Ebola virus disease: an update on post-exposure prophylaxis

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The massive outbreak of Ebola virus disease in west Africa between 2013 and 2016 resulted in intense efforts to evaluate the efficacy of several specific countermeasures developed through years of preclinical work, including the first clinical trials for therapeutics and vaccines. In this Review, we discuss how the experience and data generated from that outbreak have helped to advance the understanding of the use of these countermeasures for post-exposure prophylaxis against Ebola virus infection. In future outbreaks, post-exposure prophylaxis could play an important part in reducing community transmission of Ebola virus by providing more immediate protection than does immunisation as well as providing additional protection for health-care workers who are inadvertently exposed over the course of their work. We propose provisional guidance for use of post-exposure prophylaxis in Ebola virus disease and identify the priorities for future preparedness and further research.

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Introduction

The 2013–16 Ebola virus disease epidemic in west Africa evolved rapidly from a small outbreak in Guinea into an unprecedented global public health emergency. By the time the WHO-declared public health emergency of international concern ended in March, 2016, 28 646 cases and 11 323 deaths had been reported, mainly in Guinea, Sierra Leone, and Liberia.[1] Infection of household contacts of individuals with Ebola virus disease and exposure in the context of traditional burial practices were major factors in the transmission of Zaire ebolavirus in the west Africa outbreak.[2,3] The most effective strategies for primary prevention of person-to-person transmission are probably early identification of individuals who have contracted the infection and isolation of these individuals in suitable health-care facilities, as well as community-based infection prevention and control practices. Effective post-exposure prophylaxis could augment traditional public health measures to reduce community transmission of Ebola virus. A closely related concept was recently explored in a ring vaccination cluster-randomised trial[4] involving administration of the recombinant vesicular stomatitis virus-vectored vaccine expressing the Ebola virus surface glycoprotein (rVSV-ZEBOV) to both contacts of individuals with Ebola virus disease and contacts of contacts. Complete protection was induced by the vaccine (ie, it had 100% efficacy) in that no new cases of the disease occurred from 10 days onwards after vaccination, which was the predefined primary outcome for the study. However, on days 0–9, incident cases occurred in vaccine recipients at a similar rate to that of controls. This finding indicates that post-exposure prophylaxis interventions that provide immediate protection might be needed to augment the delayed protection induced by the vaccine.

Another tragic consequence of the west Africa epidemic was infection of almost 900 health-care workers, which resulted in more than 500 deaths and depleted an already limited health-care resource.[5] The devastating effects on the health-care infrastructure and numbers of health-care workers will reverberate for years to come in the three principally affected countries. Health-care workers have been infected in virtually every outbreak of Ebola virus disease, and often the clustering of infection or deaths of health-care workers has signalled the onset of an outbreak.[6,7] The most effective protection for health-care workers is the implementation of a safe system of work, including environmental and administrative controls and appropriate personal protective equipment to limit exposure to infectious patients and body fluids during clinical care.[8–11] Outbreaks of Ebola virus disease have largely occurred in remote and resource-limited locations where safe systems of work have been inadequate, especially early in outbreaks, resulting in numerous exposures, infections, and deaths.[6,7,12] Even when sophisticated safe systems of work are in place, accidental exposures to Ebola virus occur over the course of caring for patients,[13,14] and less commonly in laboratory workers handling clinical samples or doing filovirus research.[15–17] If the exposure is recognised—for example, a splash or sharps injury—then effective post-exposure prophylaxis could prove to be life-saving. Future outbreaks of Ebola virus disease are inevitable, and all options for protection of health-care workers must be evaluated.

Preclinical work on filovirus-specific countermeasures has been ongoing for many years, and the first therapeutic and vaccine clinical trials were done during the 2013–16 west Africa outbreak of Ebola virus disease.[4,18–22] Additionally, a small number of case reports exist of monitored experimental use of therapeutics for treatment of this disease, and use of both antivirals and vaccines for post-exposure prophylaxis.[16,23–27] We review the relevant preclinical and clinical data, and propose a clinical algorithm for use of post-exposure prophylaxis in Ebola virus disease on the basis of current evidence.

Vaccines

Human Ebola virus disease has a median incubation period of 9–10 days, and infection leads to specific immune responses that have been detected in survivors.[28–31] Therefore, active immunisation during the incubation period could plausibly stimulate protective immune responses and prevent or attenuate clinical

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disease. The vaccine most advanced in development is replication-competent rVSV-ZEBOV. Its efficacy as pre-exposure prophylaxis has been demonstrated in non-human primate models, in which it is possible to achieve 100% protection before lethal challenge with Ebola virus.[32] However, experiments in very small numbers of non-human primates suggest that the protective efficacy is time dependent: complete protection of non-human primates was achieved when the Ebola virus challenge was given 7 days after vaccination, but not all animals were protected when the virus challenge was given 3 days after vaccination.[33] The likely explanation is a delay in the generation of a protective immune response.[34] If vaccine administration is delayed in non-human primates until only 20–30 min after lethal challenge, which is perhaps more representative of post-exposure prophylaxis, then protective efficacy was 50% in one study.[35] However, active immunisation might have greater efficacy as post-exposure prophylaxis in human beings than in non-human primates because the non-human primate model differs from human Ebola virus disease in two important respects: the onset of clinical illness is faster, and it is uniformly lethal.

Development of the rVSV-ZEBOV vaccine offered the first opportunity for use of post-exposure prophylaxis in Ebola virus disease in human beings. A single use of rVSV-ZEBOV as post-exposure prophylaxis, following a laboratory needlestick injury, was reported before the recent west Africa outbreak.[16] A further seven individuals—health-care workers with varied potential exposures to Ebola virus over the course of their work in west Africa—who received rVSV-ZEBOV as post-exposure prophylaxis have been reported.[23,26,27] None of these individuals developed Ebola virus infection, but all of the reports were uncontrolled, and thus whether immunisation prevented disease remains unknown. In all but one of these cases, rVSV-ZEBOV was administered at a high dose of 1×10^8 plaque-forming units, and all recipients developed adverse effects following administration of the vaccine. Most developed transient feverishness, which is particularly problematic when managing patients who have had potential exposure to Ebola virus. In phase 1/2, placebo-controlled, double-blinded randomised trials,[18,36,37] including more than 200 participants in total, the rVSV-ZEBOV vaccine demonstrated dose-related reactogenicity and immunogenicity at doses ranging from 3×10^5 to 5×10^7 plaque-forming units. The expedited development of the rVSV-ZEBOV vaccine during the west Africa outbreak culminated in a cluster-randomised ring vaccination study,[4] in which a lower dose of vaccine (2×10^7 plaque-forming units) than that reported in the uncontrolled cases of post-exposure prophylaxis[23,26,27] was used. This dose of vaccine was generally well tolerated and had a very high efficacy in prevention of onset of Ebola virus disease from 10 days after vaccination, as noted previously.[4] However, the vaccine did not seem to provide early protection against Ebola virus disease in individuals in whom the virus is presumably already incubating. As a result of the trial design, the effectiveness reported largely reflects pre-exposure prophylaxis, and the contribution of post-exposure prophylaxis, if any, is not possible to discern.

Studies of the kinetics of immune responses after vaccination also highlight the likely delay in development of protective responses. In phase 1/2 studies[18,36,37] of rVSV-ZEBOV, none of the human volunteers had detectable antibodies against Ebola virus glycoprotein on day 7 post-immunisation, even at the highest doses of vaccine; 90–95% of vaccine recipients had detectable antibodies by day 14, and all had detectable virus-specific IgG by day 28. However, uncertainty exists regarding which antibody types and what blood levels of antibody correlate with protection against infection or disease. A weak protective effect could even be attributable to antigen non-specific activation of innate immunity by a replicating virus-vectored vaccine.[38] No new cases of Ebola virus disease were diagnosed in the ring vaccination study[4] from 10 days post-vaccination, which suggests that meaningful protective immunity probably develops in human beings within this time. When considering active immunisation for post-exposure prophylaxis, these data need to be set against the incubation period of Ebola virus in human beings, which is on average 9 days and probably shorter after percutaneous exposure.[3] Taken together, these findings suggest that vaccine-induced immunity is insufficiently rapid to reliably prevent Ebola virus disease in human beings when administered as post-exposure prophylaxis, even if the vaccine were given as quickly as possible following exposure. Whether it might still attenuate clinical disease is unknown. Additionally, current vaccines are specific for Zaire ebolavirus and might offer less or no protection against other Ebola virus species.

Several other vaccines for Ebola virus disease are in development, but no published animal or clinical data exist on their use as post-exposure prophylaxis. Unlike rVSV-ZEBOV, most are virus-vectored but non-replicating vaccines, which are generally used in heterologous, prime-boost immunisation regimens that could prove to be highly effective for pre-exposure prophylaxis.[39–53] However, they might be less well suited to the demands of post-exposure prophylaxis and the need to induce a protective immune response as rapidly as possible.

Passive immunotherapy

Humoral immune responses have been associated with survival from Ebola virus disease,[33,54,55] and passive immunotherapy has been considered for both treatment and post-exposure prophylaxis. Initial efforts focused on polyclonal antibody preparations such as hyperimmune goat and equine serum.[25,56,57] Convalescent blood products, including whole blood and plasma from survivors of

Ebola virus disease, have been administered to patients in Africa and to patients who were medically evacuated to the USA and Europe, but the benefits of this treatment are unclear.[20,58–68] In at least one patient, the use of convalescent plasma was associated with acute respiratory distress syndrome that was attributed to transfusion-related acute lung injury.[62] Results from one uncontrolled non-randomised Ebola virus disease treatment trial[20] suggest that transfusion of 500 mL of convalescent plasma with unknown levels of antibodies was not associated with a significant improvement in survival in patients with Ebola virus disease compared with historical controls, which is consistent with non-human primate data suggesting that convalescent serum is ineffective for treatment.[69] The total amounts of Ebola virus IgG antibodies administered in convalescent plasma were measured subsequently, and higher doses were associated with a lower viral load after infusion but with no significant association with mortality.[67] The use of convalescent plasma for post-exposure prophylaxis has not been reported. Hyperimmune globulin was shown to reduce mortality when administration was started 2 days after Ebola virus challenge in non-human primates,[70] but production of hyperimmune globulin against Ebola virus from convalescent plasma for human use has not been reported.

Preparations of specific monoclonal antibodies have become an area of interest. Far greater concentrations of specific antibody can be achieved reliably using monoclonal antibody preparations than with unconcentrated convalescent plasma.[66] These preparations have demonstrated remarkable efficacy in early treatment of non-human primates with clinically apparent disease. An optimised cocktail of three human–mouse chimeric monoclonal antibodies directed against the Ebola virus glycoprotein, known as ZMapp, demonstrated 100% protection when treatment was delayed until 3, 4, or even 5 days after administration of a lethal dose of Ebola virus.[71] This approach is not strictly post-exposure prophylaxis, but treatment of disease is widely assumed to be more challenging than post-exposure prophylaxis, and therefore its potential efficacy as post-exposure prophylaxis can probably be extrapolated from, although not precisely defined by, these models. During the west Africa outbreak, various preparations of three monoclonal antibody combinations (ZMapp, ZMab, and MIL77) were used for treatment of Ebola virus disease in the USA and Europe,[60,61,64–66,72–74] but no conclusions can be drawn about their efficacy from this uncontrolled experimental use. A randomised controlled trial[21] of ZMapp therapy for Ebola virus disease at the end of the outbreak was unable to recruit the planned sample size and suggested, but did not definitively establish, benefit in reducing mortality. Two individuals evacuated to the UK following very high-risk exposures to Ebola virus (penetrating sharps injuries with freshly used hollow bore needles) received monoclonal antibody therapy for post-exposure prophylaxis, in both cases starting on day 2 post-exposure.[24] Both individuals also received the antiviral agent favipiravir. These individuals did not develop laboratory or clinical evidence of Ebola virus infection, but whether infection was prevented by post-exposure prophylaxis was not possible to determine. Administration of monoclonal antibody preparations is generally safe, although a single report exists of anaphylaxis in an individual who was rechallenged with monoclonal antibody after many months during treatment of recrudescent Ebola virus infection.[72] Taken together, the data suggest that specific monoclonal antibody preparations are a promising therapeutic for both treatment of and post-exposure prophylaxis for Ebola virus disease. However, they are relatively expensive and difficult to administer; additionally, current monoclonal antibodies are not broadly cross-reactive across Ebola virus species and therefore might not work in future outbreaks, although efforts are ongoing to isolate widely cross-reactive monoclonal antibodies, including from human survivors of Ebola virus disease.[75–79]

Small-molecule antiviral agents

Minimally symptomatic Ebola virus infection has been reported, as evidenced by seropositivity in contacts who did not themselves develop overt clinical disease.[80–86] A reasonable assumption is that viral replication occurred in these individuals but was naturally controlled to a subclinical threshold. In theory, treatment with a small-molecule antiviral agent during the incubation period following exposure to Ebola virus might inhibit virus replication sufficiently to prevent or attenuate clinical disease. However, sparse experimental and observational data exist to support this strategy, and the time window for effective post-exposure prophylaxis using antiviral small molecules has not been defined.

Favipiravir was developed and licensed in Japan for treatment of novel influenza A virus infections. It has demonstrated modest but broad antiviral activity against RNA viruses through inhibition of viral RNA-dependent RNA polymerases.[87] In mouse models of Ebola virus disease, high-dose favipiravir can rescue animals following a lethal dose of Ebola virus when initiated as late as 6 days after viral challenge.[88,89] The dose used is approximately ten times higher than that needed for protection in mouse models of lethal influenza. Data for the efficacy of favipiravir against Ebola virus disease in non-human primates have not been published, but preliminary reports indicate that antiviral effects are dose related (Bavari S, US Army Medical Research Institute of Infectious Diseases, personal communication). On the basis of human safety data from phase 3 trials for treatment of influenza and availability at the time, favipiravir was evaluated in a non-comparative clinical trial[19] in the treatment of Ebola virus disease in west Africa using a dose regimen that is approximately

50% higher than that used in the influenza studies.[90] Compared with historical control data, no significant safety signal and no clear survival benefit from treatment were found at this dose, although the trial was not designed to prove efficacy. Subsequent pharmacokinetic analysis has shown that the dose regimen used, which had been derived from modelling studies, was too low to achieve reliable therapeutic drug levels for inhibition of Ebola virus replication.[91]

Taken together, the data suggest that favipiravir has relatively weak antiviral activity against Ebola virus. However, this conclusion does not necessarily preclude efficacy of the drug as post-exposure prophylaxis, considering that viraemia in the very early stages of infection, when the drug would be administered, would be very low. Favipiravir has been used as post-exposure prophylaxis in at least five health-care workers with percutaneous accidents and suspected Ebola virus exposures during the west Africa outbreak. The dose chosen was the same as that used in the west Africa treatment trial,[19] although whether this dose is sufficient is unclear. In a UK case series, four individuals received post-exposure prophylaxis with favipiravir, and two of these individuals with the highest-risk exposures (penetrating sharps injuries with freshly used hollow bore needles) received monoclonal antibody therapy in addition to the antiviral.[24] Similarly, a nurse was evacuated to Switzerland after a moderate to high-risk exposure involving the penetration of two pairs of gloves by sharp plastic from disposed waste containing infectious biological fluids, and received favipiravir as post-exposure prophylaxis (Kaiser L, Geneva University Hospitals, personal communication). None of these individuals developed laboratory or clinical evidence of Ebola virus infection, but whether any infections were prevented by the use of post-exposure prophylaxis is not possible to determine from this small number of uncontrolled cases.

Development of potent small-molecule antiviral agents against Ebola virus is a priority for treatment of Ebola virus disease. Towards the end of the west Africa outbreak, data were published showing complete protection of non-human primates following lethal Ebola virus challenge by treatment with GS-5734, an experimental nucleotide analogue that is approximately 1000 times more potent in vitro against Ebola virus than is favipiravir.[92] This study was the first to show a robust therapeutic effect for a small-molecule inhibitor against Ebola virus, even when administration was delayed until 3 days after lethal virus challenge. Whether the observed efficacy of GS-5734 in animal models of Ebola virus infection will translate into clinical efficacy in human beings is currently unknown. To date, only two patients with Ebola virus infection have been treated with GS-5734: a British nurse who developed recrudescent disease, including CNS infection, 10 months after initial infection;[73] and an infant born to a mother who was infected with the virus.[93] Both patients survived, and no serious adverse effects were reported. Phase 2 clinical development of GS-5734 for Ebola virus disease is ongoing. Further development of this drug might increase its potential for post-exposure prophylaxis in the future, especially since it has shown broad and potent antiviral activity across filoviruses in vitro.[94]

Other small-molecule inhibitors of Ebola virus are under development, including the nucleoside analogue BCX4430, which has demonstrated broad antifilovirus activity.[95] Treatment of non-human primates 48 h after lethal Ebola virus challenge was found to be capable of reducing viral load and significantly delaying, but not preventing, death; at a higher dose and starting within an hour of virus challenge, non-human primates were completely protected from death.[96] Initial phase 1 studies of BCX4430 have been done, and further studies in human beings are planned.[96] To date, BCX4430 has not been used for treatment or post-exposure prophylaxis of Ebola virus disease.

Other investigational therapeutics from the west Africa outbreak

Before the west Africa epidemic, lipid nanoparticle formulations of small interfering RNAs were under development as treatment for Ebola virus disease. The formulation TKM-100802—when administration was initiated 30 min after lethal virus challenge—demonstrated efficacy in protection of non-human primates.[97] Its development was placed on partial clinical hold after concerns arose about a cytokine release syndrome in the phase 1 study in healthy volunteers[98] but, early in the west Africa outbreak, TKM-100802 was administered to five patients with Ebola virus disease who had been medically evacuated to the USA and given once for post-exposure prophylaxis.[27,60,61] The efficacy or safety of this therapy is not possible to determine from these few uncontrolled uses. One potential advantage of small interfering RNA technology is that it can be rapidly adapted to match the outbreak strain of Ebola virus: a new formulation, TKM-130803, was specifically engineered for the variant responsible for the west Africa epidemic. TKM-130803 was shown to protect non-human primates even when administration was delayed until 3 days after lethal virus challenge;[99] however, in a single-arm phase 2 trial,[98] it did not demonstrate survival benefit in individuals with Ebola virus disease compared with historical controls. Further development of TKM-Ebola formulations is not currently anticipated, and their use for post-exposure prophylaxis is not considered further in this Review.

During the west Africa crisis, repurposed drugs with possible benefit in Ebola virus disease also generated considerable interest. Although some repurposed drugs were administered as part of treatment of Ebola virus disease, published data are not available to evaluate the efficacy or support the use of any particular compound. Careful observation at one Ebola treatment centre

determined that malaria treatment (for possible concomitant infection) that included amodiaquine, which inhibits Ebola virus replication in vitro, might be associated with improved survival from Ebola virus disease.[100] This hypothesis-generating observational study needs to be investigated further in non-human primate models before being considered for a formal clinical trial.

Recommendations for post-exposure prophylaxis

Medical countermeasures with potential effectiveness as post-exposure prophylaxis were not accessible for the most part before the recent west Africa outbreak of Ebola virus disease. Despite the unprecedented scale of the outbreak, very few individuals received post-exposure prophylaxis and no trial of this strategy was undertaken. Therefore, there are insufficient data to inform an evidence-based approach to post-exposure prophylaxis for Ebola virus disease. Generation of such data is an obvious research need, and plans to address this need should be formulated in advance of the next outbreak so that they can be implemented expeditiously. Ideally, any use of post-exposure prophylaxis for Ebola virus disease in the future should be part of clinical research, even if only as part of a systematic observational study, to build up the relevant evidence base. Inclusion of serial tests in study participants for both PCR and serology might provide evidence of exposure to the virus. The following recommendations are intended to stimulate development of studies or trials and provide guidance for emergency use outside any study protocol. They are based on first principles and the limited evidence reviewed in this article, and follow from an informal workshop on post-exposure prophylaxis for Ebola virus disease convened by WHO in Bethesda (MD, USA) in June, 2015. The recommendations address two main questions: what potential exposures to Ebola virus warrant consideration of post-exposure prophylaxis; and which medical countermeasures should currently be considered for post-exposure prophylaxis. The recommendations are consensus opinion from the authors and not graded because of insufficient high-quality evidence.

What exposure to Ebola virus warrants consideration of post-exposure prophylaxis?

Ebola virus disease has a substantial case-fatality rate even with optimal supportive treatment, which weighs heavily into the risk–benefit deliberations for administration of experimental agents. By contrast, the risk of developing Ebola virus disease following a particular type of exposure to the virus is poorly defined, making the risk–benefit assessment of experimental therapies for post-exposure prophylaxis more challenging. The key evidence about human-to-human transmission of Ebola virus has recently been reviewed,[3] and provides a framework for consideration of which potential exposures to the virus justify use of post-exposure prophylaxis. It is not possible to codify every particular event that might lead to potential exposure to the virus, but it is possible to divide exposures into broad categories of transmission risk, as shown in table 1. Following categorisation, we infer the potential benefit of post-exposure prophylaxis in different situations (table 1) on the basis of the following assumptions about any experimental medical countermeasures used: they have demonstrated relevant antiviral activity in animal models at least, at doses that are achievable in human beings; have safety data in human beings that support their use in healthy individuals; and can be administered safely and within a timeframe that is likely to be effective for post-exposure prophylaxis. Future evidence could permit further refinements to the assessment of transmission risk based on, for example, the viral load of the source. The categories are very broad and do not fully reflect the detailed risk assessment that is required for each potential exposure. For example, individuals who fall into the intermediate risk group because of intact skin exposure might be upgraded to high risk if the exposure was not recognised immediately and there was the possibility of subsequent contamination of mucous membranes, such as by rubbing their own eyes. After any recognised exposure, first-aid measures should be followed as soon as

	Example scenarios	Risk of Ebola virus transmission	Suitability for post-exposure prophylaxis
No direct contact with a patient with Ebola virus disease or their bodily fluids	Breach of personal protective equipment without risk of contamination; living in the same house as a patient with Ebola virus disease but no direct contact or contact with their bodily fluids*	Low	Not recommended
Intact-skin-only contact with a patient with Ebola virus disease (alive or deceased) or their bodily fluids	Clinical assessment of an individual with suspected Ebola virus disease before diagnosis without appropriate personal protective equipment	Intermediate	Can be considered
Broken skin or mucous membrane contact with a patient with Ebola virus disease (alive or deceased) or their bodily fluids; penetrating sharps injury from used device or through contaminated gloves or clothing	Bodily fluid in direct contact with eyes, nose, or mouth; penetrating sharps injury from used intravenous cannula	High	Recommended

*rVSV-ZEBOV vaccine should be considered as part of a ring vaccination approach to outbreak control.

Table 1: **Categories of risk of transmission of Ebola virus following potential exposure**

possible, such as skin decontamination and wound cleaning as appropriate. Optimal first-aid measures are not defined and their benefit is unknown, but the use of disinfectants such as chlorine for wound decontamination was widespread during the west Africa outbreak.

Panel: Characteristics of an ideal agent for post-exposure prophylaxis against Ebola virus disease

- Proven efficacy, preferably in human beings but at least in non-human primates
- Rapid onset of protection and efficacy for longest possible time window after exposure to Ebola virus
- Broad activity against different Ebola virus species
- Well tolerated, with no serious adverse effects
- Easily administered, preferably orally
- Stable and can be stored and transported easily
- Inexpensive and readily available

One special circumstance that might warrant consideration of post-exposure prophylaxis is sexual contact and exposure to semen from male survivors of Ebola virus disease. The virus can be recovered from semen for many months after survival from Ebola virus disease, and male-to-female sexual transmission has now been documented.[101–103] The absolute risk and upper time limit for sexual transmission of Ebola virus are not known, and post-exposure prophylaxis has not been used in this context to our knowledge. We also propose that modelling and studies of post-exposure prophylaxis as an adjunct to ring vaccination should be explored to optimise community control of future outbreaks of Ebola virus disease.

Which medical countermeasures should be considered for post-exposure prophylaxis?

Characteristics of an ideal agent for post-exposure prophylaxis are listed in the panel. None of the currently

	Potential advantages	Potential challenges	Administration and suggested dosing regimen
Vaccination			
rVSV-ZEBOV	Highly immunogenic; effective in a large clinical trial for pre-exposure prophylaxis for Zaire ebolavirus; good short-term safety data in human beings	Vaccine-induced immunity might be insufficiently rapid to reliably prevent Ebola virus disease in human beings when administered as post-exposure prophylaxis; reactogenicity can cause fever; can result in false-positive diagnostic tests for Ebola virus disease (PCR to detect presence of the gene encoding Zaire ebolavirus glycoprotein); uncertain protection against ebolavirus species other than Zaire ebolavirus; requires cold chain	Single, intramuscular injection of 2×10^7 plaque-forming units
Specific monoclonal antibody combination			
ZMapp	Promising effectiveness data from non-human primate treatment studies; suggestive but not conclusive effectiveness data from a controlled clinical trial of treatment of individuals with Ebola virus disease; no significant safety concerns in a controlled clinical trial of treatment	Very limited human use as post-exposure prophylaxis; relatively complex administration; specific for Zaire ebolavirus; requires cold chain	50 mg/kg by slow intravenous infusion every 3 days, for two or three doses
MIL77	Promising effectiveness data from a non-human primate treatment study; similar combination of monoclonal antibodies to that of ZMapp	Extremely limited human use; relatively complex administration; specific for Zaire ebolavirus; production not Good Manufacturing Practice certified; requires cold chain	50 mg/kg by slow intravenous infusion every 3 days, for two or three doses
Small-molecule antiviral agents			
Favipiravir	Established anti-Ebola virus activity in vitro and at high doses in animal models; extensive human safety data at lower doses used for treatment of influenza; no significant safety signal at higher doses in a non-comparative study in patients with Ebola virus disease; stable, oral drug	Relatively weak anti-Ebola virus activity; no proven survival benefit in treatment of Ebola virus disease in either non-human primate or human studies; very limited human use as post-exposure prophylaxis; teratogenic in several animal species at exposure levels observed in human beings	Oral administration; loading doses 2400 mg, 2400 mg, and 1200 mg every 8 h on treatment day 1, followed by a maintenance dose of 1200 mg twice a day; required duration of administration as post-exposure prophylaxis not known, but 10 days has been used
GS-5734	Broad and potent antiviral activity across filoviruses in vitro; promising effectiveness data from a non-human primate treatment study; well tolerated in phase 1 studies; in phase 2 clinical development; stable, lyophilised formulation for reconstitution and infusion	Very limited human use, never as post-exposure prophylaxis	150 mg on day 1 and then 100 mg daily administered by intravenous infusion; required duration of administration as post-exposure prophylaxis not known, but a total of 10 days is suggested for Ebola virus disease treatment
BCX4430	Broad antiviral activity across filoviruses; clear antiviral effect demonstrated in non-human primate treatment studies; in early-phase clinical development for treatment of Ebola virus disease	Not been used for treatment of or post-exposure prophylaxis for Ebola virus disease	Suitable dose and duration unknown

All of the countermeasures listed are investigational for post-exposure prophylaxis and require regulatory approval for emergency use outside approved protocols.

Table 2: **Summary of characteristics for leading investigational countermeasures for post-exposure prophylaxis in Ebola virus disease**

available countermeasures fulfils these criteria, and there are insufficient data to compare these agents directly. Nevertheless, several rational options for post-exposure prophylaxis can be considered, including passive immunotherapy with monoclonal antibodies (eg, ZMapp, which is specific to Zaire ebolavirus) and antiviral agents (such as favipiravir and GS-5734, which are probably more broadly active against Ebola virus species), and choices should be made according to the particular circumstances (and preferably as part of a study). Table 2 summarises the characteristics of leading investigational post-exposure prophylaxis countermeasures for Ebola virus disease. Accumulating evidence suggests that active immunisation alone with rVSV-ZEBOV might not induce protective immunity sufficiently rapidly to provide optimal post-exposure prophylaxis. However, immunisation with rVSV-ZEBOV vaccine and chemoprophylaxis might not be mutually exclusive options and could be used together to provide both rapid and prolonged protection. To pursue this approach, further studies would be required to ensure that the antiviral agent used does not inhibit vaccine replication and attenuate the immune response; favipiravir, for example, has antiviral activity against rabies virus, a rhabdovirus related to vesicular stomatitis virus.[104] Similarly, passive immunoprophylaxis with monoclonal antibodies directed against the Ebola virus glycoprotein that is expressed in the rVSV-ZEBOV vaccine would be expected to interfere with its replication and attenuate its immunogenicity, and therefore concurrent administration of rVSV-ZEBOV vaccine and monoclonal antibodies against the Ebola virus glycoprotein is not recommended. Availability of and access to many of these therapeutics were limiting factors during the west Africa outbreak. On the basis of first principles, it makes sense to administer the countermeasure as soon as possible after exposure, although the time window for maximum effectiveness for each agent is unknown. Particularly for active immunisation and passive immunotherapy, it would be important to know that the measures were effective against the current circulating species of Ebola virus.

Conclusion

Preparedness for the next outbreak of Ebola virus disease should include a strategy for post-exposure prophylaxis. Further evidence is needed to better define who should receive post-exposure prophylaxis and which agents should be used, and therefore studies should be developed that can be implemented quickly in future outbreaks. Study design is challenging, but at least systematic observational data should be collected on use of post-exposure prophylaxis. Predefinition of an agreed minimum dataset would enable data to be aggregated from different sites. Initial evidence suggests that pre-exposure vaccination, if available, could play a fundamental part in the protection of health-care workers in an outbreak. Post-exposure prophylaxis should also be provided in emergencies but, although potentially important both to individuals and to enhance confidence among health-care workers, most exposures to Ebola virus might not be recognised at the time, limiting its overall effectiveness in this context. The potential for post-exposure prophylaxis to prevent secondary cases—for example, within a household—warrants further modelling and trials. This approach could be an important adjunct to ring vaccination, which appears to be effective in prevention of further new infections but might not induce immunity sufficiently rapidly to prevent Ebola virus disease in individuals who have already been infected. Care will need to be taken to ensure that the approach to post-exposure prophylaxis does not interfere with the replication and hence effectiveness of the live-attenuated vaccine. Development of vaccines and immunotherapeutics that are broadly active against multiple species of Ebola virus remains a high medical priority. Access to many of the vaccines and therapeutics discussed in this Review, all of which are currently considered to be experimental, remains a substantial obstacle. Plans for a supply pipeline in advance of an outbreak, together with standard protocols for use and data collection, would assure both access for those in need and the systematic gathering of evidence needed to further refine the guidance presented here.

Search strategy and selection criteria

We searched PubMed for the term "Ebola virus" in the title or abstract for manuscripts published between Jan 1, 2013, and May 31, 2017. We included selected publications in English that provided recent information on Ebola virus with regard to transmission during an outbreak, natural history of disease, management of clinical cases, potential antiviral therapies and vaccines, immunological responses, and animal models. Additionally, we reviewed relevant articles cited in those references and included them as primary sources where appropriate.

Contributors

All authors participated in the WHO workshop on Ebola post-exposure prophylaxis in Bethesda (MD, USA) in June, 2015, and contributed to the ideas in this Review. MJ, WAF, PV, and FGH wrote the first draft, which was reviewed and revised by all authors. WAF and PV contributed equally to this work. The views expressed are those of the authors and do not necessarily represent the official views or policies of the US Centers for Disease Control and Prevention, US National Institutes of Health, US Uniformed Services University of the Health Sciences, US Department of Defense, or US Departments of the Army, Navy, or Air Force.

Declaration of interests

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