

REVIEW ARTICLE

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Ebola

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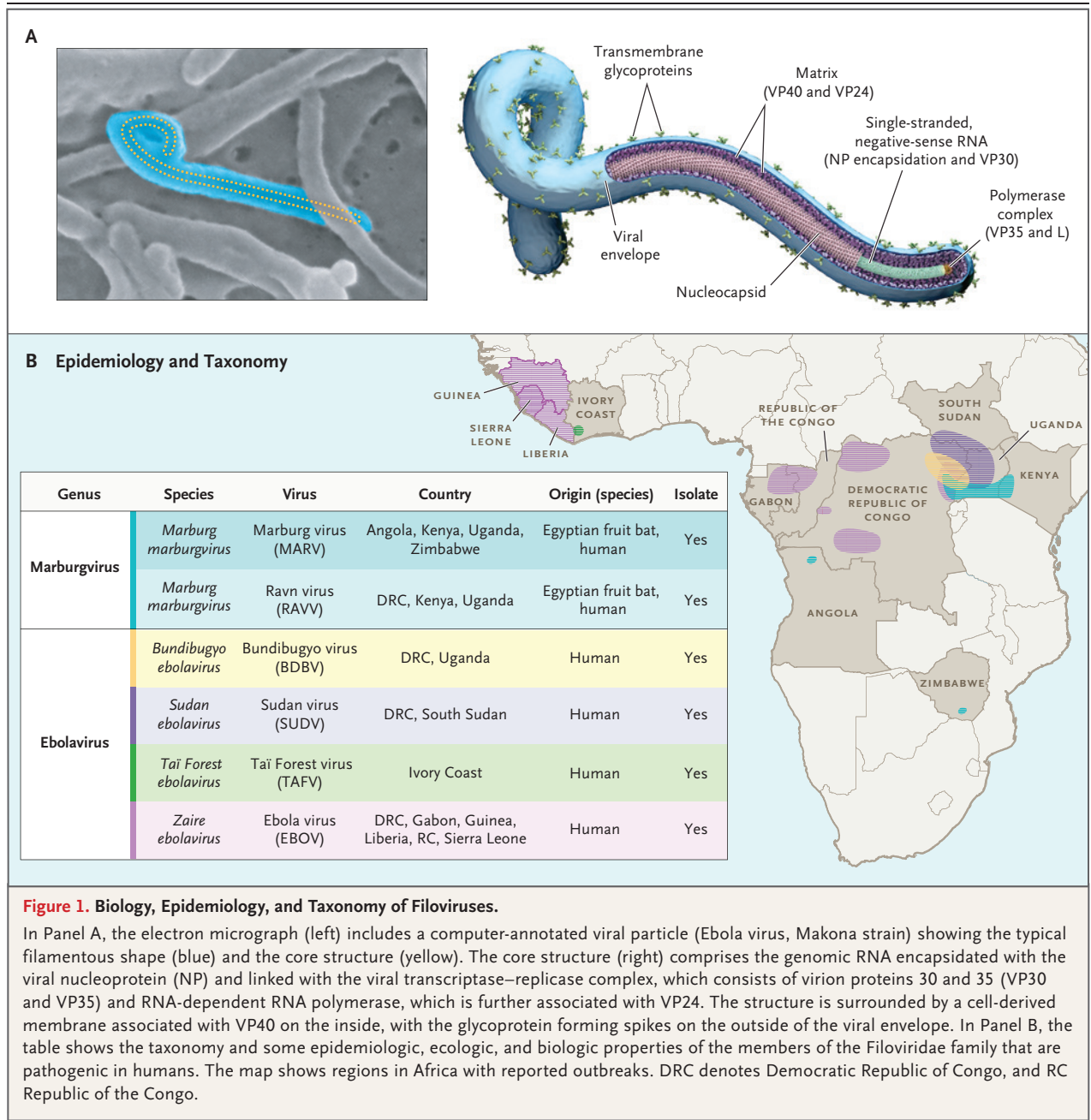
EBOLA VIRUS (EBOV) WAS THE BEST-KNOWN AND MOST EXTENSIVELY STUDIED member of the Filoviridae family (Mononegavirales order) long before the shattering 2013–2016 West African epidemic. The virologic taxon Filoviridae was defined in 1982 and subsequently amended regularly to accommodate changes.^{1,2} These amendments and the unfortunate renaming of commonly used terms has made the filovirus taxonomy confusing. Today, EBOV refers to the specific member virus of the type species *Zaire ebolavirus* in the genus ebolavirus (Fig. 1).

The history of filoviruses largely involves human outbreaks (Fig. 1). Marburg virus (MARV) was the first filovirus to be discovered, in 1967.³ EBOV and Sudan virus (SUDV) were codiscovered in 1976 in the Democratic Republic of Congo (DRC) and South Sudan, respectively.^{4,5} Subsequently, two additional ebolaviruses were found to be pathogenic in humans: Taï Forest virus (TAFV) in Côte d'Ivoire in 1994 and Bundibugyo virus (BDBV) in Uganda in 2007.^{6,7} Reston virus (RESTV), imported into the United States from the Philippines in 1989–1990, has long been the exception, since it appears to infect humans only subclinically.^{8,9} Unexpectedly, it emerged in swine in the Philippines, and RESTV sequences were detected in pigs in China, raising fear about food safety.^{10,11} The zoonotic potential of RESTV remains unclear, and investigation of that potential is urgently needed.

More recently, genomes of new filoviruses were detected in bat and fish species. Lloviu virus (LLOV), genus cuevavirus, was sequenced from bats (*Miniopterus schreibersii*) in Spain and Hungary.¹² Mënglà virus (MLAV) sequences were found in Chinese rousettus species representing the newly proposed genus, dianlovirus.¹³ Bombali virus (BOMV) sequences were discovered in bats from Sierra Leone, Guinea, and Kenya; the virus is considered to be a new ebolavirus species.¹⁴ Finally, fish-derived filoviruses constitute members of two new genera, striavirus and thamnovirus.^{2,15} Since no isolates are available, the unknown zoonotic and pathogenic potential of these new filoviruses is a public health concern.

VIROLOGIC FEATURES

Filoviruses are enveloped, filamentous particles with a nonsegmented, negative-sense RNA genome (Fig. 1).^{2,16-18} The genomic RNA is encapsidated by the nucleoprotein and, together with polymerase L, polymerase cofactor virion protein (VP) 35, and transcription activator VP30, constitutes the nucleocapsid with replicase and transcriptase function. This structure interacts with the nucleocapsid-associated VP24 and is surrounded by the matrix protein VP40, the driver of particle formation. The viral spike is formed by the sole trimeric transmembrane glycoprotein and mediates viral entry; it also represents an important target for host immune responses.^{2,16-18} With all ebolaviruses, unlike marburgviruses, RNA editing



results in glycoprotein expression. The primary product of the glycoprotein gene is a secreted, nonstructural, soluble glycoprotein that has been implicated in antigenic subversion.¹⁶

Filoviruses replicate in the cytoplasm of their target cells.¹⁶⁻¹⁸ Viral particles attach to the cell surface through the binding of glycoprotein to multiple attachment factors, such as C-type lectins, and cell uptake occurs largely through

macropinocytosis. Subsequently, cysteine proteases in the endosome cleave the glycoprotein, allowing it to bind to the receptor Niemann–Pick C1 and initiating membrane fusion. This process releases the genome into the cytosol, where transcription and replication by the viral replicase occur through a positive-sense antigenome intermediate that functions as the template for progeny negative-sense genomes. Viral

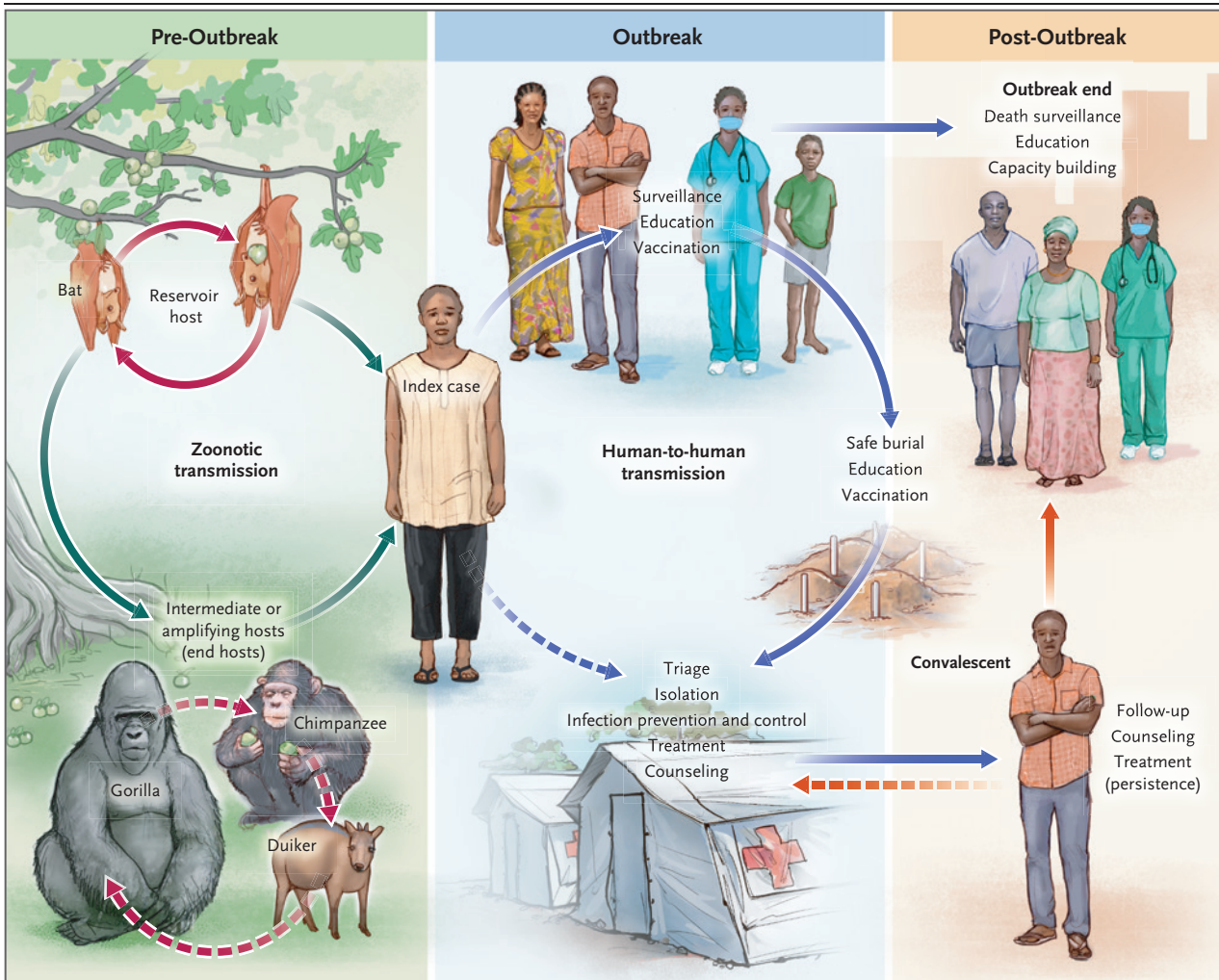


Figure 2. Outbreak Phases.
Shown are the key elements of the three phases of an Ebola virus outbreak, including control measures.

positive-sense RNA transcripts are translated by host ribosomes, leading to intracellular assembly of the nucleocapsid and budding from the plasma membrane.^{2,16-18}

Knowledge of filoviruses is largely based on studies of EBOV and MARV, but all filoviruses are thought to follow similar principles in cell biology, with certain distinctions such as alterations in genomic structure, interferon antagonistic property, and RNA editing.^{2,16-18} Over the years, life-cycle modeling systems have been established for EBOV and MARV that can be safely used in biosafety level 1 and 2 laboratories.¹⁷ These systems have been instrumental in the understanding of filovirus replication and will

foster therapeutic development. Future efforts should focus on studying differences between these viruses and the more recently discovered filoviruses with unknown pathogenic potential.

EPIDEMIOLOGIC AND ECOLOGIC FEATURES

Filoviruses are zoonotic pathogens maintained in reservoir species, perhaps bats, with occasional spillover into humans and other mammals, which may serve as end, intermediate, or amplifying hosts (Fig. 2).¹⁹ This concept, however, has been established only for MARV, with isolation from *Rousettus aegyptiacus*.²⁰ Multiple bat species

have been implicated as harboring ebolaviruses, but viral isolation has yet to be successful.²¹ This is rather uncommon and may be explained by low viral loads, low susceptibility of cell lines, or inhibitors in bat tissue. Since bats are probably hunted for food consumption in African countries,²² the lack of reservoir identification is a concern with respect to preventive measures.

Human pathogenic filoviruses appear to be epizootic in regions close to the African equator (Fig. 1). EBOV has caused most of the outbreaks in central and western African countries, whereas SUDV, BDBV, and the marburgviruses MARV and Ravn virus (RAVV) are more likely to cause disease in eastern Africa.¹⁶ RESTV is known to circulate in the Philippines and is likely to circulate elsewhere in Asia.⁹ With ongoing pathogen-detection programs, new filoviruses will probably be discovered. Evaluation of the pathogenic potential for humans will help to determine the public health threat posed by these filoviruses. Because tools for modeling and predicting outbreaks have become more sophisticated, future research should be able to focus on predicting the appearance of filoviruses in order to facilitate public health preparedness.

Epizootic and endemic viruses circulate in animals and humans, respectively, but this has not been convincingly shown for any filovirus.²³ The frequent reemergence of EBOV in the DRC and Gabon around 2000 and that of MARV in Uganda a decade later supports the hypothesis that these filoviruses are regionally epizootic.¹⁶ The discovery of EBOV persistence in humans may indicate a potential to circulate temporarily in persons.²⁴ Currently, however, neither EBOV nor other filoviruses can be considered to be endemic anywhere; if they were, continuing human-to-human transmission could result, a disturbing thought.²³

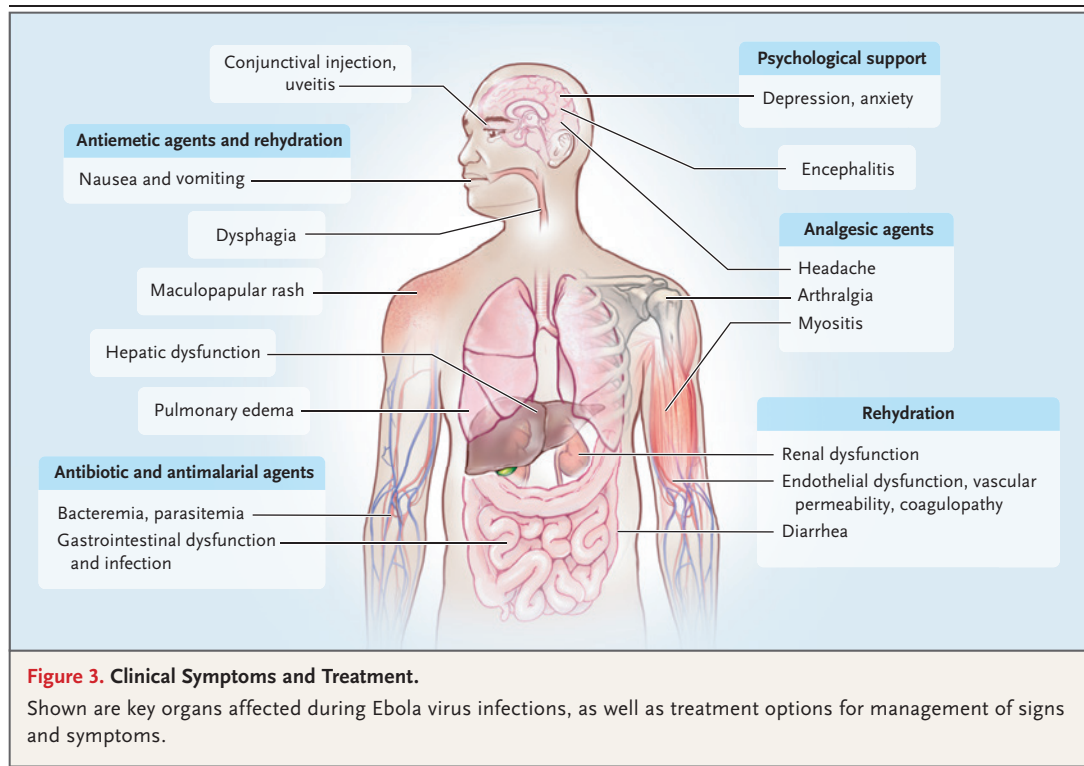
DISEASE AND PATHOGENESIS

The clinical disease is no longer referred to as Ebola or Marburg hemorrhagic fever but rather as Ebola or Marburg virus disease (EVD or MVD), which better reflects the variable symptoms and downplays bleeding as a clinical hallmark. The incubation period is 2 to 21 days (typically, 6 to 10 days) and probably depends on the filovirus, as well as the exposure dose and

route.^{18,25,26} Initially, infection is manifested as a nonspecific febrile illness characterized by malaise, fatigue, and myalgia. A few days later, gastrointestinal manifestations develop in many patients, with anorexia, nausea, vomiting, and diarrhea (Fig. 3). Fluid losses can be substantial — up to 10 liters per day. Other common signs and symptoms are dysphagia, headache, conjunctival injection, abdominal pain, arthralgia, and a maculopapular rash. Bleeding abnormalities occur in less than half of affected patients, usually manifested as bleeding from the gums, petechiae, oozing from venipuncture sites, subconjunctival hemorrhage, and blood in vomitus and stool.^{18,25-27}

Filovirus infections usually begin with the deposition of viral particles on mucous membranes and perhaps skin; occasionally infection occurs percutaneously.¹⁸ After uptake of the viral particles by dendritic cells and macrophages, filovirus replication potently shuts down early innate immune responses by blocking interferon production and signaling.^{28,29} Dissemination probably occurs through the migration of dendritic cells to lymphoid tissues and release of virus into the circulation, leading to infection of fixed macrophages in the liver, spleen, and other tissues. Infection then spreads to adjacent hepatocytes, fibroblasts, and other cells.^{18,26,28-30}

Disease is caused by direct effects of viral replication and host responses to infection.¹⁸ Viral replication leads to the formation of intracellular inclusion bodies, followed by cell lysis.^{30,31} Islands of necrosis appear in the liver, with a commensurate elevation in liver enzyme levels. Myositis causes muscle aches and weakness, coupled with elevation of creatine kinase and aspartate aminotransferase levels. Renal tubular cells and glomerular epithelium are affected, contributing to renal dysfunction (Fig. 3). Host responses include the production of proinflammatory cytokines and chemokines by infected dendritic cells, macrophages, and monocytes.^{28-30,32} These immune responses cause T-cell activation, which is rendered ineffective in severe or fatal cases because of T-cell exhaustion and apoptosis, followed by an impaired adaptive immune response. Proinflammatory mediators cause endothelial-cell dysfunction, followed by increased vascular permeability and fluid extravasation.^{18,26,28,29,32} Infected macrophages produce



tissue factor with fibrin deposition in the spleen, lymphoid tissues, glomeruli, and renal proximal tubules. Consumption of clotting factors (from disseminated microthrombi), endothelial dysfunction, and inhibition of platelet function contribute to coagulopathy.^{18,26,28-30,32} Microvascular anomalies, hypovolemia, and further fluid losses through vomiting and diarrhea ultimately lead to tissue hypoperfusion and multiorgan failure (Fig. 3).^{18,25,26,29,32}

During the 2013–2016 EBOV epidemic, musculoskeletal pain, headache, encephalitis, and ocular problems were noted in survivors and were referred to collectively as the “post-Ebola syndrome.”³³ Historically, filoviruses have been detected in multiple body fluids, including breast milk and semen, in survivors of infection. The persistence in semen, with the potential for sexual transmission more than 500 days after disease onset, is a serious concern. However, transmission this long after disease onset is very rare, with undetermined effects.³⁴⁻³⁶

DIAGNOSIS

Multiple techniques have been established for laboratory diagnostic methods of filovirus de-

tection, including assays for the detection of viral genome, viral antigen, and host immune responses, even in field operations.^{37,38} In the West African EBOV epidemic, on-site, high-end sequencing technology was implemented to improve outbreak response.³⁹ In addition, simple bedside tests to detect viral antigen have become available.^{37,38} The most widely used technique to diagnose acute infections is a quantitative real-time polymerase-chain-reaction assay (qRT-PCR), preferably targeting two distinct genome locations to minimize false negative results due to evolving genome mutations. The qRT-PCR assay is expected to be positive in symptomatic patients, with increasing viremia in fatal cases. Since the assay may be negative early in the disease course, however, follow-up testing is warranted in patients with initially negative tests who have continuing symptoms. In the past, negative results on at least two sequential tests have been required for discharge from the treatment center. Despite improved laboratory diagnosis, individual EVD or MVD cases may still be difficult to diagnose, since clinical assessment is critical. In ill-prepared primary health care settings, diagnosis is further hampered by lack of technical capabilities. Technology transfer and training

are still in their infancy in many African countries, but awareness of filoviruses has grown, and with simple, more reliable technologies, there is a prospect for improvement.

PATIENT CARE

Care of patients has traditionally had three components: supportive care to maintain or restore normal physiology, treatment of discomfort or distress, and presumptive treatment of any concurrent, undiagnosed infections (Fig. 3).^{40,41} The most serious derangement is hypoperfusion stemming from volume deficits due to gastrointestinal losses and vascular leakage, as well as intravascular coagulation. Thus, volume replacement through oral rehydration or intravenous crystalloid infusion is the primary intervention. With the advent of on-site biochemical testing, care now involves correcting electrolyte levels and hypoglycemia, as well as meeting nutritional needs (Fig. 3). In advanced critical care settings, additional support may be used, such as parenteral nutrition or renal-replacement therapy. Patients with headache, myalgias, and arthralgias may be offered analgesic agents. Nausea and vomiting may be relieved with the use of antiemetic agents. No less important is psychological support to help patients cope with anxiety, stress, and fear (Fig. 3).^{40,41}

Coinfection, whether a coincident tropical illness or an infection due to EVD or MVD, has been documented.^{42,43} The frequency of coinfections and the limited diagnostic options in most care settings have led to presumptive treatment with antimalarial agents and broad-spectrum antibiotics. Future advances in diagnostics should allow for more targeted antimicrobial treatment.

INVESTIGATIONAL TREATMENT

Efforts to develop specific treatments began shortly after the discovery of filoviruses, but when the West African Ebola epidemic struck, efficacy had been shown only in preclinical studies. Clinical trials of promising therapies were carried out during the West African outbreak, including convalescent plasma or whole blood,^{44,45} antibodies,⁴⁶ small interfering RNAs,⁴⁷ and small-molecule inhibitors (favipiravir),⁴⁸ but none showed significant efficacy^{49,50} (Table 1).

In the recent Ebola outbreak in the DRC, four

investigational drugs, the monoclonal-antibody cocktails ZMapp (Mapp Biopharmaceutical) and REGN-EB3 (Regeneron Pharmaceuticals), a single monoclonal antibody (MAB114, Ridgeback Biotherapeutics), and remdesivir (Gilead Sciences), a small-molecule antiviral drug, have been given to hundreds of patients under the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) framework and in a randomized, clinical trial (Table 1).^{55,56} The interim results of the Pamoja Tulinde Maisha (PALM) trial⁵⁴ suggested significantly improved survival for patients receiving MAB114 or REGN-EB3, as compared with those receiving remdesivir or ZMapp; the patients receiving ZMapp served as a control group on the basis of the results from the Partnership for Research on Ebola Virus in Liberia II (PREVAIL II) trial.⁴⁶ Surprisingly, ZMapp performed worse in the PALM trial than in the PREVAIL II trial. The reasons remain unclear, and further analysis may be needed to shed more light on potential differences among treatment groups. Interestingly, patients receiving care and treatment earlier in the course of illness fared better than those who entered Ebola treatment units later, which had not been the case previously.⁵⁷ Also surprising was the fact that extremes of age, which had adversely affected outcomes in past outbreaks,⁵⁸ were not associated with differences in outcome in the PALM trial.⁵⁴ Patients in whom EVD developed despite previous vaccination for EBOV had much better outcomes than patients who had not been vaccinated.⁵⁴ An analysis involving the patients who received the same therapeutics under MEURI that were provided in the PALM trial showed strikingly similar results, despite the lack of randomized treatment assignments and trial procedures.

Overall, under MEURI and in the PALM trial, antibody specificity, initially higher antibody doses, and perhaps the more favorable pharmacokinetics of human antibodies may have conferred an advantage. Remdesivir may have a delayed onset of action as compared with antibodies; however, the drug has broader applicability and, with antibodies, may represent a synergistic therapeutic approach. The preliminary results of MEURI and the PALM trial provide hope for further incremental improvements in the treatment of EVD with newer and improved investigational therapeutics or different

Table 1. Clinical Trials of Vaccines and Antiviral Therapies for Ebola Virus Infection in Humans.*

| Treatment and Study Design (Country) | Filovirus Species (Strain) | Dose | Regimen | No. of Patients and Outcome | Study |
|---|----------------------------|--|--|--|---|
| Vaccine | | | | | |
| rVSV-ZEBOV; open-label, cluster, randomized trial of ring vaccination (Guinea) | Ebola (Makona) | 2 × 10 ⁷ PFU | Single injection (IM) | 5837 vaccinated; estimated efficacy, 100% (95% CI, 79.3–100.0) | Henao-Restrepo et al. ⁵¹ |
| rVSV-ZEBOV; randomized, placebo-controlled phase 2–3 trial (Liberia) | Ebola (Makona) | 2 × 10 ⁷ PFU | Single injection (IM) | 500 vaccinated (phase 3 eliminated because of decline of Ebola in Liberia) | Kennedy et al. ⁵² |
| rVSV-ZEBOV; open-label, cluster, randomized trial of ring vaccination (DRC) | Ebola (Kivu) | 2 × 10 ⁷ PFU | Single injection (IM) | 93,965 vaccinated; efficacy, 97.5% (95% CI, 95.8–98.5) | World Health Organization ⁵³ |
| ChAd3-EBO-Z; randomized, placebo-controlled phase 2–3 trial (Liberia) | Ebola (Makona) | 2 × 10 ¹¹ particle units | Single injection (IM) | 500 vaccinated (phase 3 eliminated because of decline of Ebola in Liberia) | Kennedy et al. ⁵² |
| Antiviral Therapy | | | | | |
| Convalescent plasma; nonrandomized comparative study | Ebola (Makona) | Unknown | Two consecutive IV transfusions of 200–250 ml each | 84 enrolled; no significant survival benefit | van Griensven et al. ⁴⁴ |
| Convalescent blood; nonrandomized comparative study | Ebola (Makona) | Unknown | One IV transfusion of 450 ml given over a period of 1–4 hr | 43 enrolled; no significant survival benefit | Sahr et al. ⁴⁵ |
| ZMapp; phase 2–3 trial (Liberia, Sierra Leone, Guinea, United States) | Ebola (Makona) | 50 mg/kg | One dose every 3 days (IV) for a total of three doses | 36 enrolled, 28 survived (77.8% survival rate) | PREVAII II Writing Group ⁴⁶ |
| ZMapp; PALM trial (DRC) | Ebola (Kivu) | 50 mg/kg | One dose every 3 days (IV) for a total of three doses | 323 enrolled, 160 survived (49.5% survival rate) | Mulangu et al. ⁵⁴ |
| MAB114; PALM trial (DRC) | Ebola (Kivu) | 50 mg/kg | One dose (IV) | 174 enrolled, 113 survived (64.9% survival rate) | Mulangu et al. ⁵⁴ |
| REGN-EB3; PALM trial (DRC) | Ebola (Kivu) | 150 mg/kg | One dose (IV) | 155 enrolled, 103 survived (66.5% survival rate) | Mulangu et al. ⁵⁴ |
| Remdesivir (GS-5734); double-blind, placebo-controlled, natural history trial (Liberia) | Ebola (Makona) | 100 mg | Once daily for 5 days (IV) | Ongoing, with planned enrollment of 60 survivors to assess viral shedding in semen | Siegel et al. ⁵⁵ |
| Remdesivir (GS-5734); PALM trial (DRC) | Ebola (Kivu) | 200 mg loading dose; 100 mg thereafter | Once daily for 9–13 days (IV) | 175 enrolled, 82 survived (46.9% survival rate) | Mulangu et al. ⁵⁴ |
| Favipiravir (T-705); single-group trial with historical controls (Guinea) | Ebola (Makona) | 6000 mg loading dose; 2400 mg thereafter | Two 1200-mg doses daily on days 1–9 (oral) | 126 enrolled; no significant survival benefit | Sissoko et al. ⁴⁸ |
| TKM-130803; single-group, phase 2 trial with historical controls (Sierra Leone) | Ebola (Makona) | 0.3 mg/kg | Once daily for up to 7 days (IV) | 12 enrolled; no significant survival benefit | Dunning et al. ⁴⁷ |

* CI denotes confidence interval, IM intramuscular, IV intravenous, PALM Pamoja Tulinde Maisha, and PFU plaque-forming units.

approaches (e.g., combination therapy). Notably, ZMapp, REGN-EB3, and MAb114 provide protection against EBOV alone, whereas more recent preclinical success with strategically engineered, next-generation human antibodies (i.e., MBP134, FVM04, and CA45) has shown protection against EBOV, SUDV, and BDBV — a promising advance.^{59,60}

VACCINES

Vaccine development started in the 1970s with inactivated viral preparations and was followed in the 1980s and 1990s by subunit and DNA vaccine approaches.^{61,62} The past two decades have seen intensified use of vectored vaccines and combined approaches. Except for the EBOV DNA and adenovirus-based vaccines, none of these vaccine candidates had made it past the preclinical stage when the West African Ebola epidemic hit.^{61,62} This lack of preparedness for EBOV was finally corrected with several approaches that quickly moved to clinical trials (Table 1). One of the approaches is a single-shot, live-attenuated, vectored vaccine based on a recombinant vesicular stomatitis virus expressing the *Zaire ebolavirus* glycoprotein (rVSV-ZEBOV-GP [ERVEBO, Merck]), which was successfully tested for efficacy in a randomized trial in Guinea during the West African epidemic.^{51,52} The vaccine, which was approved by the European Medicines Agency and the U.S. Food and Drug Administration, has been widely administered in the DRC EBOV outbreak, with promising preliminary results (97.5% efficacy for vaccinees with an onset of illness more than 10 days after vaccination, and 88.1% for all those with EVD, regardless of the timing of illness onset).^{53,63} Advances in the development of other vaccines, such as the chimpanzee adenovirus 3 vaccine (ChAd3-EBO-Z, GlaxoSmithKline)⁵² and the heterologous prime–boost regimen containing the Janssen AdVac for priming, followed by Bavarian Nordic modified vaccinia Ankara (MVA-BN) technologies for boosting (Johnson & Johnson), are closing the gap between investigational and clinical use.^{64,65}

Since safe and immunogenic vaccine candidates are available, the question remains what strategy to choose for a specific target group. The single-shot rVSV-ZEBOV appears to be valuable when rapid immunity is needed — for ex-

ample, when the objective is to target contacts of infected patients, as well as potential future contacts of current contacts, well ahead of their exposure.^{51,53} The prime–boost regimen may provide a more durable immune response, which takes longer to develop. Since the MVA boost contains glycoprotein sequences for multiple filoviruses and a nucleoprotein sequence for TAFV,⁶⁴ it may provide cross-protection. In general, a prime–boost approach may be preferable for persons who are at risk for exposure because of their occupation, such as health care workers, but the level of efficacy that can be achieved with the prime regimen alone is unknown. Nevertheless, the prime–boost regimen was recently added to ring vaccination in the DRC as a second approach, in the form of pop-up vaccination and targeted geographic vaccination to address security concerns and community tensions (www.who.int/immunization/policy/position_papers/interim_ebolavirus_recommendations_may_2019.pdf), in areas where there is no active transmission.⁶⁵ In the future, issues such as vaccine efficacy, stability, storage, transport, and administration, as well as supply adequacy, need to be addressed for several of the vaccine products.

The protective immune responses to filovirus infections in nature are still not defined, and correlates or even mechanisms of protection are unknown.^{61,62} Furthermore, the protective immune response provided by vaccination may well differ among vaccine candidates and may also differ from the immune response to natural infection. The closest correlate today appears to be the total IgG response to EBOV glycoprotein.^{61,62}

OUTBREAK MANAGEMENT

A comprehensive response to a filovirus outbreak is a complex undertaking (Fig. 2). The principle objectives are identifying and isolating suspected cases to prevent transmission and caring for patients with EVD or MVD in order to save lives. Given the vague early clinical presentation and its similarities to common tropical illnesses, case identification requires reliable case definitions, epidemiologic linkage, and laboratory confirmation.

Another important component of the response to an outbreak is follow-up of contacts of infected patients (Fig. 2). Contacts, historically

averaging 10 to 15 per patient, are monitored daily for 21 days, the maximum incubation period, making contact follow-up a resource-intensive effort.⁶⁶ There is a high risk of disease transmission during traditional funerals, requiring burial practices that minimize the risk of transmission while respecting cultural values.⁶⁷ Disinfection of the environment (e.g., at funerals and treatment centers), contaminated by infected persons and deceased bodies, is another important disease-control activity.⁶⁸

Complicating nearly every aspect of outbreak management is the crucial need to protect health care workers.^{69,70} With the small infectious inoculum, few treatments, and severe disease, a zero-tolerance practice has evolved. The iconic image of health care workers is their personal protective equipment. This equipment has many inconveniences, but none greater than heat stress, which severely limits the time safely spent in a care setting under tropical conditions.

The introduction of effective vaccines and therapeutics has great potential not only to improve outcomes for patients but also to improve outbreak control. The availability of these agents can provide a strong incentive for patients with EVD or MVD to rapidly bring themselves to the attention of surveillance systems and for persons at risk for exposure to respond to contact tracing, so long as the benefit of vaccines is clearly perceived.

Nothing may be as important as community engagement and public perception.⁷¹ Disease transmission stops only when the community is no longer caring for the sick in unprotected settings and burying the dead in an unsafe manner. Programs are aimed at encouraging the population to quickly alert authorities about febrile cases or unexplained deaths rather than provide care at home or engage in unprotected burials.^{67,72} Another important component is public education about the disease and control measures. These messages will be effective only if the community trusts the messenger. Outbreaks may occur in locations where mistrust of the national government and outside intervention is very high, as currently seen in the DRC.^{73,74} In environments of mistrust, the introduction of experimental countermeasures may actually bolster further mistrust. When people die in villages where vaccines were deployed and in treat-

ment centers where experimental drugs are used, rumors of unsavory experimentation may begin to spread. Unless the ground is prepared for intervention, actions are explained, and questions answered, these new developments may be regarded as a threat.

PERSPECTIVE ON THE FUTURE

We have come a long way since the epidemic that devastated West Africa. We have managed to translate the fruits of laboratory research into new diagnostics, therapies, and vaccines. Now we are facing the challenges of producing and implementing these tools and moving them toward licensure, which has recently been achieved for ERVEBO.^{75,76} To meet these challenges, programs such as the Coalition for Epidemic Preparedness Innovations will be helpful. The next great challenge is successfully using these tools to help control outbreaks. Providing resources that are available to those most in need requires the trust of the recipient population. The current DRC outbreak shows that trust is not a given and that the value of these tools is not self-evident.

EBOV is just one of many neglected pathogens for which we are ill prepared. Can we generate the impetus and secure the funding to tackle other neglected tropical diseases? To do so would require an environment in which global strategies addressing infectious disease and health could be rapidly and effectively implemented. Efforts to achieve this goal start with surveillance and include rapid communication; unrestricted information and reagent sharing; early collaborative engagement of government, industry, and academia; rapid and coordinated responses; community education and the fostering of trust; and finally, the establishment and maintenance of local response capacities. Are we there yet? No, but we are moving slowly in the right direction.

The opinions, conclusions, and recommendations in this report are those of the authors and do not necessarily represent the official positions of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health, the University of Texas Medical Branch, or Médecins sans Frontières.

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REFERENCES

- Kiley MP, Bowen ET, Eddy GA, et al. Filoviridae: a taxonomic home for Marburg and Ebola viruses? *Intervirology* 1982;18:24-32.
- Kuhn JH, Amarasinghe GK, Basler CF, et al. ICTV virus taxonomy profile: Filoviridae. *J Gen Virol* 2019;100:911-2.
- Siegert R, Shu HL, Slenczka W, Peters D, Müller G. On the etiology of an unknown human infection originating from monkeys. *Dtsch Med Wochenschr* 1967;92:2341-3. (In German.)
- Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ* 1978;56:271-93.
- Ebola haemorrhagic fever in Sudan, 1976: report of a WHO/International Study Team. *Bull World Health Organ* 1978;56:247-70.
- Le Guenno B, Formenty P, Wyers M, Gounon P, Walker F, Boesch C. Isolation and partial characterisation of a new strain of Ebola virus. *Lancet* 1995;345:1271-4.
- Towner JS, Sealy TK, Khristova ML, et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog* 2008;4(11):e1000212.
- Jahrling PB, Geisbert TW, Dalgard DW, et al. Preliminary report: isolation of Ebola virus from monkeys imported to USA. *Lancet* 1990;335:502-5.
- Cantoni D, Hamlet A, Michaelis M, Wass MN, Rossman JS. Risks posed by Reston, the forgotten Ebolavirus. *mSphere* 2016;1(6):e00322-16.
- Barrette RW, Metwally SA, Rowland JM, et al. Discovery of swine as a host for the Reston ebolavirus. *Science* 2009;325:204-6.
- Pan Y, Zhang W, Cui L, Hua X, Wang M, Zeng Q. Reston virus in domestic pigs in China. *Arch Virol* 2014;159:1129-32.
- Negredo A, Palacios G, Vázquez-Morón S, et al. Discovery of an ebolavirus-like filovirus in Europe. *PLoS Pathog* 2011;7(10):e1002304.
- Yang XL, Tan CW, Anderson DE, et al. Characterization of a filovirus (Mênglà virus) from *Rousettus* bats in China. *Nat Microbiol* 2019;4:390-5.
- Goldstein T, Anthony SJ, Gbakima A, et al. The discovery of Bombali virus adds further support for bats as hosts of ebolaviruses. *Nat Microbiol* 2018;3:1084-9.
- Shi M, Lin XD, Chen X, et al. The evolutionary history of vertebrate RNA viruses. *Nature* 2018;556:197-202.
- Emanuel J, Marzi A, Feldmann H. Filoviruses: ecology, molecular biology, and evolution. *Adv Virus Res* 2018;100:189-221.
- Hoenen T, Groseth A, Feldmann H. Therapeutic strategies to target the Ebola virus life cycle. *Nat Rev Microbiol* 2019;17:593-606.
- Baseler L, Chertow DS, Johnson KM, Feldmann H, Morens DM. The pathogenesis of Ebola virus disease. *Annu Rev Pathol* 2017;12:387-418.
- Munster VJ, Bausch DG, de Wit E, et al. Outbreaks in a rapidly changing Central Africa — lessons from Ebola. *N Engl J Med* 2018;379:1198-201.
- Towner JS, Amman BR, Sealy TK, et al. Isolation of genetically diverse Marburg viruses from Egyptian fruit bats. *PLoS Pathog* 2009;5(7):e1000536.
- Olival KJ, Hayman DT. Filoviruses in bats: current knowledge and future directions. *Viruses* 2014;6:1759-88.
- Frick WF, Kingston T, Flanders J. A review of the major threats and challenges to global bat conservation. *Ann N Y Acad Sci* 2019 April 2 (Epub ahead of print).
- Sprecher A, Feldmann H, Hensley LE, et al. Ebola virus is unlikely to become endemic in West Africa. *Nat Microbiol* 2016;1:16007.
- Dokubo EK, Wendland A, Mate SE, et al. Persistence of Ebola virus after the end of widespread transmission in Liberia: an outbreak report. *Lancet Infect Dis* 2018;18:1015-24.
- Leligdowicz A, Fischer WA II, Uyeki TM, et al. Ebola virus disease and critical illness. *Crit Care* 2016;20:217.
- McElroy A. Understanding bleeding in Ebola virus disease. *Clin Adv Hematol Oncol* 2015;13:29-31.
- Nicastrì E, Kobinger G, Vairo F, et al. Ebola virus disease: epidemiology, clinical features, management, and prevention. *Infect Dis Clin North Am* 2019;33:953-76.
- Prescott JB, Marzi A, Safronetz D, Robertson SJ, Feldmann H, Best SM. Immunobiology of Ebola and Lassa virus infections. *Nat Rev Immunol* 2017;17:195-207.
- Muñoz-Fontela C, McElroy AK. Ebola virus disease in humans: pathophysiology and immunity. *Curr Top Microbiol Immunol* 2017;411:141-69.
- Martines RB, Ng DL, Greer PW, Rollin PE, Zaki SR. Tissue and cellular tropism, pathology and pathogenesis of Ebola and Marburg viruses. *J Pathol* 2015;235:153-74.
- Hoenen T, Shabman RS, Groseth A, et al. Inclusion bodies are a site of ebolavirus replication. *J Virol* 2012;86:11779-88.
- Falasca L, Agrati C, Petrosillo N, et al. Molecular mechanisms of Ebola virus pathogenesis: focus on cell death. *Cell Death Differ* 2015;22:1250-9.
- Jagadesh S, Sevalie S, Fatoma R, et al. Disability among Ebola survivors and their close contacts in Sierra Leone: a retrospective case-controlled cohort study. *Clin Infect Dis* 2018;66:131-3.
- Vetter P, Fischer WA II, Schibler M, Jacobs M, Bausch DG, Kaiser L. Ebola virus shedding and transmission: review of current evidence. *J Infect Dis* 2016;214:Suppl 3:S177-S184.
- Sissoko D, Keita M, Diallo B, et al. Ebola virus persistence in breast milk after no reported illness: a likely source of virus transmission from mother to child. *Clin Infect Dis* 2017;64:513-6.
- Diallo B, Sissoko D, Loman NJ, et al. Resurgence of Ebola virus in Guinea linked to a survivor with virus persistence in seminal fluid for more than 500 days. *Clin Infect Dis* 2016;63:1353-6.
- Coarsey CT, Esiobu N, Narayanan R, Pavlovic M, Shafiee H, Asghar W. Strategies in Ebola virus disease (EVD) diagnostics at the point of care. *Crit Rev Microbiol* 2017;43:779-98.
- Shorten RJ, Brown CS, Jacobs M, Rattenbury S, Simpson AJ, Mepham S. Diagnostics in Ebola virus disease in resource-rich and resource-limited settings. *PLoS Negl Trop Dis* 2016;10(10):e0004948.
- Quick J, Loman NJ, Duraffour S, et al. Real-time, portable genome sequencing for Ebola surveillance. *Nature* 2016;530:228-32.
- Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med* 2016;374:636-46.
- Case definition recommendations for Ebola or Marburg virus diseases. Geneva: World Health Organization, August 9, 2014 (https://apps.who.int/iris/bitstream/handle/10665/146397/WHO_EVD_CaseDef_14.1_eng.pdf?sequence=1).
- de Wit E, Falzarano D, Onyango C, et al. The merits of malaria diagnostics during an Ebola virus disease outbreak. *Emerg Infect Dis* 2016;22:323-6.
- Carroll MW, Haldenby S, Rickett NY, et al. Deep sequencing of RNA from blood and oral swab samples reveals the presence of nucleic acid from a number of pathogens in patients with acute Ebola virus disease and is consistent with bacterial translocation across the gut. *mSphere* 2017;2(4):e00325-17.
- van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N Engl J Med* 2016;374:33-42.
- Sahr F, Ansumana R, Massaquoi TA, et al. Evaluation of convalescent whole blood for treating Ebola virus disease in Freetown, Sierra Leone. *J Infect* 2017;74:302-9.
- The PREVAIL II Writing Group for the Multi-National PREVAIL II Study Team. A randomized, controlled trial of ZMapp for Ebola virus infection. *N Engl J Med* 2016;375:1448-56.
- Dunning J, Sahr F, Rojek A, et al. Experimental treatment of Ebola virus disease with TKM-130803: a single-arm

- phase 2 clinical trial. *PLoS Med* 2016;13(4): e1001997.
48. 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(3):e1001967.
 49. Cross RW, Mire CE, Feldmann H, Geisbert TW. Post-exposure treatments for Ebola and Marburg virus infections. *Nat Rev Drug Discov* 2018;17:413-34.
 50. Dodd LE, Follmann D, Proschan M, et al. A meta-analysis of clinical studies conducted during the West Africa Ebola virus disease outbreak confirms the need for randomized control groups. *Sci Transl Med* 2019;11(520):eaaw1049.
 51. 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.
 52. Kennedy SB, Bolay F, Kieh M, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N Engl J Med* 2017;377:1438-47.
 53. 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. Geneva: World Health Organization, 2019 (<https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf>).
 54. 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.
 55. Siegel D, Hui HC, Doerffler E, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem* 2017;60:1648-61.
 56. Nakkazi E. Randomised controlled trial begins for Ebola therapeutics. *Lancet* 2018;392:2338.
 57. Fitzpatrick G, Vogt F, Moi Gbaba OB, et al. The contribution of Ebola viral load at admission and other patient characteristics to mortality in a Médecins Sans Frontières Ebola case management centre, Kailahun, Sierra Leone, June-October 2014. *J Infect Dis* 2015;212:1752-8.
 58. Cherif MS, Koonrungsomboon N, Diallo MP, et al. The predictor of mortality outcome in adult patients with Ebola virus disease during the 2014-2015 outbreak in Guinea. *Eur J Clin Microbiol Infect Dis* 2017;36:689-95.
 59. Bornholdt ZA, Herbert AS, Mire CE, et al. A two-antibody pan-Ebolavirus cocktail confers broad therapeutic protection in ferrets and nonhuman primates. *Cell Host Microbe* 2019;25(1):49-58.e5.
 60. Brannan JM, He S, Howell KA, et al. Post-exposure immunotherapy for two ebolaviruses and Marburg virus in non-human primates. *Nat Commun* 2019;10:105.
 61. Feldmann H, Feldmann F, Marzi A. Ebola: lessons on vaccine development. *Annu Rev Microbiol* 2018;72:423-46.
 62. Gross L, Lhomme E, Pasin C, Richert L, Thiebaut R. Ebola vaccine development: systematic review of pre-clinical and clinical studies, and meta-analysis of determinants of antibody response variability after vaccination. *Int J Infect Dis* 2018;74:83-96.
 63. Ebola virus disease, Democratic Republic of the Congo: external situation report 74/2019. Geneva: World Health Organization, January 7, 2020 (<https://www.who.int/publications-detail/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-74-2019>).
 64. Callendret B, Vellinga J, Wunderlich K, et al. A prophylactic multivalent vaccine against different filovirus species is immunogenic and provides protection from lethal infections with Ebolavirus and Marburgvirus species in non-human primates. *PLoS One* 2018;13(2):e0192312.
 65. WHO adapts Ebola vaccination strategy in the Democratic Republic of the Congo to account for insecurity and community feedback. Geneva: World Health Organization, May 7, 2019 (<https://www.who.int/news-room/detail/07-05-2019-who-adapts-ebola-vaccination-strategy-in-the-democratic-republic-of-the-congo-to-account-for-insecurity-and-community-feedback>).
 66. Saurabh S, Prateek S. Role of contact tracing in containing the 2014 Ebola outbreak: a review. *Afr Health Sci* 2017;17:225-36.
 67. How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease. Geneva: World Health Organization, October 2017 (https://apps.who.int/iris/bitstream/handle/10665/137379/WHO_EVD_GUIDANCE_Burials_14.2_eng.pdf?sessionid=EF497CD6DB66A714B02F87F50B348C43?sequence=1).
 68. Poliquin PG, Vogt F, Kasztura M, et al. Environmental contamination and persistence of Ebola virus RNA in an Ebola treatment center. *J Infect Dis* 2016;214:Suppl 3:S145-S152.
 69. Coca A, DiLeo T, Kim JH, Roberge R, Shaffer R. Baseline evaluation with a sweating thermal manikin of personal protective ensembles recommended for use in West Africa. *Disaster Med Public Health Prep* 2015;9:536-42.
 70. Interim infection prevention and control guidance for care of patients with suspected or confirmed filovirus haemorrhagic fever in health-care settings, with focus on Ebola. Geneva: World Health Organization, December 2014 (<https://apps.who.int/iris/bitstream/handle/10665/130596?jsessionid=3DB5CDD877C5B452E1BBAC11BB462A62?sequence=1>).
 71. Wilkinson A, Parker M, Martineau F, Leach M. Engaging 'communities': anthropological insights from the West African Ebola epidemic. *Philos Trans R Soc Lond B Biol Sci* 2017;372:20160305.
 72. Agua-Agum J, Ariyaratna A, Aylward B, et al. Exposure patterns driving Ebola transmission in West Africa: a retrospective observational study. *PLoS Med* 2016;13(11):e1002170.
 73. Vinck P, Pham PN, Bindu KK, Bedford J, Nilles EJ. Institutional trust and misinformation in the response to the 2018-19 Ebola outbreak in North Kivu, DR Congo: a population-based survey. *Lancet Infect Dis*. 2019;19:52936.
 74. Kudra Maliro A-H, Anna C. Attackers kill doctor at hospital in Congo's Ebola epicenter. *AP News*. April 19, 2019 (<https://apnews.com/3b99e6c8b646404288dc4a288b402044>).
 75. Terry M. Merck's Ervebo is the world's first approved Ebola vaccine. *BioSpace*. November 14, 2019 (<https://www.biospace.com/article/merck-s-ebola-vaccine-approved-in-europe/>).
 76. First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. Silver Spring, MD: Food and Drug Administration, December 19, 2009 (<https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health>).

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