Meeting Report

WHO Informal Consultation on Recommendations to Assure the Quality, Safety and Efficacy of Enterovirus 71 Vaccines

8–10 June 2020 via WebEx
Summary

Enterovirus A71 (EV71) is one of the major causative agents of hand, foot and mouth disease (HFMD) and is sometimes associated with severe central nervous system syndromes. Vaccines against EV71 infection have been developed or are in development in several countries and a few have been licensed in China. In response to requests from some of these countries, WHO convened a working group meeting in Shanghai, China, from 11 to 12 September 2019 to develop WHO Recommendations to assure the quality, safety and efficacy of Enterovirus 71 vaccines. Following the working group meeting, a drafting group prepared the first draft of the recommendations based on the consensus reached at the meeting. This draft document was posted on WHO’s website for public consultation and comments were received from relevant regulators, manufacturers and individual experts. To review the draft recommendations further, as well as the comments received through the public consultation, an informal consultation was convened in June 2020 via WebEx with participation by members of the drafting group, representatives of regulators and vaccine manufacturers. Following intense discussion, consensus was reached and a revised draft was finalized. It was agreed to submit the final draft to the Expert Committee on Biological Standardization (ECBS) for review and adoption this year.

Introduction

Enterovirus A71 (EV71) is a major cause of hand, foot and mouth disease (HFMD) and is sometimes associated with severe central nervous system (CNS) diseases. It was first isolated and characterized from cases of neurological disease in California in 1969. Outbreaks of EV71 have occurred throughout the world and have included some serious epidemics, particularly in the Asia-Pacific region. EV71 infection causes a range of effects, from asymptomatic infection to mild HFMD, severe complications with CNS, and cardiopulmonary failure. Several vaccines against EV71 infection are under development and three inactivated EV71 vaccines have already been licensed in China. Some national regulatory authorities (NRAs) requested the development of WHO recommendations to guide regulators and vaccine manufacturers in the development, manufacture and quality control of EV71 vaccines, as well as in the evaluation of their safety and efficacy. In response to this request, WHO is developing such recommendations for EV71 vaccines to provide guidance to vaccine manufacturers and NRAs. On the basis of this International Standard document, WHO could prequalify this vaccine and enable UN agencies and other organizations to purchase the vaccine to prevent EV71 infection.

A working group – including experts from the NRAs of EV71 vaccine-producing countries, academia, other experienced NRAs and representatives from industry – was convened in 2019 in Shanghai, China, to review the development and regulation of these vaccines and to discuss issues related to their quality, safety and efficacy. On the basis of the outcomes of that working group meeting (1), the drafting group prepared the first draft of the recommendations which was posted on the WHO website for the first round of public consultation from April to May 2020. Comments and suggestions were received from regulators, manufacturers and experts.
To review the first draft of the recommendations further, as well as the comments received through the public consultation, an informal consultation was convened via WebEx on 8–10 June 2020 and was attended by members of the drafting group, representatives of regulators and vaccine manufacturers.

Background and EV71 vaccines development

The meeting was opened by Dr Ivana Knezevic, Head of the Norms and Standards for Biologicals team of the World Health Organization, who welcomed the participants. Following the welcome and introductory remarks by Dr Dianliang Lei, Norms and Standards for Biologicals, WHO, and Dr Knezevic, meeting participants introduced themselves and there was the obligatory assessment of participants’ declarations of interests.

Dr Knezevic presented an overview of WHO’s EV71 recommendations in the context of the current workplans of WHO vaccine standardization activities and the forthcoming ECBS meeting. The presentation covered both the development of written and measurement standards and projects related to the review of the scientific evidence for standards development. Some international and national measurement standards were already available for EV71 vaccines as a result of the collaborative work of the National Institute for Biological Standards and Control (NIBSC), United Kingdom, and the National Institutes for Food and Drug Control (NIFDC), China, both of which are WHO Collaborating Centres for the Standardization and Regulatory Evaluation of Vaccines. Dr Knezevic noted that three EV71 vaccines had already been licensed in China and more were under development there and in several other countries.

It was pointed out that WHO’s guidelines and recommendations were living documents and would be updated in the future in the light of further scientific developments and new knowledge. The development of the current draft recommendations for EV71 vaccines was described, including an account of the working group meeting held in Shanghai in September 2019. Following a global public consultation and discussions at the WebEx meeting, the document would be updated and submitted to the ECBS in 2020. Two other documents also to be considered at the next ECBS meeting were Recommendations on Typhoid Conjugate Vaccines and an updated version of the WHO Guidelines on DNA vaccines. The latter would be useful for the consideration of the DNA vaccine candidates currently under development and evaluation to combat the COVID-19 pandemic.

Access to vaccines and other medicines is considered a major goal of WHO. However, so far WHO has had no policy recommendations for EV71 vaccines. Policy on vaccine use is the responsibility of WHO’s Strategy Advisory Group of Experts (SAGE) on immunization and the next meeting of SAGE would be informed of the progress made with the development of WHO Recommendations to assure the quality, safety and efficacy of Enterovirus 71 vaccines.

Dr Lei then gave a presentation explaining the development of the EV71 vaccine recommendations to date. This had included a face-to-face working group meeting with the drafting group, representatives of NRAs, manufacturers and other experts in Shanghai in September 2019 (1). Dr Lei indicated that the objectives of the WebEx consultation were to review the current draft recommendations and comments received following the public consultation, to discuss pending issues and to propose improvements/modifications to the first draft of the document. He introduced members of the drafting group and explained the process of the preparation of the document.
Review of draft WHO recommendations on EV71 vaccines

To put into perspective some of the issues raised in the public consultation, Dr Miao Xu (NIFDC) presented an overview of production and application of EV71 vaccines, including the three products licensed in China, as well as EV71 vaccines in development. Dr Xu described the background to the need for these vaccines, the very serious HFMD situation in China and some other countries in the region, and the significance of prevention and control of this disease. The situation regarding the licensed vaccines was summarized, including the process flowcharts for their production, focusing on the all-important virus inactivation process and the inclusion – or not – of filtration steps prior to and during inactivation to deal with possible virus aggregation problems.

Dr Xu’s summary was expanded with input from the three licensed manufacturers who focused in particular on whether there was a filtration step prior to and during inactivation, the kinetics of inactivation and the measurement of effective inactivation, which were all issues raised in the public consultation. Two production pathways had been adopted by the manufacturers – one involving harvest of the virus followed by purification and inactivation, and the other involving virus harvest followed by inactivation and purification. The current draft of WHO’s recommendations accommodates both approaches. There was considerable discussion of whether a filtration step should be introduced to take care of possible problems from aggregates, leading possibly to incomplete virus inactivation and a major safety concern, as was encountered by the early inactivated polio vaccine in the so-called Cutter incident.

Two manufacturers explained that their current processes did not include a pre-inactivation filtration step although they appeared willing to explore this possibility. They indicated that they were willing to consider introducing a filtration step before inactivation as well as during the inactivation process itself in order to strengthen even further the safety of the product.

Dr Lei then led participants through proposed updates and amendments to the recommendations, focusing only on major points of discussion/concern. There had been suggestions for updating the Terminology section, clarification of the section on tests for haemadsorbing viruses with respect to which red blood cells should be used (section A 4.1.2), and clarification of a section on observation of cultures for adventitious agents (A 4.2.1) which was thought to be unclear and unhelpful. It was decided to update these sections but to delete the unclear part of section A 4.2.1 regarding use of animal serum in cell culture. The main issue, however, concerned the need for a filtration step before and during the inactivation process which was discussed at length on Day 2 of the meeting.

On Day 2, Dr Lei and Dr Javier Martin (NIBSC) briefly summarized the key discussions of Day 1, focusing on the main issue of concern, namely the filtration step prior to and during the virus inactivation process. It was clear that manufacturers were using different approaches to virus production and that the issue of possible aggregate formation required resolution in order to minimize any inactivation inefficiencies. Participants were reminded that positions needed to be clarified and appropriate text in the recommendations agreed.

The meeting therefore continued with its consideration of sections A 4.4.3 (Filtration before inactivation) and A 4.5.1 (Inactivation procedure). Following extensive discussion and explanation of the importance of the filtration step in assuring that no aggregate formation interfered with the efficiency of virus inactivation – especially due to crosslinking reactions with formaldehyde, and as a
sensible precautionary safety measure – agreement was reached to include a filtration step not only prior to the start of the inactivation process but also during the process. These filtration steps were considered to be important in view of the fact that WHO recommendations necessarily take a global perspective. In view of the above agreements, the current small-print text describing the second filtration step (A 4.5.1 Inactivation procedure) would be converted into large print.

Several other suggestions and proposed amendments to Part A of the WHO Recommendations to assure the quality, safety and efficacy of Enterovirus 71 vaccines were then reviewed and, when agreed, the text was modified accordingly. These included the deletion of a confusing small-print statement in section A 4.5.3.1 and amendment of the statement concerning the quantity of inactivated virus pool to be tested for effective inactivation, as well as the sensitivity of the assay. The point concerning testing for inhibitors in small print in A 4.5.3.1 was to be retained, as well as the statement in small print dealing with beta-propiolactone in section A 4.5.3.4. It was also agreed that recommendations on potency tests (A 4.6.2 and A 6.4) should be clarified and aligned with text referring to aluminium adsorption and changed to large print (A 4.6.2). The protein content of final product (A 6.5) was discussed. As the protein has been adsorbed to aluminium, at this stage only the content can be calculated from the data determined at bulk stage. Therefore, it was agreed to delete it. Also, it was agreed that tests both for degree of adsorption to adjuvant and adjuvant content (A 6.10), as well as residual antibiotics (A 6.11) could be omitted from routine lot release upon demonstration of product consistency. It was also agreed that proposed new text concerning vaccine vial monitors (VVMs) should not be included in these recommendations because it concerns a specific issue regarding the WHO prequalification programme and is clearly set out in WHO prequalification documents; it is not usually included in WHO recommendations/guidelines for vaccine production and quality control.

Dr Yuansheng Sun reviewed Section B on Nonclinical evaluation of EV71 vaccines but few amendments had been raised in the public consultation. Small alterations to the text of B 2.1 were agreed in order to give a little more detail on serum neutralizing antibody testing and to B 2.2 to include the use of newborn and transgenic mice in challenge studies. Otherwise it was agreed that this section should remain fairly general without too much detail.

Dr Heidi Meyer led the discussion on Clinical evaluation of EV71 vaccines (Section C) where again the public consultation had raised little comment. The use of the term “encourage” in the Introduction section (C 1) in the context of the evaluation of protective vaccine efficacy post-licensure had been raised in the context of changes in sub-genogroups in different countries at different times. However, participants considered the term to be the most appropriate in this context and agreed that it should be retained. A statement concerning prevaccination testing for EV71 sero-status (C 3.1) was clarified to indicate that this was not feasible in routine use because of programmatic reasons. It was also agreed that the use of the term “clinically apparent” instead of “symptomatic” better reflects the intention of the text in C 4.2.1 and was retained. Small clarifying changes to C 4.2.4.2 concerning laboratory confirmation of EV71 disease were agreed, specifically to say that the testing laboratory should be qualified and the testing methods validated.

No other issues were raised and the document review was considered completed in record time! Dr Lei noted that many difficult issues had been resolved thanks to the goodwill and hard work of the participants. He explained that the next steps for the draft WHO Recommendations to assure the
quality, safety and efficacy of Enterovirus 71 vaccines would be that the drafting group would now review the outcomes of the present consultation and finalize the revision of current draft which would be shared with all WebEx participants. A final draft would be submitted to the ECBS to be considered at the October 2020 meeting. He thanked the meeting participants for their considerable contributions, collaboration and positive approach to resolving difficult issues.

Dr Knezevic added her thanks to the Chair, Rapporteur, drafting group and participants for their hard work at this informal consultation. It had been a great achievement to reach agreement on many difficult issues, and particularly in two days and not three! This she considered to be due to a lot of preparatory work and discussions that had been held beforehand and which had led to a satisfactory conclusion. The next steps would be to finalize a new draft based on the discussions and agreements achieved at the informal consultation; the new draft would then undergo a final global public consultation in the usual way prior to discussion at the ECBS meeting in October 2020.

Authors:

Dr Elwyn Griffiths, Kingston upon Thames, United Kingdom; and Dr Dianliang Lei, WHO, Geneva, Switzerland; on behalf of the WHO Informal consultation on Recommendations to assure the quality, safety and efficacy of enterovirus 71 vaccines.

Reference:

WHO Informal consultation on Recommendations to assure the quality, safety and efficacy of Enterovirus 71 vaccines

8-10 June 2020

WebEx meeting

List of participants

Dr M. Alali, World Health Organization, Switzerland; Dr X. Chen, Wuhan Institute of Biological Products Co. Ltd., China; Dr E. Griffiths, Kingston upon Thames, United Kingdom; Mr C. Guo, Wuhan Institute of Biological Products Co. Ltd., China; Ms Y. Hu, Sinovac Biotech Co. Ltd., Beijing, China; Mrs T. Jivapaisarnpong, King Mongkut’s University of Technology, Thonburi, Thailand; Dr E. Jung, CJ HealthCare R&D Biomedicine, Republic of Korea; Dr I. Knezevic, World Health Organization, Switzerland; Dr H. Langar, World Health Organization, Regional Office for the Eastern Mediterranean, Egypt; Dr D. Lei, World Health Organization, Switzerland; Ms L. Li, Wuhan Institute of Biological Products Co. Ltd., China; Ms Q. Li, Wuhan Institute of Biological Products Co. Ltd., China; Dr Q. Li, Institute of Medical Biology, Chinese Academy of Medicine Science, China; Dr Z. Li, Beijing Minhai Biotechnology Co. Ltd., China; Dr Z. Liang, National Institutes of Food and Drug Control, China; Mr J. Liu, Beijing Minhai Biotechnology Co. Ltd., China; Ms W. Lv, Wuhan Institute of Biological Products Co. Ltd., China; Dr Q. Mao, National Institutes for food and Drug Control, Beijing, China; Dr J. Martin, National Institute for Biological Standards and Control, United Kingdom; Dr S. Phumiamorn, Institute of Biological Products, Thailand; Dr H. Shimizu, National Institute of Infectious Diseases, Japan; Dr J. Shi, Wuhan Institute of Biological Products Co. Ltd., China; Dr J. Shin, World Health Organization, Regional Office for the Western Pacific, Philippines; Dr Y. Sun, Paul-Ehrlich-Institut, Germany; Mr Y. Tang, WHO China Office, China; Dr J. Wang, National Institutes for Food and Drug Control, China; Dr Y. Wang, National Institutes of Food and Drug Control, China; Dr M. Xu, National Institutes of Food and Drug Control, China. Mr L. Yi, Institute of Medical Biology, Chinese Academy of Medical Sciences, China; Ms J. Zou, Institute of Medical Biology, Chinese Academy of Medical Sciences, China.
WHO Informal consultation on WHO Recommendations to assure the quality, safety and efficacy of EV71 vaccines

WebEx meeting

8-10 June 2020

Agenda

Chairperson:  Javier Martin

Rapporteur:  Elwyn Griffiths

Day 1, 8 June 2020 (Monday)

9.00-9.30  Session 1.  Opening of the meeting

Opening remarks  I Knezevic WHO

Self-introduction  All participants

Statement on DoI assessment  WHO

Objectives and expected outcomes of the meeting  D Lei WHO

Update on WHO position on EV71 vaccines in the context of WHO biological standardization  I Knezevic WHO

9.30-10.00  Session 2.  Background and EV71 vaccines development

Overview of development and production of EV71 vaccine  

M Xu with input of vaccine manufacturers

10.00-12.30  Session 4. Review of draft WHO recommendations on EV71 vaccines
Development of the Recommendations and key comments received from first round public consultation

Drafting group

Review draft Recommendations and comments received

- Introduction
- Scope
- General consideration
- Terminology

Day 2, 9 June 2020 (Tuesday)

9.00-12.30  Session 4. Review of draft WHO recommendations (cont.)

Review the draft Recommendations and comments received

- Manufacturing recommendations
- Clinical evaluation of recombinant EV71 vaccines

Day 3, 10 June (Wednesday)

9.00-12.30  Session 4.  Review of draft WHO recommendations (cont.)

- Nonclinical evaluation of recombinant EV71 Vaccines
- Recommendations for NRAs
- Appendices

Recap the discussion and feedback

Next steps

12.30  Closure of meeting