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Improving Ebola virus disease outbreak control through targeted post-exposure prophylaxis

Elin Hoffmann Dahl, Placide Mbala, Sylvain Juchet, Abdoulaye Touré, Alice Montoyo, Beatrice Serra, Richard Kojan, Eric D'Ortenzio, Bjorn Blomberg, Marie Jaspard



Ebola virus disease kills more than half of people infected. Since the disease is transmitted via close human contact, identifying individuals at the highest risk of developing the disease is possible on the basis of the type of contact (correlated with viral exposure). Different candidates for post-exposure prophylaxis (PEP; ie, vaccines, antivirals, and monoclonal antibodies) each have their specific benefits and limitations, which we discuss in this Viewpoint. Approved monoclonal antibodies have been found to reduce mortality in people with Ebola virus disease. As monoclonal antibodies act swiftly by directly targeting the virus, they are promising candidates for targeted PEP in contacts at high risk of developing disease. This intervention could save lives, halt viral transmission, and, ultimately, help curtail outbreak propagation. We explore how a strategic integration of monoclonal antibodies and vaccines as PEP could provide both immediate and long-term protection against Ebola virus disease, highlighting ongoing clinical research that aims to refine this approach, and discuss the transformative potential of a successful PEP strategy to help control viral haemorrhagic fever outbreaks.

Introduction

Ebola virus disease is notable for its high case-fatality rates. In addition to close family members and caregivers, health-care workers are particularly vulnerable to infection in the beginning of outbreaks, as they care for sick individuals before the cause of their illness is known. Larger outbreaks have decimated local health-care workforces, hampering whole health-care systems and leading to increased mortality among other patient groups. Despite the discovery of new medical countermeasures, the overall mortality rate during outbreaks in the Democratic Republic of the Congo in 2020–22 remained high.¹

Of the six identified species in the genus *Orthoebolavirus*, Ebola virus (*Orthoebolavirus zairensis*; formerly Zaire ebolavirus) has been responsible for the majority of Orthoebolavirus disease outbreaks, including the large west African outbreak,² and available countermeasures are directed towards this species.^{3,4} The two available vaccines follow different strategies. rVSV-ZEBOV (Ervebo, Merck, Rahway, NJ, USA) is administered to contacts and contacts of contacts, a method known as ring vaccination, during Ebola virus disease outbreaks, whereas the two-dose vaccine regimen with Ad26.ZEBOV and MVA-BN-Filo (Johnson & Johnson, New Brunswick, NJ, USA) is proposed for use outside of active outbreak zones. The two immune-mediated treatments, mAb114 (ansuvimab, Ridgeback Biotherapeutics, Miami, FL, USA) and REGN-EB3 (atoltivimab–maftivimab–odesivimab, Regeneron Pharmaceuticals, Tarrytown, NY, USA), are currently used primarily for the treatment of symptomatic Ebola virus disease. No antiviral treatment or oral agent has proven adequate against Ebola virus disease.

Since Ebola virus is maintained in nature in animal reservoirs,⁵ the disease cannot be eradicated with current interventions, can re-emerge at any time, and poses a continuous threat to public health. Next-generation sequencing studies have unveiled secondary outbreaks

attributed to viral relapse in a previously convalescent individual⁶ and to viral dissemination from enduring reservoirs within immunoprivileged sites in a surviving individual years after their initial infection.⁷ After spillover transmission from animal reservoirs to the human population, further spread occurs through human-to-human contact. Exposure to bodily fluids such as blood, vomit, and diarrhoeal stools poses a high risk of transmission. Secondary attack rates of Ebola virus disease range from 8% to 83% depending on the type of contact (correlated with viral exposure)⁸ and have been estimated at 48% when nursing care is provided.⁹ Consequently, follow-up and monitoring of contacts is an important pillar in Ebola virus disease outbreak response. Identifying individuals at the highest risk of developing disease and targeting interventions specifically towards them holds the potential to substantially influence onward transmission.

Ebola virus disease is classified by WHO as a disease with pandemic potential.¹⁰ Expanding our tools for managing and limiting the spread of such diseases is vital not only for the affected regions, but for the global community at large. A comprehensive post-exposure prophylaxis (PEP) strategy for all exposed individuals does not exist for Ebola virus disease. Instead, although not intended for this purpose, the current ring vaccination strategy for Ebola virus disease leads to vaccines being used as PEP in contacts at high risk of developing disease during Ebola virus disease outbreaks. However, this strategy does not provide sufficient protection for individuals who are at highest risk of falling ill next.

The most advanced candidates for PEP for Ebola virus disease are two US Food and Drug Administration (FDA)-approved monoclonal antibodies. These drugs are recommended as PEP for neonates born to mothers positive for Ebola virus disease¹¹ and are given to health-care workers on a case-by-case basis according to WHO

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expert guidance from 2018.¹² However, the scarce supply of monoclonal antibodies has justified a safeguarding of their use and has restricted use beyond treatment in the general population. If existing definitions of high-risk exposure are applied, precise selection of people eligible for PEP is challenging, leading to a warranted fear of misspending scarce doses of monoclonal antibodies on people less likely to benefit from them. Nevertheless, we urge that an expansion of this use be explored further while other preventive agents are developed. If monoclonal antibodies prove effective as PEP, they could halt onward transmission, thereby curtailing outbreak propagation.

In the following sections we will discuss the strengths and weaknesses of monoclonal antibodies and other candidates for PEP, highlighting why we believe expanding access to monoclonal antibodies is vital. This Viewpoint outlines the background for our two planned clinical trials (IMOVA and EBO-PEP), which will also be detailed in later sections.

PEP: overview of the relevant candidates

The principle of PEP in Ebola virus disease is to intervene after exposure but within the asymptomatic 2–21-day incubation period in which an individual is neither ill nor able to transmit the virus to others.¹³ The primary

objective of this intervention is to prevent disease from developing. This approach not only benefits individuals who would otherwise have become sick directly but also, by halting the infectious phase, potentially disrupts onward transmission, aiding in outbreak containment.³ WHO emphasises the need for development of an effective PEP strategy in its Strategic Research Agenda for Filovirus Research and Monitoring (WHO-AFIRM) roadmap for 2021–31.¹⁴ However, with the exception of neonates aged 0–7 days with unconfirmed Ebola virus disease statuses who were born to mothers with confirmed Ebola virus disease, current WHO guidelines do not recommend any therapeutics as PEP.¹¹ Although not its primary aim, after the implementation of the ring vaccination strategy in 2019, some individuals have been inadvertently receiving the vaccine as PEP because the vaccine is administered to contacts regardless of their level of exposure risk. In our view, this intervention is not sufficiently effective to meet the primary objective of PEP and a targeted PEP strategy with specific therapies should be offered to contacts at high risk of developing disease instead of, or in addition to, vaccination (figure).

An ideal PEP candidate would be administered as a single, oral dose to facilitate administration outside of health-care settings; have no need for cold chain supply and storage; and have already proven its effectiveness

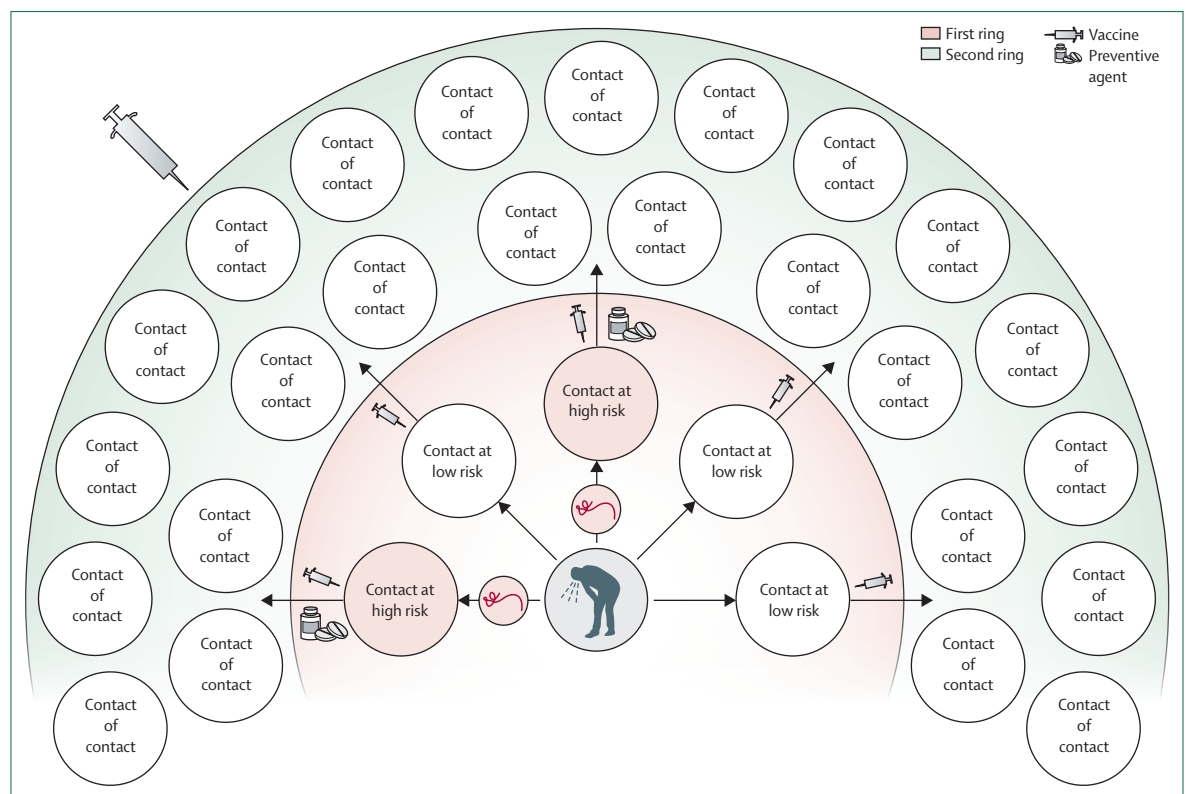


Figure: Proposed differentiated post-exposure prophylaxis strategy for Ebola virus disease depending on exposure level

The first ring includes a differentiated approach. Contacts at high risk of already being infected and in the incubation period are given a preventive agent with or without vaccination. Contacts at low risk of already being infected are given post-exposure vaccination. The second ring includes vaccination for everyone.

	Working definition (2018) ^{22*}	National Institute of Biomedical Research (Democratic Republic of the Congo) definition (2021) [†]	Proposed new working definition
High-risk exposure	Broken skin or mucous membrane contact with an individual with Ebola virus disease (alive or deceased) or their bodily fluids; or a penetrating sharps injury from a used device or through contaminated gloves or clothing	Carrying or kissing a living individual with Ebola virus disease with diarrhoea, vomiting, or bleeding (wet patient); or carrying, kissing, or cleaning the dead body of an individual with confirmed Ebola virus disease	Direct contact with an individual with confirmed Ebola virus disease with diarrhoea, vomiting, or external bleeding (wet symptoms), or their bodily fluids; direct contact with the dead body of an individual with confirmed or probable Ebola virus disease; or a child born to or breastfed by an individual with Ebola virus disease

*Adapted from Fischer and colleagues (2018).²¹ †Unpublished data.

Table 1: Previous working definitions of high-risk exposure to Ebola virus and new proposed definition

against Ebola virus disease in clinical research. It should also not interfere with the development of vaccine antibodies if administered concomitantly with the vaccine, not result in any side-effects that could be mistaken for Ebola virus disease symptoms, and have a low cost. Unfortunately, no such candidate exists. Instead, there are three potential candidate categories that could be used as PEP: vaccines, monoclonal antibodies, and antivirals, each with their specific benefits and limitations.

Vaccines: delayed response

The efficacy of the rVSV-ZEBOV vaccine in preventing disease when given as pre-exposure prophylaxis has been shown in clinical trials.¹⁵ As expected for vaccines, there is an interim period without protection before an effective antibody response. Only estimations are available to establish a sufficient amount of antibodies needed to prevent disease,¹⁶ but in a non-human primate model, there is a clear correlation between the vaccine's ability to prevent disease and the presence of antibodies.¹⁷ In the Partnership for Research on Ebola Vaccination study,¹⁸ which evaluated the immune responses of three vaccine regimens against Ebola virus, 2% of 560 participants receiving the rVSV-ZEBOV vaccine had an antibody response at day 7 and 44% of 561 participants receiving the vaccine had an antibody response at day 14.¹⁸ The delayed antibody response raises important concerns regarding the potential for vaccines alone as PEP. Previous studies of rVSV-EBOV vaccination as PEP in macaques have not shown efficacy in disease prevention, as all vaccinated animals developed clinical symptoms. Additionally, the survival outcomes after PEP vaccinations were inconsistent, with survival rates varying from one (17%)¹⁹ of six individuals to four (50%) of eight individuals.²⁰ In the first ever trial of the rVSV-ZEBOV vaccine in humans,¹⁵ the Ebola ça Suffit trial's evaluation of all clusters showed that, at 10 days or more after randomisation, there were no cases of Ebola virus disease among immediately vaccinated contacts and contacts of contacts following a ring vaccination design. 20 of the 21 Ebola virus disease cases that occurred before day 10 after vaccination occurred in individuals who were defined as contacts at high risk of developing disease (following the 2018 working definition; table 1),

showcasing that vaccination does not yield adequate protection against developing disease in this group.¹⁵

Since these findings, the ring vaccination trial design has been extrapolated to a real-life setting, in which rVSV-ZEBOV was administered to contacts and contacts of contacts during subsequent outbreaks. During the tenth Ebola virus disease outbreak in the Democratic Republic of the Congo from 2018 to 2020, WHO estimated that the vaccine's effectiveness reached 97·5% (95% CI 92·4–99·1) for individuals vaccinated more than 10 days before the onset of symptoms. Unsurprisingly, most (54 [76·5%] of 71) cases reported in vaccinated individuals occurred in contacts at high risk of developing disease.²²

In the same outbreak, around a third of people with Ebola virus disease admitted to an Ebola treatment centre had previously received the rVSV-ZEBOV vaccine.^{23–25} Reassuringly, a retrospective analysis of 2279 patients that relied on self-reported vaccination data (with 37% missing vaccination status) showed that previous administration of the rVSV-ZEBOV vaccine was correlated with lower mortality rates among people with confirmed Ebola virus disease.²³ The study revealed a markedly reduced case-fatality rate of 27% (27 of 99 cases, adjusted relative risk 0·56, 95% CI 0·36–0·82; $p=0·0046$) among individuals vaccinated within 2 days before symptom onset (ie, post-exposure vaccination) compared with a rate of 56% among their unvaccinated counterparts (570 [56%] of 1015; $p<0·0001$). The association between vaccination and decreased mortality persisted after adjusting for age, sex, and use of specific treatments such as monoclonal antibodies. Notably, vaccination was linked to lower viral loads (with cycle threshold values as the proxy)—a recognised risk factor inversely correlated with mortality rates—supporting earlier evidence for vaccine activation of innate immunity, which might limit virus replication before the development of antibodies.²⁶

The finding that vaccination as PEP might reduce mortality if the vaccinated individual falls ill is highly welcome and supports vaccination being part of the strategy to mitigate disease in contacts. Nevertheless, a remaining case-fatality rate of up to 27% emphasises the importance of a strategy to prevent disease from developing in the first place.

Monoclonal antibodies: remaining uncertainties

Monoclonal antibodies are seen as a promising candidate for Ebola virus disease PEP due to their rapid inhibition of viral entry into host cells, rapid effect on the virus itself, ease of administration (as a single intravenous infusion), and good tolerability. In the animal studies that led up to human trials of mAb114 as a treatment for Ebola virus disease, the drug showed a 100% efficacy (N=3) when given up to 5 days after exposure to the virus.²⁷ In the non-human primate rhesus macaque model of Ebola virus disease, the first observable signs of illness usually present on day 5 after exposure.²⁸ Hence, administration of a therapeutic before this timepoint would accurately be described as PEP.

The monoclonal antibodies mAb114 and REGN-EB3 have since shown higher efficacy in reducing the case-fatality rate in people with Ebola virus disease than the triple monoclonal antibody ZMapp, constituting the control group in the PALM trial.²⁵ The trial ran during the tenth Ebola virus disease outbreak in the Democratic Republic of the Congo, with death at 28 days after randomisation occurring in 35·1% of affected individuals in the mAb114 group, 33·5% of affected individuals in the REGN-EB3 group, and 49·7% of individuals in the ZMapp group.²⁵ Moreover, the PALM trial showed a clear benefit to prompt treatment administration, as the odds of death increased by 11% for each day after the onset of symptoms that individuals did not present to the treatment centre.²⁵ Following the PALM trial, mAb114 and REGN-EB3 were approved by the FDA to treat Ebola virus disease caused by Ebola virus in adults and children.

In parallel, during the tenth Ebola virus disease outbreak in the Democratic Republic of the Congo, the feasibility of using these two monoclonal antibodies as PEP in contacts at high risk of developing disease was investigated. In a case study,²⁹ 23 non-vaccinated contacts at high risk received monoclonal antibodies (21 received mAb114 and two received REGN-EB3) after a median delay of 1 day between contact and receiving PEP. Although whether these individuals were incubating the virus or not is inevitably difficult to confirm, on day 14 post administration of PEP, all were free of symptoms and tested negative with PCR.²⁹

Taken together, the available data provide compelling support for the use of monoclonal antibodies as PEP. Nevertheless, the efficacy of monoclonal antibodies as PEP against Ebola virus disease has not yet been proven in prospective clinical trials. Consequently, we hypothesise that, when used as PEP after high-risk contact with an individual with Ebola virus disease, monoclonal antibodies yield better protection than the current strategy of universally vaccinating contacts with rVSV-ZEBOV regardless of their potential exposure level. To investigate this hypothesis, the efficacy of monoclonal antibodies as PEP in contacts at high risk of

developing disease will be compared with the current vaccination practice in a randomised controlled trial (the EBO-PEP trial) in future Ebola virus disease outbreaks in Africa. The EBO-PEP project was recently awarded funding through the 2023 European and Developing Countries Clinical Trials Partnership funding call, with sponsorship by the French National Research Agency for HIV/AIDS, viral hepatitis, tuberculosis, sexual transmitted infections and emerging infectious disease, and the study protocol is currently under development. Studies to provide this key evidence about PEP strategy have been called for by several stakeholders, including WHO.^{4,21}

Provided successful, an evidence-based PEP strategy has the potential to be groundbreaking, not only in disease caused by Ebola virus, but also disease caused by Sudan virus and Bundibugyo virus, in addition to other viral haemorrhagic fevers such as Marburg virus disease, for which no disease-specific medical countermeasures are approved in humans, but for which several monoclonal antibodies have shown promising results in animal studies.^{30,31} For these viruses, vaccine development has been challenging, in part due to previously smaller-sized outbreaks.³² An effective monoclonal antibody could potentially be used as short-term passive immunisation, PEP, and treatment against disease.

Although monoclonal antibodies are good candidates for PEP, they do not provide sustained immunity. Therefore, questions remain regarding how monoclonal antibodies can most effectively be used in conjunction with a vaccination strategy. The median half-life of validated monoclonal antibodies is approximately 25 days.^{33,34} Developing a strategy that combines monoclonal antibodies for immediate protection against a recent exposure with vaccination for long-term protection against potential future exposure is therefore imperative. This strategy is especially relevant during extended outbreaks and in repeatedly affected areas. Between these two goals, the clear priority must be to first avoid death here and now, before providing long-term protection against a future hypothetical threat.

There are three potential approaches to combine vaccination with administration of monoclonal antibodies as PEP (table 2). To evaluate these three alternative approaches, the upcoming IMOVA study (NCT05202288) will compare the immune responses induced by rVSV-ZEBOV in healthy volunteers who receive either only the vaccine, a combination of the vaccine and a monoclonal antibody simultaneously, or a combination of a monoclonal antibody and the vaccine with different periods of delay. This approach will allow for the assessment of potential interactions between monoclonal antibodies and vaccination.

Unfortunately, in preparing both the IMOVA and the EBO-PEP studies, we are experiencing first-hand the challenge of accessing monoclonal antibodies (panel).

Approach	Advantage	Disadvantage
Option 1 Vaccinate with rVSV-ZEBOV, wait for the vector to replicate (ie, for 2–3 days), then administer the monoclonal antibody	Potential synergistic effect: recent administration of rVSV-ZEBOV (ie, 1 day before or less than 2 days after symptoms) does not seem to decrease the treatment efficacy of monoclonal antibodies and might even provide a synergistic effect leading to increased survival ^{23,35}	No immediate protection: this strategy could jeopardise the immediate protection of exposed individuals since prevention of disease might be impaired by delaying the administration of monoclonal antibodies ²⁵
Option 2 Administer the vaccine and monoclonal antibody concomitantly	Increased operational feasibility: this strategy reduces the risk of loss to follow-up before administration of the vaccine	Potential reduction in long-term protection: since existing monoclonal antibodies and the rVSV-ZEBOV vaccine share the same viral target and the rVSV-ZEBOV is a replicative vaccine, monoclonal antibodies could plausibly prevent the replication of rVSV-ZEBOV, thus hampering the vaccine's long-term efficacy against future exposure ^{3,4,21,36}
Option 3 Administer the monoclonal antibody, then delay vaccination until the residual concentration of monoclonal antibodies is low enough to avoid potential rVSV-ZEBOV replication; a booster dose regimen could also be considered	Immediate protection: as monoclonal antibodies would confer protection before notable vaccination immunity develops, the vulnerability window could be narrowed	Reduced operational feasibility: this strategy increases the risk of loss to follow-up before administration of the vaccine

Table 2: Outline of the alternative strategies proposed for combining vaccination and monoclonal antibodies to optimise short-term and long-term protection against Ebola virus disease

Neither of the two companies, Regeneron Pharmaceuticals (REGN-EB3) and Ridgeback Biotherapeutics (mAb114), nor the US Government appear to have existing stock available for research on PEP. As a result, the IMOVA trial has been delayed and we fear that the EBO-PEP trial will be impossible to conduct.

Antivirals: less advanced candidates

A great advantage of oral antivirals would be their ease of administration in communities and the fact that they are not expected to interact with concomitant vaccination. However, to date, no antiviral treatment or oral agent has proven effective against Ebola virus disease.^{3,25,32} Two antiviral drugs have been evaluated against Ebola virus: favipiravir and remdesivir.⁴

Although there have been promising results in animal studies⁴¹ when evaluating the pharmacokinetics of favipiravir for use in Ebola virus disease in humans, the drug did not show high enough therapeutic levels to inhibit Ebola virus replication.⁴² However, given the results from a single-arm, non-randomised trial with historical controls in which favipiravir lowered mortality to 20% when administered intravenously to adults and adolescents with confirmed Ebola virus disease with a lower viral load (cycle threshold score ≥ 20),⁴³ there could still be a role for favipiravir as PEP. This role has been proposed by several authors.²¹ The drug's oral formula makes it an attractive candidate, and favipiravir has been given as PEP in humans in a handful of individuals.⁴⁴ However, animal studies indicate that the drug might be teratogenic, limiting its use in people of fertile age.⁴⁵

Remdesivir did not show efficacy against Ebola virus in the PALM trial²⁵ compared with the control arm (ie, ZMapp), leading current WHO Ebola virus treatment guidelines to recommend against its use in favour of the two approved monoclonal antibodies, REGN-EB3 and mAb114. As remdesivir seems to reduce mortality when administered 3 days post challenge in non-human primates,⁴⁶ however, some people still consider that

Panel: Challenging access to monoclonal antibodies

Following the US Food and Drug Administration's approval of two monoclonal antibodies for Ebola virus disease (mAb114 and REGN-EB3) in 2020, real-world use of these treatments has been insufficient during outbreaks. Given the severity of the disease and potential benefit of these drugs, the in-centre treatment rate with monoclonal antibodies should ideally aim to reach 100% for confirmed cases. However, during the five outbreaks in the Democratic Republic of the Congo and Guinea between 2020 and 2022, only 32 (41%) of 78 people with Ebola virus disease who arrived in Ebola virus disease centres received treatment with either mAb114 or REGN-EB3.³

There are several reasons for this low treatment coverage rate, including logistical issues ensuring access in remote areas,³⁷ Ebola virus disease-specific monoclonal antibodies not having been registered in any endemic country, the high estimated price of monoclonal antibody production and supply, and the scarce availability of products due to low stock.^{38,39} Currently, these treatments can only be accessed through donations from the two pharmaceutical companies or the US Government's stockpile, which is held by the US Biomedical Advanced Research and Development Authority.

WHO has signalled an interest in holding an Ebola virus disease therapeutic stockpile alongside the existing Ebola virus disease vaccine stockpile. However, the scarce global supply and estimated high price of the products will probably hamper efforts to maintain a sufficiently sized stockpile. Consequently, WHO has expressed concern about access to the recommended therapeutics in their Ebola virus disease therapeutics guideline.¹¹ A small stockpile will also prevent the widening of indications to include post-exposure prophylaxis (PEP) and rather force the need to strictly prioritise the drugs for treatment. We therefore anticipate that, if proven effective as PEP, access to Ebola virus disease monoclonal antibodies might become even more challenging, exacerbating inequalities regarding how and where future medical guideline recommendations will be implemented.

Ebola virus disease outbreak responses are inevitably costly. The response against the long-standing tenth Ebola virus disease outbreak in the Democratic Republic of the Congo was estimated to have received US\$1 billion from the international community over its 2-year period.⁴⁰ Channelling some of these funds towards an effective PEP strategy could, in turn, prove to be cost-effective, as successful containment during the initial stages of an outbreak could lower the aggregated demand for monoclonal antibodies.

remdesivir could be a candidate for PEP. However, the need for multiple intravenous administrations on subsequent days makes it an impractical option.

The investigative drug, obeldesivir, can be taken orally, and is metabolised to the same active metabolite as remdesivir.⁴⁷ Although originally developed for COVID-19, there is hope that this oral drug could also have a place in therapy for or prevention of filovirus disease, including Ebola virus disease.³² Newly published data have shown promising results when used as PEP in non-human primates infected with Sudan virus,⁴⁸ but no studies have yet been conducted against Ebola virus. As outlined, experience with developing drugs for Ebola virus disease has shown that promising non-human primate data are not always translated into effective results in humans. However, if future studies confirm obeldesivir's efficacy against Ebola virus in non-human primates, it could be considered for inclusion in the EBO-PEP trial.

Selecting eligible individuals for PEP

Before implementing new policies, considering who might benefit from this intervention and postulating what potential level of exposure should make a person eligible for PEP is crucial. Thus, there is a need for consensus on the definition of risk after contact with an individual with Ebola virus disease. Several definitions have already been developed, primarily for use in the management of occupational exposure.^{4,12} However, clinical experience acquired during outbreaks in the Democratic Republic of the Congo have identified two main challenges with these definitions: first, the notion of skin invasion is often difficult to show in practice and second, the clinical state of the source patient must be considered in the classification, as the inoculum effect is entirely different between secreting and non-secreting patients. Building on these identified challenges, we propose a new working definition (table 1).

According to our proposed definition, PEP with monoclonal antibodies should only be offered to contacts at high risk of developing disease; all contacts at low risk and contacts of contacts should continue to be offered post-exposure vaccination only (figure) and could be offered an oral antiviral if one becomes available. In the tenth Ebola virus disease outbreak in the Democratic Republic of the Congo, contact rings had a median of 104 people, and contacts at high risk of developing disease (following the 2018 working definition of high-risk contact; table 1) accounted for 9% of the members of contact rings.²² Through our revised definition, we believe the people defined as being at high risk could be better selected, safeguarding the scarce supply of monoclonal antibodies for those most likely to benefit.

Conclusion

Current outbreak control measures for Ebola virus disease offer insufficient protection for people who have already been exposed and are consequently incubating the virus. One of four people with confirmed Ebola virus disease died even after receiving supportive care and virus-directed treatment during the tenth Ebola virus

outbreak in the Democratic Republic of the Congo. This statistic highlights the urgent need to identify and implement an effective PEP strategy in contacts at high risk of developing disease. There are strong arguments supporting use of monoclonal antibodies as PEP as a potential game changer that could obviate the need for treatment, saving health-care resources, and helping curb outbreaks earlier. Already funded research programmes to establish the effectiveness of monoclonal antibodies as PEP in contacts at high risk of developing Ebola virus disease are currently hampered by poor access to the two US FDA-approved monoclonal antibodies, undermining efforts to effectively control future Ebola virus disease outbreaks and protect communities.

Contributors

EHD, MJ, and BB wrote the initial manuscript. RK, ED'O, PM, AT, SJ, AM, and BS reviewed and added their input to the manuscript, including by contributing key references. All authors approved the final submitted version. MJ, EHD, RK, PM, AT, BS, and BB worked in previous Ebola outbreaks.

Declaration of interests

We declare no competing interests.

References

- 1 US Centres for Disease Control. History of Ebola disease outbreaks. US Centres for Disease Control, 2024. https://www.cdc.gov/ebola/outbreaks/?CDC_AAref_Val=https://www.cdc.gov/vhf/ebola/history/chronology.html (accessed Feb 9, 2024).
- 2 Biedenkopf N, Bukreyev A, Chandran K, et al. Renaming of genera *Ebolavirus* and *Marburgvirus* to *Orthoebolavirus* and *Orthomarburgvirus*, respectively, and introduction of binomial species names within family Filoviridae. *Arch Virol* 2023; **168**: 220.
- 3 Crozier I, Britton KA, Wolfe DN, et al. The evolution of medical countermeasures for Ebola virus disease: lessons learned and next steps. *Vaccines* 2022; **10**: 1213.
- 4 Moso MA, Lim CK, Williams E, Marshall C, McCarthy J, Williamson DA. Prevention and post-exposure management of occupational exposure to Ebola virus. *Lancet Infect Dis* 2024; **24**: e93–105.
- 5 Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature* 2005; **438**: 575–76.
- 6 Mbala-Kingebeni P, Pratt C, Mutafali-Ruffin M, et al. Ebola virus transmission initiated by relapse of systemic Ebola virus disease. *N Engl J Med* 2021; **384**: 1240–47.
- 7 Keita AK, Koundouno FR, Faye M, et al. Resurgence of Ebola virus in 2021 in Guinea suggests a new paradigm for outbreaks. *Nature* 2021; **597**: 539–43.
- 8 Bower H, Johnson S, Bangura MS, et al. Exposure-specific and age-specific attack rates for Ebola virus disease in Ebola-affected households, Sierra Leone. *Emerg Infect Dis* 2016; **22**: 1403–11.
- 9 Dean NE, Halloran ME, Yang Y, Longini IM. Transmissibility and pathogenicity of Ebola virus: a systematic review and meta-analysis of household secondary attack rate and asymptomatic infection. *Clin Infect Dis* 2016; **62**: 1277–86.
- 10 WHO. Prioritizing diseases for research and development in emergency contexts. World Health Organization. <https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts> (accessed Feb 9, 2024).
- 11 WHO. Therapeutics for Ebola virus disease. World Health Organization, 2022. <https://www.who.int/publications/i/item/9789240055742> (accessed Feb 9, 2024).
- 12 WHO. Notes for the record: technical elements to consider for the use of investigational therapeutics and investigational vaccine for post-exposure prophylaxis for frontline healthcare workers potentially exposed to Ebola virus in the current outbreak involving the eastern Democratic Republic of Congo. Geneva: World Health Organization, 2018.

- 13 Feldmann H, Sprecher A, Geisbert TW. Ebola. *N Engl J Med* 2020; **382**: 1832–42.
- 14 WHO. A WHO-strategic research agenda for Filovirus research and monitoring (WHO-AFIRM). World Health Organization, 2022. [https://www.who.int/publications/m/item/a-who-strategic-research-agenda-for-filovirus-research-and-monitoring----\(who-afirm\)](https://www.who.int/publications/m/item/a-who-strategic-research-agenda-for-filovirus-research-and-monitoring----(who-afirm)) (accessed Feb 9, 2024).
- 15 Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola ça Suffit!). *Lancet* 2017; **389**: 505–18.
- 16 Grais RF, Kennedy SB, Mahon BE, et al. Estimation of the correlates of protection of the rVSVΔG-ZEBOV-GP Zaire ebolavirus vaccine: a post-hoc analysis of data from phase 2/3 clinical trials. *Lancet Microbe* 2021; **2**: e70–78.
- 17 Marzi A, Engelmann F, Feldmann F, et al. Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. *Proc Natl Acad Sci USA* 2013; **110**: 1893–98.
- 18 Kieh M, Richert L, Beavogui AH, et al. Randomized trial of vaccines for Zaire Ebola virus disease. *N Engl J Med* 2022; **387**: 2411–24.
- 19 Bushmaker T, Feldmann F, Lovaglio J, et al. Limited benefit of postexposure prophylaxis with VSV-EBOV in Ebola virus-infected rhesus macaques. *J Infect Dis* 2023; **228** (suppl 7): S721–29.
- 20 Feldmann H, Jones SM, Daddario-DiCaprio KM, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog* 2007; **3**: e2.
- 21 Fischer WA 2nd, Vetter P, Bausch DG, et al. Ebola virus disease: an update on post-exposure prophylaxis. *Lancet Infect Dis* 2018; **18**: e183–92.
- 22 WHO. Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response. World Health Organization, 2019. https://cdn.who.int/media/docs/default-source/ebola/ebola-ring-vaccination-results-12-april-2019.pdf?sfvrsn=b9cca6aa_1&download=true (accessed Feb 9, 2024).
- 23 Coulborn RM, Bastard M, Peyraud N, et al. Case fatality risk among individuals vaccinated with rVSVΔG-ZEBOV-GP: a retrospective cohort analysis of patients with confirmed Ebola virus disease in the Democratic Republic of the Congo. *Lancet Infect Dis* 2024; **24**: 602–10.
- 24 Jaspard M, Mulangu S, Juchet S, et al. Development of the PREDS score to predict in-hospital mortality of patients with Ebola virus disease under advanced supportive care: results from the EVISTA cohort in the Democratic Republic of the Congo. *EClinicalMedicine* 2022; **54**: 101699.
- 25 Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019; **381**: 2293–303.
- 26 Pinski AN, Messaoudi I. Therapeutic vaccination strategies against EBOV by rVSV-EBOV-GP: the role of innate immunity. *Curr Opin Virol* 2021; **51**: 179–89.
- 27 Corti D, Misasi J, Mulangu S, et al. Protective monotherapy against lethal Ebola virus infection by a potentially neutralizing antibody. *Science* 2016; **351**: 1339–42.
- 28 Warren T, Zumbun E, Weidner JM, et al. Characterization of Ebola virus disease (EVD) in rhesus monkeys for development of EVD therapeutics. *Viruses* 2020; **12**: 92.
- 29 Jaspard M, Juchet S, Serra B, et al. Post-exposure prophylaxis following high-risk contact with Ebola virus, using immunotherapies with monoclonal antibodies, in the eastern Democratic Republic of the Congo: an emergency use program. *Int J Infect Dis* 2021; **113**: 166–67.
- 30 Kuang E, Cross RW, McCavitt-Malvido M, et al. Reversion of Ebolavirus disease from a single intramuscular injection of a pan-Ebolavirus immunotherapeutic. *Pathogens* 2022; **11**: 655.
- 31 Brannan JM, He S, Howell KA, et al. Post-exposure immunotherapy for two ebolaviruses and Marburg virus in nonhuman primates. *Nat Commun* 2019; **10**: 105.
- 32 Sprecher A, Cross R, Marzi A, et al. Perspectives on advancing countermeasures for Filovirus disease: report from a multisector meeting. *J Infect Dis* 2023; **228** (suppl 7): S474–78.
- 33 Sivapalasingam S, Kamal M, Slim R, et al. Safety, pharmacokinetics, and immunogenicity of a co-formulated cocktail of three human monoclonal antibodies targeting Ebola virus glycoprotein in healthy adults: a randomised, first-in-human phase 1 study. *Lancet Infect Dis* 2018; **18**: 884–93.
- 34 Gaudinski MR, Coates EE, Novik L, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. *Lancet* 2019; **393**: 889–98.
- 35 Cross RW, Bornholdt ZA, Prasad AN, et al. Prior vaccination with rVSV-ZEBOV does not interfere with but improves efficacy of postexposure antibody treatment. *Nat Commun* 2020; **11**: 3736.
- 36 Iversen PL, Kane CD, Zeng X, et al. Recent successes in therapeutics for Ebola virus disease: no time for complacency. *Lancet Infect Dis* 2020; **20**: e231–37.
- 37 Mbaya OT, Kingebeni PM, Dodd LE, Tamfum JM, Lane C. On the importance and challenges of global access to proven life-saving treatments for Ebolavirus. *Lancet Infect Dis* 2023; **23**: 406–07.
- 38 Torreele E, Boum Y 2nd, Adjaho I, et al. Breakthrough treatments for Ebola virus disease, but no access—what went wrong, and how can we do better? *Lancet Infect Dis* 2023; **23**: e253–58.
- 39 Médecins Sans Frontières Access Campaign. Médecins Sans Frontières, ensuring access to new treatments for Ebola virus disease. Médecins Sans Frontières Access Campaign, 2023. <https://msfaccess.org/ensuring-access-new-treatments-ebola-virus-disease> (accessed Feb 9, 2024).
- 40 Zeng W, Samaha H, Yao M, et al. The cost of public health interventions to respond to the 10th Ebola outbreak in the Democratic Republic of the Congo. *BMJ Glob Health* 2023; **8**: e012660.
- 41 Guedj J, Piorkowski G, Jacquot F, et al. Antiviral efficacy of favipiravir against Ebola virus: a translational study in cynomolgus macaques. *PLoS Med* 2018; **15**: e1002535.
- 42 Nguyen THT, Guedj J, Anglaret X, et al. Favipiravir pharmacokinetics in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted. *PLoS Negl Trop Dis* 2017; **11**: e0005389.
- 43 Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med* 2016; **13**: e1001967.
- 44 Jacobs M, Aarons E, Bhagani S, et al. Post-exposure prophylaxis against Ebola virus disease with experimental antiviral agents: a case-series of health-care workers. *Lancet Infect Dis* 2015; **15**: 1300–04.
- 45 Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Japanese Ministry of Health, Labour and Welfare. Pharmaceuticals and Medical Devices Agency, report on the deliberation results—avigan. Pharmaceuticals and Medical Devices Agency, 2014. <https://www.pmda.go.jp/files/000210319.pdf> (accessed March 15, 2024).
- 46 Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016; **531**: 381–85.
- 47 Mackman RL, Kalla RV, Babusis D, et al. Discovery of GS-5245 (obeldesivir), an oral prodrug of nucleoside GS-441524 that exhibits antiviral efficacy in SARS-CoV-2-infected African green monkeys. *J Med Chem* 2023; **66**: 11701–17.
- 48 Cross RW, Woolsey C, Chu VC, et al. Oral administration of obeldesivir protects nonhuman primates against Sudan ebolavirus. *Science* 2024; **383**: eadk6176.

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