

Therapeutics for Ebola virus disease Guideline Development Group meeting

17 NOVEMBER 2021

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Acknowledgements

WHO Steering Committee

Janet Diaz (Lead, Clinical Management, Health Care Readiness, Geneva, World Health Organization (WHO)); Julienne Anoko (Focal Point, Risk Communication and Community Engagement, WHO Regional Desk for Health Emergencies, Dakar); Lisa Askie (Scientist, Methods Lead, Methods and Standards Team, Quality Assurance Norms and Standards, Science Division); Mercedes Bonet (Sexual and Reproductive Health and Research, Geneva, WHO); Alejandro Javier Costa (Health Emergencies Operations, Geneva, WHO); Luca Fontana (Health Emergencies Operations, Geneva, WHO); Pierre Formenty (Team Lead, Viral Haemorrhagic Fevers; Health Emergency Interventions, Health Emergencies Programme, Geneva); Patrice Kabongo (Case Management, WHO African Region); Rashidatu Fouad Kamara (Case Management Lead, WHO African Region); Krutika Kuppalli (Clinical Management, Health Care Readiness, Geneva, WHO); Marta Lado (Clinical Management, Health Care Readiness, Geneva, WHO); Lorenzo Moja (Essential Medicines List, Geneva, WHO); Maurice Nzogu (Clinical Management, Health Care Readiness, Geneva, WHO); Andreas Reis (Health Ethics and Governance Unit, Geneva, WHO); Pryanka Relan (Clinical Management, Health Care Readiness, Geneva, WHO); Victoria Willet (Infection Prevention and Control, Health Care Readiness, Geneva, WHO); Daniel Youkee (Clinical Management, Health Care Readiness, Geneva, WHO).

Thanks are also due to the Chairs, Dr Robert Fowler and Dr Richard Kojan, and Methodologist, Professor Gordon Guyatt, and importantly, the panel members for their outstanding contributions during the meeting. See Annex 2 for the complete lists of members.

WHO would also like to thank the translation team, Elodie Flachaire and Kim Ottavi, who were key to enabling participation and understanding throughout the meeting.

Declarations of interest

Declarations of interest (DOI) were collected and assessed for all members of the GDG and external contributors. No conflicts of interest were judged to be significant.

Funding

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Abbreviations

anti-IL-6	anti-interleukin-6 inhibitor
anti-TNF	
DOI	declaration of interests
EVD	Ebola virus disease
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PICO	population, intervention, comparator, outcomes
RCT	randomized controlled trial



Background

Ebola virus disease (EVD) is a life-threatening disease caused by Ebola virus. During early infection patients present with a non-specific febrile illness, followed by gastrointestinal signs and symptoms, that frequently lead to hypovolaemia, metabolic acidosis, hypoglycaemia and multi-organ failure (1). EVD case fatality remains high, with a pooled case fatality rate of 60% (95% CI: 47–73%) in outbreaks from 2010–2020 (2). In recent years, several outbreaks of EVD have occurred in Africa; from the prolonged 2013–2016 EVD outbreak in West Africa to the outbreaks in the Democratic Republic of the Congo in 2017 and October 2021 (3), and in Guinea in 2021.

WHO proposed a new guideline development group (GDG) following publication of a randomized controlled trial (RCT) demonstrating efficacy for two EVD therapeutics (4). This GDG will follow the WHO methodology for guideline development (5), assess the evidence on therapeutics for EVD, and provide new GRADE (Grading of Recommendations Assessment, Development and Evaluation) based recommendations for their use. It is anticipated that the new guideline will increase availability of new therapeutics and guide clinical implementation, which should deliver higher standards of care and lead to a reduction in the case fatality rate in future EVD outbreaks. The Therapeutics for Ebola virus disease (EVD) Guideline Development Group (GDG) held its first meeting on 17 November 2021 (13:00–16:00 CET). This document reports on the meeting.

Objective

The overarching objective of the GDG is to develop a new WHO living guideline for therapeutics for EVD and provide GRADE-based recommendations for their use. This first GDG meeting introduced the members of the GDG to the WHO guideline development process and explained GRADE methodology. The GDG was tasked to review and finalize the research question (population, intervention, comparator, outcomes (PICO)), decide which population subgroups to include, select therapeutic interventions of interest, consider variation in the standard of care comparator and prioritize patient important outcomes.



Brief summary of presentations

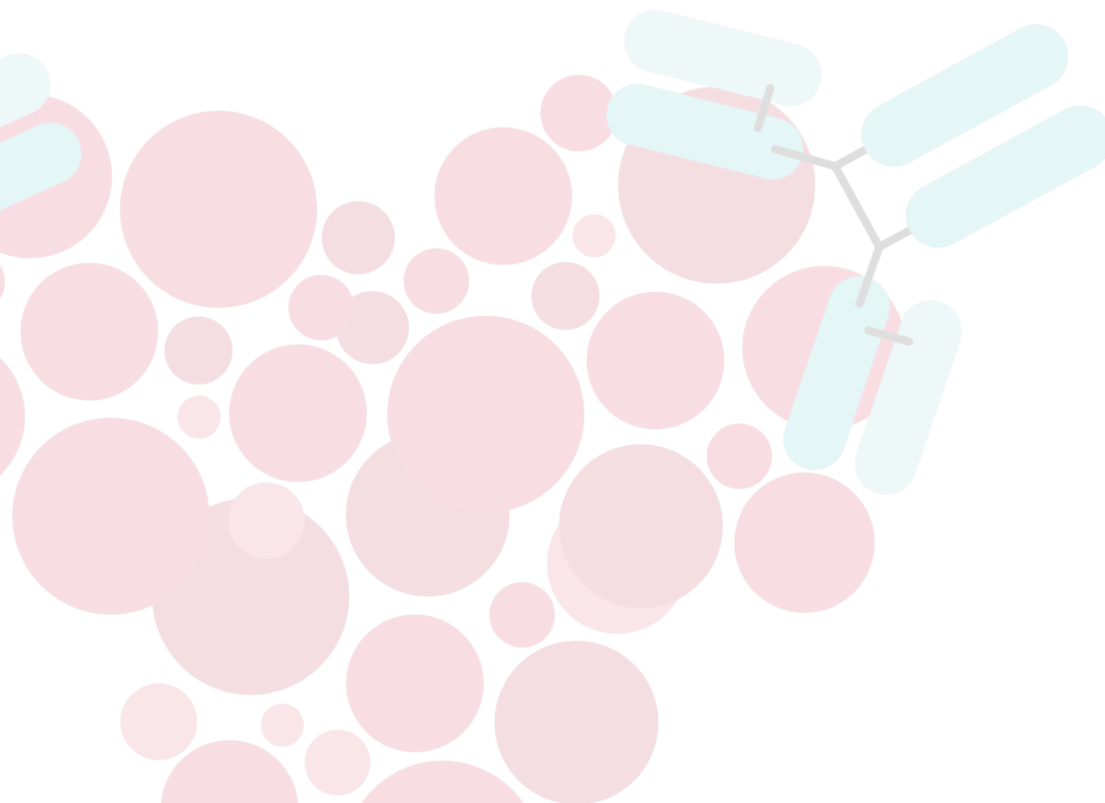
Dr Janet Diaz opened the meeting and welcomed the members. Dr Diaz discussed the DOI of two members and reported that there were no significant conflicts of interest. Dr Diaz then introduced the Clinical Co-chairs, Dr Rob Fowler and Dr Richard Kojan, and the external Methodologist, Professor Gordon Guyatt.

Dr Rob Fowler explained the overall objective of this GDG to create a new living guideline for therapeutics for EVD and provide GRADE-based recommendations for their use. He described the three guidelines versions anticipated: the first focusing on therapeutics for acute EVD; the second for therapeutics for viral persistence; and the third on therapeutics for post-exposure prophylaxis. Dr Fowler explained the background of high case fatality in EVD outbreaks, and highlighted that there is a current outbreak of EVD in North Kivu, which should remind the GDG of the importance and the urgency of the task. Dr Fowler highlighted the three pillars of case management for EVD: the development of well designed, patient-centred EVD treatment centres; the implementation of optimized supportive care; and EVD-specific therapeutics. Dr Fowler gave a brief overview of the timeline of previous EVD RCTs and then described the PALM RCT of EVD therapeutics in the Democratic of the Congo (published in 2019).

Dr Janet Diaz resumed, describing the WHO guideline development process and then reported on the WHO Steering Committee meeting on 14 October 2021 and its relevant decisions.

The Methodologist, Professor Gordon Guyatt, gave a presentation on GRADE methodology, highlighting the steps to formulate the research question and the PICO format. He described the steps that will be taken to retrieve, assess and analyse the evidence, and the GRADE system to appraise the evidence and the evidence to decision framework. Finally, he described the different types of recommendation and their significance.

Dr Rob Fowler then explained the draft PICO developed by the WHO Steering Committee and the decision by the Steering Committee to focus only on RCTs. He then opened up the meeting for discussion focused on the PICO.



Summary of discussions

There was broad consensus with the primary research question and the overarching PICO. There was detailed discussion on population subgroups that could be considered – those suggested were:

- female/male
- pregnant women (per trimester)
- paediatric
- older people
- symptom duration to admission (direction of effect: earlier presentation = improved survival)
- disease severity: presence of organ failure (liver function, renal function, neurological, respiratory), viral load, other
- pre-existing conditions (e.g. diabetes, hypertension, sickle cell disease), co-infections (malaria, HIV, TB), nutritional status (especially paediatric)
- prior therapeutic received, prior EVD vaccination (disaggregated by vaccine type), previous EVD infection.

GDG members then discussed potential therapeutic agents to consider:

- antiviral agents
- monoclonal antibodies
- convalescent plasma
- anti-inflammatories
- corticosteroids
- anti-TNF
- anti-IL-6
- blood products
- endothelial stabilization agents (Fxo6)
- interferon
- antimalarials
- anti-fibrinolytics
- combination therapies.

The GDG discussed the variation in standard of care over time and by geographical location. The GDG suggested it was important to consider standard of care variation both within RCTs and across RCTs. The GDG noted that it was important to take a holistic view of patient well-being to inform standard of care, encompassing medical, psychological and social well-being. The GDG suggested the availability and/or use of clinical interventions such as haemodialysis or intubation and ventilation may be a useful approach to structuring the level of standard care.

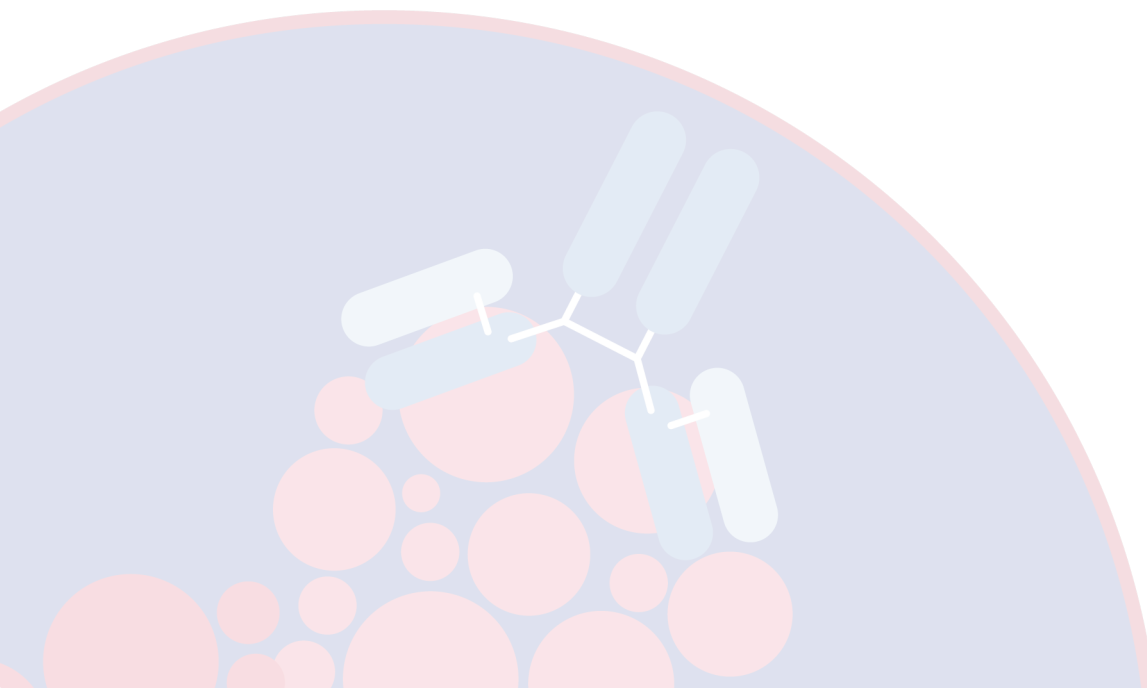
The GDG then suggested outcomes of interest from a patient perspective:

- mortality
- time to viral clearance
- viraemia during course of disease
- time to symptom resolution
- serious adverse events
- other drug reactions
- length of stay
- interruption of treatment/completion
- adverse maternal outcomes
- adverse perinatal outcomes
- functional status
- residual morbidity (renal, neurological)
- family/partner perspective: risk of transmission
- fertility outcomes
- relapse
- viral persistence, clinical phenotypes (convalescent clinical sequelae) in survivors
- mental health outcomes.

Conclusions and next steps

Next steps were discussed. The next task for the GDG is to prioritize outcomes. The GDG will be sent a survey to rank the outcomes reported in the meeting on a numeric 1–9 scale, as per GRADE methodology. If the outcome prioritization exercise reports unambiguous results, then the PICO will be finalized and the evidence retrieval, synthesis and appraisal will take place. In this case it was proposed that the next meeting of the GDG will be in February 2022.

Dr Janet Diaz provided a vote of thanks for the members, Co-chairs, WHO Steering Committee and translators.



References

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2. Kawuki J, Musa TH, Yu X. Impact of recurrent outbreaks of Ebola virus disease in Africa: a meta-analysis of case fatality rates. Public Health. 2021;195:89-97.
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4. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293-303.
5. WHO Handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 30 December 2021).



Annex 1: Agenda

Therapeutics for Ebola virus disease (EVD) Guideline Development Group (GDG)

WEDNESDAY, 17 NOVEMBER 2021, 13:00–16:00 CET

VIRTUAL MEETING

Meeting background and draft agenda

Background

Ebola virus disease (EVD) is a life-threatening disease caused by Ebola virus. During early infection patients present with a non-specific febrile illness, followed by gastrointestinal signs and symptoms, that frequently lead to hypovolaemia, metabolic acidosis, hypoglycaemia and multi-organ failure. EVD case fatality remains high, with a pooled case-fatality rate of 60% (95% CI: 47–73%) in outbreaks from 2010–2020. In recent years, several outbreaks of EVD have occurred in Africa; from the prolonged 2013–2016 EVD outbreak in West Africa to outbreaks in the Democratic Republic of the Congo in 2017 and October 2021, and in Guinea in 2021.

Objectives of the meeting

To address new evidence of novel therapeutics and build on the clinical expertise from the latest outbreaks of EVD. This guideline development group will assess the evidence on therapeutics for EVD and provide new GRADE-based recommendations for their use. It is anticipated that implementation of these guidelines will deliver higher standards of care and lead to a reduction in the case fatality rate in future EVD outbreaks.

WEDNESDAY, 17 NOVEMBER 2021

	Session	Speakers
13:00–13:15	Welcome/Introductions/Read COI/DOI	Dr Janet Diaz Lead, Clinical Management, WHO Health Emergencies Programme
13:15–13:30	Scope and objectives	Dr Robert Fowler Co-chair GDG
13:30–13:40	Process	Dr Janet Diaz
13:40–14:00	GRADE methodology	Professor Gordon Guyatt GDG Methodologist
14:00–15:00	Review research questions	Dr Robert Fowler
15:00–15:45	Open discussion and queries	Dr Robert Fowler
15:45–16:00	Summary and next steps	Dr Robert Fowler/Dr Janet Diaz

Annex 2: Participants

GDG members

Professor Aasim Ahmad, Ms Cindy Albertson, Dr Séverine Caluwaerts, Dr A Modet Camara, Professor Ian Crozier, Dr Hilde De Clerck, Professor Susanna Dunachie, Dr William A Fischer, Dr Robert Fowler, Dr Bushra Jamil, Dr Patrice Kabongo, Dr Patricia Kabuni, Ms Charline Kahambu Ngorombi, Dr Maurice Kakule, Dr Richard Kojan, Dr Marie-Claire Kolié, Dr Sulaiman Lakoh, Dr Hans-Jörg Lang, Dr J Soka Moses, Dr Isekusu Mpinda Fiston, Mr Philippe Mukumbayi Mulumba, Professor Srinivas Murthy, Mr Sorie Samura.

A list of GDG members with accompanying biographies can be found on the WHO Health Care Readiness and Clinical Unit website: WHO Guideline Development Group for Therapeutics for Ebola Virus Disease ([link](#)).

WHO participants

Janet Diaz (Lead, Clinical Management, Health Care Readiness, Geneva, WHO); Julianne Anoko (Focal Point, Risk Communication and Community Engagement, WHO Regional Desk for Health Emergencies, Dakar); Lisa Askie (Scientist, Methods Lead, Methods and Standards Team, Quality Assurance Norms and Standards, Science Division); Mercedes Bonet (Sexual and Reproductive Health and Research, Geneva, WHO); Alejandro Javier Costa (Health Emergencies Operations, Geneva, WHO); Vanessa Cramond (Clinical Management, Health Care Readiness, Geneva, WHO); Luca Fontana (Health Emergencies Operations, Geneva, WHO); Pierre Formenty (Team Lead, Viral Haemorrhagic Fevers; Health Emergency Interventions, Health Emergencies Programme, Geneva); Patrice Kabongo (Case Management, WHO African Region); Rashidatu Fouad Kamara (Case Management Lead, WHO African Region); Krutika Kuppalli (Clinical Management, Health Care Readiness, Geneva, WHO); Marta Lado (Clinical Management, Health Care Readiness, Geneva, WHO); Lorenzo Moja (Essential Medicines List, Geneva, WHO); Maurice Nzogu (Clinical Management, Health Care Readiness, Geneva, WHO); Andreas Reis (Health Ethics and Governance Unit, Geneva, WHO); Pryanka Relan (Clinical Management, Health Care Readiness, Geneva, WHO); Julie Viry (Clinical Management, Health Care Readiness, Geneva, WHO); Victoria Willet (Infection Prevention and Control, Health Care Readiness, Geneva, WHO); Daniel Youkee (Clinical Management, Health Care Readiness, Geneva, WHO).

External participants

Professor Gordon Guyatt (Methodologist); Dr QiuKui Hao (Systematic Review Lead).

The meeting was organized by the Clinical Management team, Health Care Readiness, Geneva, WHO. The responsible Technical Officer was Dr Janet Diaz..

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