:1135-1143

[2] Hayden E.C (2015) Pint-sized DNA sequencer impresses first users. Nature 521:15-16
Buguliskis J (2015) Nanopore sequencing: The New Frontline of Infectious Disease Diagnostics. Clinical OMICS July 2015:8-11

[3] BWC/MSP/2013/5 paragraph 29(c)(iv)

developed and evaluated.[4] Such assays have been found to perform well in an operational setting, and can be conducted and interpreted with minimal training, providing results in 15-20 minutes. Further studies are still required for complete assessment of the diagnostic accuracy of the tests in broader settings; however, their potential utility has been demonstrated, particularly as a 'rule-out' screening test to improve rapid case identification and appropriate allocation of healthcare resources.

7. Rapid diagnostics based on other technologies are also under development. Initial testing of a liquid crystal-based rapid pathogen detection system has recently been reported.[5] The system combines liquid crystal technology with highly specific antibody-coated paramagnetic microspheres for selective capture and detection of Ebola virus. Tests conducted under Biosafety Level 4 containment demonstrated detection at variable concentrations of live Ebola virus in serum samples in less than 20 minutes.

8. Diagnosis of EVD in West Africa has relied on collection of blood samples, their transport to a field laboratory with adequate biocontainment and testing by real-time reverse transcription-PCR (RT-PCR). This presents logistical challenges, requires skilled laboratory staff and has a significant turnaround time. Since rapid diagnostic tests such as those described above still require further study, confirmatory diagnostic testing by RT-PCR remains necessary. However, recent developments in PCR systems show potential to improve performance for field applications, for example, mobility in vehicles, automation that allows push-button operation by locally trained technicians, and electronic real-time reporting in less than 90 minutes. Such features have the capacity to transform the speed and accuracy of clinical results and epidemiological mapping, which could enable more rapid and effective responses to contain future outbreaks.[6]

Vaccines and Therapeutics

9. Progress in the response to the EVD outbreak was hampered by the lack of vaccines and therapeutics to protect against and treat the disease. This has resulted in a surge in research and fast-tracked design and evaluation processes. Clinical trials for several vaccine candidates are now in various phases. In particular, two recombinant viral vector candidates have reached advanced stages of testing in Guinea, Liberia and Sierra Leone and have been shown to be safe and well-tolerated in humans. They are based on genetically modified viruses in which vector genes have been replaced with Ebola virus genes for expression of glycoproteins that elicit an immune response. It is hoped that the clinical trials will result in the identification of a safe and effective vaccine by the end of 2015.[7]

10. The rapid evolution of the EVD outbreak underlined the need to expedite the necessary regulatory and ethical approvals for novel therapeutics and vaccines in such circumstances. This has included collaboration with the countries concerned to devise

[4] Walker et al (2015) Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, Western Area, Sierra Leone, January to February 2015. Eurosurveillance 20(12): pii=21073
Broadhurst et al (2015) ReEBOV Antigen Rapid Test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study. The Lancet published online June 26 2015 (http://dx.doi.org/10.1016/S0140-6736(15)61042-X)

[5] http://www.prweb.com/releases/2015/07/prweb12838280.htm

[6] Perkins M.D & Kessel M (2015) What Ebola tells us about outbreak diagnostic readiness. Nature Biotechnology 33:464-469

[7] http://www.who.int/medicines/emp_ebola_q_as/en/

accelerated processes such as joint reviews and real-time information exchange, as well as logistical and technical support to operationalise clinical trials.[8]

11. Randomised controlled trials (RCTs) based on clinical disease endpoints are considered the 'Gold Standard' as the most efficient study design to generate reliable vaccine efficacy data, but alternative approaches need to be considered as the incidence of EVD declines. Regulatory approval of vaccines in some countries, for example in Europe and North America, although requiring demonstration of quality and safety, do not necessarily require demonstration of efficacy based on a clinical end-point. Accelerated approval may be based on evidence of effectiveness of the product on a surrogate endpoint, such as an immune response, or on the basis of studies in an animal species expected to have a response predictive for humans. In cases where it is not feasible to carry out traditional clinical trials to show that a candidate vaccine is effective in preventing clinical occurrence of disease, there is thus a means of determining vaccine efficacy if the human immunological response to an Ebola vaccine candidate reaches a level associated with clinical benefit. If such approaches are used, post-licensure studies may be required during current or future outbreaks to verify clinical benefit and additional information about vaccine effectiveness and safety.[9]

12. Other relevant developments in the design, production and delivery of vaccines were highlighted in the 2013 Report of the Meeting of Parties and in the UK Working Paper on vaccine development submitted to the 2013 Meeting of Experts.[10] In particular, the development of vaccines that can be designed, constructed and produced rapidly in response to an emerging threat, or that could be produced without biological containment and in geographically dispersed facilities, could significantly enhance the capability for provision of effective, lower cost, rapidly manufactured and widely accessible vaccines. Advances that avoid the need for cold chain handling and for administration by trained personnel reduce costs and logistical burden, and help get effective vaccines to where they are needed most.

13. Several therapeutic approaches are under consideration for treatment of EVD.[11] ZMapp is an experimental therapy that was used to treat several infected aid workers during the outbreak; however it was not possible to determine if it benefited those patients who survived. It is comprised of three different monoclonal antibodies that bind to surface glycoproteins to neutralise the Ebola virus. The monoclonal antibodies are produced in transgenic tobacco plants; this technology is reported to be readily scalable to mass production and can be carried out indoors under tightly controlled conditions allowing operation under 'Good Manufacturing Practices'.[12] Clinical trials are underway, including in the affected countries.

14. Another experimental post-exposure intervention in small numbers of infected medical personnel used short interfering RNAs (siRNAs) encapsulated in lipid nanoparticles (LNPs). These RNA sequences cleave Ebola RNA and prevent viral replication, while the LNPs facilitate cellular delivery. Again it could not be determined if the treatment contributed to the patients' recovery, thus further assessment is required. A

[8] 2015 WHO Strategic Response Plan: West Africa Ebola Outbreak

[9] Krause et al (2015) Approaches to demonstration of Ebola virus vaccine efficacy. The Lancet 25:627-629

[10] BWC/MSP/2013/5 paragraph 29(c) & BWC/MSP/2013/MX/WP.8

[11] http://www.who.int/medicines/emp_ebola_q_as/en/
Haque et al (2015) Addressing therapeutic options for Ebola virus infection in current or future outbreaks. Antimicrobial Agents and Chemotherapy doi:10.1128/AAC.01105-15

[12] Zhang et al (2014) Fighting Ebola with ZMapp: spotlight on plant-made antibody. Science China Life Sciences 57:987-988

recent report suggests that the use of a cocktail format instead of a single siRNA increases the likelihood of activity against newly emergent viral strains. The siRNA component can be adjusted to reflect emerging strain sequence data while maintaining the delivery functionality provided by the LNP component. This highlights the potential of the technology as a treatment that might be rapidly adapted to address the changing viral strain landscape during an outbreak.[13]

15. Other research continues to identify other potential drug candidates and therapeutic targets. For example, a small class of molecules called diazachrysenes have been found to exhibit potent antiviral activity against the Ebola virus. They are easily synthesised and in initial studies protected 70-90% of exposed mice without showing any toxicity, suggesting their potential as EBV therapeutics.[14] A recent publication reports the identification of a key stage in Ebola virus infectivity as a potential therapeutic target. A host protein called Niemann-Pick C1 (NPC1) is an essential entry receptor for Ebola virus; without binding to NPC1 it cannot infect and replicate within host cells. Future research to identify compounds that interfere with the virus' interaction with the NPC1 receptor may lead to the development of antiviral drugs that prevent infection with Ebola virus, as well as other highly virulent viruses that also depend on this receptor.[15]

16. As well as efforts for discovery of new therapeutics, repurposing approved drugs for emerging infections is a critical resource for potential anti-viral therapies. This approach involves screening drugs already approved for treatment of other diseases for activity against Ebola virus or other infectious disease agents. Selecting such approved drugs has the advantage that their safety in humans has been established, and they have proven manufacturing and formulation feasibility, thus they may be suitable for rapid advancement to human trials, and supplies may be readily available in the event of an outbreak.[16] Several drugs identified as having antiviral activity using this approach span multiple mechanistic classes, including antihistamines, calcium channel blockers, antidepressants and antipsychotics. Some have been prioritised for further evaluation as therapeutics for Ebola virus either alone or in combination with other identified inhibitors.

Other issues

17. In addition to the impacts such as those described above on research and development, the response to the EVD outbreak has had other consequences. The provision of equipment, materials and scientific and technological information, including portable biocontainment systems and genomic surveillance facilities, has allowed the development of in-country capabilities for the analysis of infected samples and the provision of novel therapies for the care of EVD patients. If adequately sustained, such capabilities, along with access to expertise in-country, could improve the response to future outbreaks of EVD or other infectious diseases.

18. Information gathered from the EVD outbreak can be used to progress research into pathogenesis and epidemiology of Ebola virus. One example is in the understanding of

[13] Thi et al (2015) Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates. Nature 521:362–365

[14] Selakovic et al (2015) Anti-Ebola activity of diazachrysene small molecules. ACS Infectious Diseases 1:264-271

[15] Herbert et al (2015) Niemann-Pick C1 is essential for Ebolavirus replication and pathogenesis *in vivo*. mBio 6(3):e00565-15. doi:10.1128/mBio.00565-15

[16] Johansen et al (2015) A screen of approved drugs and molecular probes identifies therapeutics with anti-Ebola virus activity. Science Translational Mediciine 7:290ra89

Ebola virus transmission; a recent review highlights a number of areas requiring further study, including the impact of strain differences and the potential for respiratory transmission as well as several other factors.[17] The extent of the EVD outbreak has meant that there are many stored clinical samples that could be exploited for research purposes, or in clinical trials of vaccine and therapeutic candidates.

19. The international cooperation effort established during the current outbreak will further the development and application of scientific discoveries for EVD prevention and containment. However, to facilitate this it is essential to ensure that data is readily accessible to the relevant communities to allow its optimum exploitation in outbreak responses. Modern technologies such as rapid sequencing, combined with new ways to collect clinical and epidemiological data, could transform the response to outbreaks. However, this requires the means to share the potentially vast quantities of data generated as widely and rapidly as possible, which may require the development of appropriate guidelines and safeguards.[18] A recent report highlights a multi-effort collaboration between public and private organisations in several countries to analyse genome sequences from samples collected during the EVD outbreak.[19] This work was facilitated by a bioinformatics pipeline that has now been made available to the global biomedical community on a secure platform, enabling consistent analysis across laboratories with limited computational resources. Real-time genomic sequencing and analysis shared rapidly with research teams around the world may provide insight into the origin of the outbreak and also track the evolution of the virus over time to inform development of diagnostics, vaccines and therapeutics.

Implications and conclusions

20. Although the EVD outbreak in West Africa was naturally occurring, the lessons identified from the response are also relevant to consideration of the technological assistance that would likely be available if requested under Article VII as a result of a deliberate release of a biological agent. They would also allow analysis of additional requirements to enable a more effective response to future outbreaks. The call for investment in research and development on diagnostics, drugs and vaccines, and any benefits resulting from work in this area will have positive implications also for assistance under Article VII.

21. The application of discoveries in some of the technologies described may have key implications for progress on the global response to infectious disease outbreaks, whether natural, accidental or deliberate. This is of significance for other aspects of implementation of the BTWC, including activities related to Article X cooperation on development and application of scientific discoveries for disease prevention. As well as considering research advances, it will be essential also to take account of regulatory and ethical issues. Advances in technologies for surveillance, detection and diagnosis may also provide useful tools to assist in any investigation carried out under the provisions in Article VI of the Convention, or launched by the UN Secretary General under the Mechanism for Investigation of Alleged Use of Chemical and Biological Weapons.

[17] Osterholm et al (2015) Transmission of Ebola Viruses: What we know and what we do not know. mBio 6(2): e00137-15. doi:10.1128/mBio.00137-15

[18] Yozwiak et al (2015) Make outbreak research open access. Nature 518:477-479

[19] Park et al (2015) Ebola virus epidemiology, transmission, and evolution during seven months in Sierra Leone. Cell 161:1516-1526

22. The implications of scientific and technological issues related to the EVD outbreak for the BTWC underline the benefits of bringing in knowledge and expertise from those closely involved in the relevant fields to assist in our review of advances in science and technology. They also emphasise the need for a structured and systematic ongoing process for the review of relevant advances, with the flexibility to address emerging issues as they arise, and link them with particular provisions of the Convention. This could be reflected in the report of the 2015 Meeting of States Parties to inform decisions at the Eighth Review Conference on the future role of scientific and technological reviews.