**What Do We Know About Controlling Ebola Virus Disease Outbreaks?**

Colin Stewart Brown1,2, Catherine Frances Houlihan3,4, Marta Lado1, Natalie Mouter1 and Daniel Youkee1

1King’s Sierra Leone Partnership, King’s Centre for Global Health, King’s College London, London, UK. 2National Infection Service, Public Health England, London, UK. 3Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK. 4Faculty of Medical Sciences, University College London, London, UK.

**ABSTRACT:** The West African Ebola Virus Disease outbreak was unprecedented in size, dwarfing all previous outbreaks by some magnitude. Nearly, more than 28,000 people had been infected, with more than 11,000 deaths recorded. This review article will highlight some of the major public health and therapeutic advances realised during this outbreak, as well as pointing readers to key review articles on the different aspects of disease control. It will describe the multifaceted international response and detail how the response efforts allied traditional public health approaches and novel models of intervention. It will review the shift from a humanitarian response paradigm to real-time evidence-based decision making, including modelling of potential interventions, novel interventional treatment studies, and pragmatic vaccine trials.

**KEYWORDS:** Ebola, viral haemorrhagic fever, emergency response, preparedness, public health, vaccination

**Introduction**

The West African Ebola virus disease (EVD) outbreak was unparalleled in size for Ebola epidemics, with more than 28,000 people infected and some 11,000 deaths.1 This represented EVD transmission at an unprecedented scale, with pervasive viral spread occurring across the 3 most affected countries of Sierra Leone, Liberia, and Guinea, travelling from rural villages to densely populated urban centres. The outbreak provoked an international multilateral epidemic response, using traditional public health approaches, as well as novel models of intervention. It created a large body of research on models of epidemic control effectiveness, as well as shifting the humanitarian research paradigm to real-time evidence-based decision making, modelling of potential interventions, novel interventional treatment studies, and pragmatic vaccine trials. This review will highlight some of the major public health and therapeutic advances realised during this outbreak, as well as pointing readers to key review articles on the different aspects of disease control. It will also show how the stalwarts of infectious disease outbreak control were used, including rapid case identification, large-scale contact tracing, community engagement, adequate diagnostics, appropriate infection prevention, and control measures including waste management, scaled-up isolation treatment facilities, and, where necessary, safe burial (see Figure 1).

**Case Detection**

Early case detection remains key to limit outbreak spread and prevent onward transmission of cases through undiagnosed infections.2 This relies on a functioning surveillance system for case detection supported by the laboratory capacity to diagnose EVD. These structures were largely unavailable in countries affected by the West African Outbreak; the 2 exceptions to this were Nigeria, which through rapid diagnosis and isolation of cases, averted widespread transmission,3 and Kenema Government Hospital in Sierra Leone which could test for Zaire Ebola virus (EOBV) in addition to Lassa fever but which was quickly overwhelmed at the start of Sierra Leone’s epidemic. Early case detection was hampered by the low positive predictive value of the current World Health Organization (WHO) case definition, with clinical symptoms that differed somewhat from previous outbreaks, such as significantly less haemorrhage.4 Several large case series have highlighted the limitations in using fever or history of fever as a criteria, with the potential to miss up to 20% of cases using this definition.5–7 Obstructed obstetric deliveries8,9 and acute abdominal surgical emergencies10 in combination with a wide range of infectious and non-infectious medical presentations, closely mimic the early stages of EVD. Further work is needed to validate and refine a useable case definition at different stages of outbreak response.11

**Contact Tracing**

A fundamentally different approach is needed to respond to outbreaks in rural isolated areas compared with outbreaks in densely populated urban centres12: in Uganda, early case detection was noted to be the most effective intervention in 5 rural outbreaks from 2000 to 2012, but in Gulu, the involvement of slum areas hampered outbreak control.13 Urban outbreaks have been characterised by higher population density, leading to higher attack rates; a more mobile
population, inhibiting adequate contact tracing; and reduced social networks, rendering social mobilisation less effective. In the Western Area of Sierra Leone, including the capital Freetown, more than 75% of new confirmed EVD cases were not listed as contacts at the start of their illness. Confirmed cases in urban areas had twice as many listed contacts as those in rural areas, and contacts were more likely to be unrelated neighbours as opposed to family members, with direct implications on the ease and quality of contact tracing. Several applications have been developed to assist in contact tracing and were tested during the West African outbreak, for example, an updated version of free desktop epidemiologic software or smartphone applications that use Global Positioning Systems.

A review of contact tracing in the Western Area of Sierra Leone highlighted many missed opportunities attributable to both tracers and communities, which delayed the public health response. They conclude that in future outbreaks, early community engagement and participation in contact tracing, establishment of appropriate mechanisms for selection, adequate training and supervision of qualified contact tracers, establishment of a well-managed and complete contact tracing database, and provision of basic needs to quarantined contacts are recommended as measures to enhance effective contact tracing.

**Surveillance and Community Engagement**

Initial lack of surveillance mechanisms were a key aspect to allowing EVD to take hold across the region. In the first phase of the response, Ebola surveillance consisted of 2 primary components: case investigation and reporting and contact tracing. Cases were reported either from walk-in patients at the facility level or through calls to the national Ebola telephone hotline. Within the Kono region of Sierra Leone, early passive surveillance was hampered by underreporting of symptomatic individuals from the community. Active case finding was found to be a necessary adjunct to limit disease spread and was augmented by nationally imposed ‘lockdowns’ with door-to-door active case finding. Early engagement with communities and early social mobilisation allows the development of culturally appropriate messaging and the spread of central themes including trust in the Ebola treatment centres (ETCs), which in turn facilitates patients’ attending. Using these methods, 1 locally based community-engagement model halted the epidemic 4 months earlier than the rest of Sierra Leone and showed a significant reduction in newly diagnosed cases compared with the country as a whole. Widespread public misconceptions of EVD were evident in Guinea, highlighting the need for cultural sensitivity and appropriate messaging when a novel disease is introduced into a population that has not encountered it before. Alongside social mobilisation for disease prevention, improving clinical outcomes through effective supportive care and novel therapeutics improves case fatality and acts as an incentive for infected individuals to seek care, reducing the risk of ongoing transmission and increasing public trust in prevention messages. Community event–based surveillance was implemented in Sierra Leone in June 2015, it demonstrated that a community-based surveillance system can be scaled to the national level and can offer an alternative for case detection for the tail of the epidemic or as an adjunct in countries lacking fully resourced surveillance systems. An overview of the challenges the Centers for Disease Control and Prevention (CDC) encountered in helping developing surveillance mechanisms in countries with limited infrastructure and during a humanitarian emergency response has been recently published.
Coordination

Centralised coordination and operational centres were key to bringing effective coordination to the response. The Western Area Ebola Response Centre/National Ebola Response Centre in Freetown was an operational centre which brought together the main pillars of the response: safe burials, contact tracing, live case management, laboratories, and quarantine. This structure proved to be effective and was replicated throughout the districts in Sierra Leone, as well as in Liberia and Guinea. Nigeria capitalised on the preexisting organisational structure of its polio eradication network and experience gained from responding to a major lead poisoning outbreak, adapting it to the needs of Ebola outbreak response. King’s Sierra Leone Partnership developed a standardised operating procedure that detailed construction, staffing, and troubleshooting of Ebola holding units (EHUs), in addition to suggesting mechanisms for real-time monitoring of bottlenecks in outbreak response, such as bed capacity and utilisation, and laboratory testing. There is recognition that international governance mechanisms need to be strengthened to provide better resilience for future large-scale outbreaks. For the first time, military, intergovernmental agencies, public health departments, nongovernmental organisations, and academia have collaborated in various facets of outbreak response; lookback exercises to identify which aspects need strengthened will be key to developing harmonious responses in the future.

Quarantine

Individual household quarantine as well as district quarantine was used across the West African outbreak, including in Nigeria, where individuals were largely allowed to remain at home unless crowded home environments mandated group cohorting. Vertical, imposed quarantine was much less accepted than community-led quarantine, and in several areas, increased public mistrust and negatively influenced health seeking behaviour and engagement with EVD response efforts. Logistical problems including the delivery of water, food, and medications to quarantined household compounded these problems, as well as social stigmatisation. This led to reports of individuals fleeing from quarantined households and delays in notification of symptoms. In the tail end of the outbreak in Sierra Leone and in Nigeria, group quarantine, the isolation of contact cases in a secure facility, was used for those who were deemed unlikely to adhere to household quarantine or lacked the WASH (Water, Sanitation, and Hygiene) and physical facilities to be safely isolated within their household.

Laboratory and Field Diagnosis

Current EVD detection depends on polymerase chain reaction (PCR)-based diagnosis, largely conducted in centralised laboratories and often not available, although there have been advances and field deployment of rapid laboratories. The Cepheid GeneXpert platform, a real-time PCR (RT-PCR) with an automated and integrated configuration that reports faster than conventional RT-PCR methods, has been successfully evaluated in the field. However, the operational requirements are still relatively complex for deployment in truly resource-limited settings: an operator with some laboratory expertise is required for platform and assay validation, quality control, and maintenance.

Whole genome sequencing was used for outbreak investigation as well as phylogenetic analysis to determine genetic drift and mutation with EBOV sequences, including real-time sequencing using portable devices.

There is a significant need for rapid diagnostic test (RDT) development; models have suggested the magnitude of the Sierra Leone outbreak would have been reduced by at least a third if RDTs were available. Several lateral flow assays have shown encouraging results, including those tested in the field with and without the need for cold-chain storage and also within laboratory settings. A sensitive RDT would allow for rapid rule-out of EVD in those who present with non-specific symptoms. This is particularly important in allowing for the sustained functioning of hospital services that are likely to cease during generalised outbreaks. Loop-mediated isothermal amplification tests have also been successfully developed and deployed to rural areas in a mobile field laboratory in Guinea to assist diagnosis in areas without easy access to reference diagnostic services. Deployable field laboratories have also been successfully used in Liberia. Several recent review articles detail the development of EVD-specific diagnostics and the use of biochemical testing to augment care in resource-poor and resource-rich settings.

Staff Deployment

There were large-scale deployments of military, international governmental and public health agency, non-governmental organisation, academic, industry (including pharmaceutical and diagnostics companies), and civilian clinical staff during the outbreak. The response was both international, coordinated by the WHO, and national within each of the 3 main affected countries; assistance was predominately from the United States to Liberia, the United Kingdom to Sierra Leone, and France to Guinea. National re-distribution of local hospital and military staff to work within dedicate EVD settings was also instrumental. At the beginning of the outbreak, the number of health care workers (HCWs) and other staff working in any EVD capacity was extremely limited due to lack of experience with the disease and its associated infection prevention measures and personal protective equipment (PPE) and the paucity of national and international expertise. In Sierra Leone, the Royal Sierra Leone Armed Forces (RSLAF) took initial leadership, whereas the international response was being readied, positioning them as the experts within the country following the death of the countries only infectious disease physician.
Sheikh Khan. Ways to develop regional responses that are harmonised across porous borders are required for future outbreaks. There is increasing recognition that epidemic preparedness should include international and national capacity to rapidly deploy teams of individuals that have clinical, laboratory, surveillance, communication and community engagement, epidemiologic, and organisational capability. To do this, mechanisms for releasing experienced personnel for short notice response are necessary and should include predeployment clearances. The development of the WHO’s Emerging Diseases Clinical Assessment and Response Network (EDCARN) is one instrument to achieve this. A rapid response CDC team assisted 15 high-risk African countries in outbreak preparedness and response, deploying personnel to Nigeria, Mali, and Senegal following EVD introductions during the West African outbreak.

Different Models of Providing Care
Safe isolation of suspected and confirmed patients is essential to prevent ongoing community transmission of EVD. The traditional approach to EVD response, focused solely on building large stand-alone ETCs, often distant from government health facilities and using international staff, was shown to be inadequate in the West African outbreak. New models of integrating EVD isolation and testing within preexisting government facilities were shown to be successful. These EHUs were cost-effective; rapidly constructed; isolated patients early, often when other facilities were not available; were safe for HCWs, both within the EVD facility and on the general wards, allowing the hospitals to remain operational; and were sustainable, using local staff who remain within the government system, with trained HCWs who can respond to future need. Patients without EVD were then able to access care in the general hospital, but patients with EVD required transfer to dedicated ETCs, another vital component of the national and international response. National staff were instrumental in developing response capacity, for example, the RSLAF, who set up and ran several ETCs, published some of the earliest experience of national staff were instrumental in developing response capacity, for example, the RSLAF, who set up and ran several ETCs, published some of the earliest experience of

Health Systems
The 3 most affected countries already suffered from poor health care systems prior to the outbreak, with preexisting inadequate numbers of trained HCWs, bed spaces, hospital consumable supplies, laboratory support, financing, and health information systems. In the existing health care facilities, the introduction of EVD into general wards largely caused widespread closure of hospitals and other health care settings, resulting in significant interruptions in health system functioning. Tuberculosis prevention and control services in all 3 countries were severely disrupted, as were human immunodeficiency (HIV) programmes and malaria services. An estimated excess of more than 6000 excess deaths in Guinea, 2800 deaths in Sierra Leone, and 1500 deaths in Liberia was attributable to these diseases during the EVD outbreak. A mixed-methods analysis concluded that all-cause mortality was more than 3 times higher than normal during the EVD outbreak, disproportionately in the under-5-year-old population. Where advance contingency planning had been implemented, services were able to be maintained at reasonable levels, and countermeasures such as additional mass drug administration for malaria during the outbreak were effective. A recent systematic review highlighted long-lasting indirect health system effects on all aspects of communicable and non-communicable disease prevention and management; it is likely these will become more apparent as further evidence emerges and longitudinal studies are performed. A robust health system is the cornerstone of any response, and it is essential to invest in getting the basics right before any emergency arises.

Infection Prevention and Control
Lack of adequate infection prevention and control (IPC) practices were identified as a key factor that exacerbated the severity of the West Africa outbreak. This is in keeping with historical outbreaks in the Democratic Republic of the Congo.
and Uganda, and they remain a vital element in preventing and reducing the impact of future outbreaks.

There is historical evidence that good IPC practices inside ETCs reduce HCW and nosocomial infections during outbreaks. However, all clinical staff are at risk of contracting EVD, with or without working in a designated EVD unit, if there are not robust screening practices in place to triage patients into general hospital care or an ETC. A 2014 study at Kenema Government Hospital, Sierra Leone, showed that rates of contracting EVD were higher in HCWs that did not work in ETCs, compared with those working inside the hospital’s ETC where patients were known to have EVD or were suspected. This was attributed to several factors, including the obligation for HCWs to care for sick friends and relatives outside of the hospital setting; community transmission during EVD outbreaks is often high and HCWs are of course part of the community.

Interviews in Guinea highlighted the use of approaching community members with medical experience for advice during an EVD outbreak, rather than presenting to health care facilities. There is, therefore, a need for good IPC knowledge and practice in all settings: the ETC, the general ward or clinic, and the community.

Fundamental IPC practices include hand hygiene, waste management, correct use of PPE, decontamination of equipment and the environment, safe use and disposal of sharps, strict screening and triage of patients seeking medical treatment, and the safe management and burial of corpses. These need to be practised strictly in all health care settings during an EVD outbreak. Units caring specifically for suspected and confirmed patients with EVD need even more regimented procedures, for example, in the donning and doffing of PPE.

All these elements need to be supported by a structured IPC system within the health care facility (ideally linked into a national IPC structure) that involves the following: policy implementation, ongoing and regular IPC training and monitoring and assessments of facilities, and adequate maintenance and supply of PPE. The ability to practice good IPC can be greatly hindered by the lack of essential supplies and lack of proper infrastructure, for example, running water with which to wash hands. Lack of appropriate PPE and isolation facilities (particularly at the beginning of the outbreak) has been attributed to further exacerbating transmission.

There is evidence that EBOV RNA has been detected on surfaces in facilities, both before and following routine decontamination, although this was not seen in the single published study examining this prior to the West African outbreak. Robust measures, therefore, need to be implemented to allow for continual evaluation of IPC measures during an outbreak, with reinforced training and updated practice as required.

Poor staffing levels can have a significant impact on transmission rates for HCWs. During the West African outbreak provision of IPC training, consistent availability of PPE and effective triage systems reduced fear among HCWs and led to improved staffing levels in health care facilities during EVD outbreaks.

Isolation of suspected and confirmed patients with EVD is essential to control outbreaks and has been shown to significantly reduce transmission in the community. Once patients are admitted to ETCs, patient placement inside the unit (which may involve cohorting of patients depending on their symptoms into ‘wet’ and ‘dry’ areas for those with and without gastrointestinal symptoms) can help reduce the levels of nosocomial infections.

As this and previous outbreaks have highlighted, many patients can be nosocomially infected with a novel pathogen before an index patient is identified and the disease confirmed. This reinforces the need to have resilient IPC structures in place before a novel pathogen is discovered. A checklist for infection control readiness has been prepared based on an international survey of IPC specialists. A detailed open-access book chapter review of IPC measures implemented within one central referral hospital is available.

Funerals as a High-Risk Activity for EVD Transmission

Transmission of Ebola is related to close contact with a person during the most severe stages of acute illness, including after death. Ebola virus disease is a disease of social intimacy as the main infection pathways are through nursing of the sick and preparation of corpses for burial.

Funeral-related events are a well-recognised source of infection transmission, although not all studies have found an association between attending funerals and disease risk. For those attending funerals in which transmission was known to have occurred, only certain activities were found to be associated with transmission risk, washing and dressing the cadaver, and being in direct contact with the corpse, its body fluids or soiled items. Viable virus has been isolated from animal tissues or fluids in the laboratory as late as 7 days post-mortem.

Activities with no evidence of risk include viewing of the body, and therefore, traditional rituals pre- and post-funeral that do not involve direct contact with the deceased body could be considered low risk. However, one report from Guinea describes a specific traditional funeral where 21% of 85 cases infected during a burial had direct physical contact with the cadaver, but the remaining 79% described only having contact with individuals who had touched the body and not the body itself. Sharing a communal meal during the funeral was also found to be a high risk, perhaps due to crowded conditions. The intimate tasks (washing and dressing) associated with preparing a body for funeral and burial tend to confer a very high risk of disease transmission, although again data are inconsistent.

In certain largely rural areas of Sierra Leone, traditional funeral practices include cleaning a corpse, with men washing men’s bodies and women washing women’s bodies. The women include the deceased women’s sisters, with risks of spreading the EBOV to other villages. Other traditional practices which could lead to EVD transmission include shaving the
counselling programmes have been initiated in Liberia, and in cases where a deceased wife came from a different area or village, transporting the body back to that village, a task which lies with the men, often using a hammock.

Guidance is now available from the WHO to facilitate safe and respectful burial in village conditions and covers both religious practices and community involvement in developing safe burial techniques. Corpse washing is discouraged, but if it cannot be avoided, then it should be conducted only with biohazard protection. It is possible for dignified funerals to be held without high risk to those attending. Unfortunately, efforts to persuade local populations to change funeral traditions during outbreaks, and in particular to allow cremation, often meet cultural resistance and highlights the need for early community involvement in messaging during EVD outbreaks.

Newly Recognised Sources of Transmission

Given the large number of EVD survivors in the region, there is increasing recognition of the significant post-EVD sequelae that include musculoskeletal complications, ocular problems, neurological symptoms, and skin disorders. Survivors are known to excrete EBOV RNA in many body fluids including urine, stool, sweat, vaginal fluid, cerebrospinal fluid, tears, saliva, and amniotic fluid. Disease recrudescence has been observed within the cerebrospinal fluid in meningoccephalitis and within the ocular cavity as anterior uveitis – immune privileged sites, which have been called a ‘paradigm shift’ when considering long-term disease control, and survivor care must be able to appropriately manage potentially infected bodily fluids.

Although seminal excretion was recognised in prior outbreaks, the West African outbreak was the first to document sexual transmission of EVD. A landmark paper in 2014 demonstrated persistence of EVD RNA in the semen of Sierra Leonean survivors for up to 9 months; however, this was surpassed by evidence of culture-positive virus at day 70 in a US cohort, followed by evidence of sexual transmission at day 450 with detectable RNA at day 500 following contraction of EVD. This episode caused a new cluster of infections in Guinea and Liberia, and there are several transmission events with molecular or strong epidemiologic links to survivor sexual transmission. To counter the concerns of onward spread following the outbreak close, national semen testing and counselling programmes have been initiated in Liberia, although operational challenges have been encountered. Recent data from a Guinea cohort demonstrate the fluctuating presence of EVD, complicating such programmes.

The large numbers of EVD cases in West African saw many pregnant women become infected. The case-fatality ratio for foetuses delivered from pregnant women with acute EVD approached 100%, although the mothers survived. There are reports of pregnant women who survived EVD, were discharged to the community, but subsequently underwent spontaneous abortion and either the stillbirth or products of conception were found to be PCR positive for Ebola. Delivery from EVD-positive mothers, even in recovery, therefore remains a very high-risk transmission event and requires careful management.

Modelling

This outbreak saw the greatest use of modelling during an EVD response. This was initially used in determining case numbers, with very high projections from the CDC that suggested by January 2015, 1.4 million people may have been infected. It is, however, very difficult to model how societal structure changes at such high numbers of case projections, with tens of thousands being infected every day in worst case projections. Other models were more cautious in projected size of the outbreak. However, these figures coincided with a galvanising of the international response, coming shortly after the WHO declaration on August 6, 2014 that the outbreak was a Public Health Emergency of International Concern. Modelling was also used to assess the utility of different models of care, such as deciding whether CCCs, a proposed novel isolation method which used existing structures, such as school buildings and family members, survivors, and HCWs for staff, would help abate or further reduce transmission. Initial estimates of bed numbers needed to curtail spread were thought to be higher than what was promised by international agencies; however, subsequent models have demonstrated the increases in bed capacity in Sierra Leone helped aver nearly 60,000 cases. Travel restrictions and airport entry screening were proposed as a method of limiting international spread, with contemporaneous and retrospective models suggesting that curtailing the outbreak at source was the most efficient method of disease control, including screening on exit from affected countries. Early models suggested the likelihood of airborne spread to be much higher than what was observed. Models have been used to estimate the added impact of sexual transmission or reintroduction into communities thought to be disease free. Finally, modellers have estimated the likelihood of disease recurrence in the region, thought to be within 20 years in the absence of vaccination campaigns.

Medical Countermeasures

Despite the very large numbers of EVD cases during the West African outbreak, relatively little is known about the best interventions to manage patients with EVD, including appropriate fluid management; strategies to control and replace electrolyte losses, for example, through appropriate management of diarrhoea; methods to limit the consequences of haemorrhage; and the adjunct use of broad-spectrum antimicrobials. The vastly different case fatality rates seen during the outbreak in Western settings, with under 20% mortality compared with 70% in early case series in West Africa, very likely reflects the crucial role of critical care involvement, laboratory monitoring, and blood
arguably, the greatest medical advance in EVD disease management in recent years has been the development of effective vaccines. although several have shown promise in phase 1 studies, vesicular stomatitis virus (rVSV) expressed glycoprotein (GP) vaccines, which are under development by PH, are reportedly rapidly scalable.158 a nano-particle VLP has been developed by PH in the United States and in Uganda.154,155 the 4-week delay before cellular and humoral responses peak, and a 3-dose regimen indicates that this vaccine may not be feasible alone for outbreak control and may be less desirable than single-dose or prime-boost vaccine schedules.159

**Vaccination**

Arguably, the greatest medical advance in EVD disease management in recent years has been the development of effective vaccines. although several have shown promise in phase 1 studies, vesicular stomatitis virus (rVSV) expressed glycoprotein (GP) vaccines, which are under development by PH, are reportedly rapidly scalable.158 a nano-particle VLP has been developed by PH in the United States and in Uganda.154,155 the 4-week delay before cellular and humoral responses peak, and a 3-dose regimen indicates that this vaccine may not be feasible alone for outbreak control and may be less desirable than single-dose or prime-boost vaccine schedules.159

**Table 1. Summary of published evidence available for the use of novel therapeutic agents with potential anti-EVD activity.**

<table>
<thead>
<tr>
<th>TRIAL (REFERENCE)</th>
<th>DESIGN</th>
<th>SITES</th>
<th>PATIENTS</th>
<th>ENROLMENT DATES</th>
<th>END POINT REACHED</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir144</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>4</td>
<td>January 1, 2015 to January 31, 2015</td>
<td>No – trial terminated</td>
<td>All 4 enrolled patients died</td>
</tr>
<tr>
<td>Favipiravir – JI145</td>
<td>Single-arm phase 1 trial</td>
<td>4</td>
<td>126 (540 historic controls)</td>
<td>December 17, 2014 to April 8, 2015</td>
<td>No – reported differently</td>
<td>Nuanced conclusions – limited tolerability</td>
</tr>
<tr>
<td>Favipiravir – Juy146</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>39 (85 historic controls)</td>
<td>November 1, 2014 to November 10, 2014</td>
<td>NA</td>
<td>Survival rate (56% [22/39] vs 35% [30/85]; P = .027)</td>
</tr>
<tr>
<td>TKM-Ebola147</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>14 (3 cohorts, observational)</td>
<td>March 11, 2015 to June 15, 2015</td>
<td>Yes – stopped due to futility</td>
<td>No survival benefit</td>
</tr>
<tr>
<td>ZMapp148</td>
<td>RCT (non-blinded)</td>
<td>11</td>
<td>36 (35 controls), Guineans had Favipiravir (FVP), unclear if matched</td>
<td>March 1, 2015 to November 1, 2015</td>
<td>No – stopped early due to low EVD numbers</td>
<td>Mortality rate (37% [13/35] vs 22% [8/36]; 91.2% posterior probability)</td>
</tr>
<tr>
<td>Convalescent plasma149</td>
<td>Non-random comparative study</td>
<td>1</td>
<td>99 (507 controls)</td>
<td>February 17, 2015 to August 3, 2015</td>
<td>No – also uncertain if any neutralising antibody present</td>
<td>Mortality rate (38% [158/418] vs 31% [26/84]; P = .92 after age/Cycle Threshold value (CT) adjustment)</td>
</tr>
</tbody>
</table>

Abbreviations: EVD, Ebola virus disease; RCT, randomised controlled trial.

product support142 and wildly differing staff to patient ratios compared with routine practice in West Africa.143 there have been 6 reported trials of 5 novel therapeutic agents: Table 1 displays the results of the trial interventions. Convalescent plasma was recommended by the WHO for compassionate use,150 given its role in treating other viral haemorrhagic fevers, such as Crimean-Congo haemorrhagic fever.151 levels of neutralising antibodies were not assessed prior to administration, and there was no treatment effect.148 The cidofovir trial, an oral nucleotide analogue, was halted early by the manufacturer after recruiting 4 patients.144 there were 2 trials of favipiravir, a broad-spectrum antiviral effective against influenza: one was a proof-of-concept trial145 and the other showed evidence of prolonged survival and a reduction in viral load in the historically controlled treatment arm.146 Tkm-Ebola, a short interfering RNA experimental agent, did not show any clinical effect.147 ZMapp, a combination of humanised monoclonal antibodies, was the only agent that was tested in a randomised controlled trial and showed some evidence of treatment effect in both Bayesians and frequentist analyses.148 only 1 trial reached their pre-defined enrolment endpoints (TKM-Ebola, of futility), and none provided conclusive proof for any single agent that would be recommended for future clinical use. Favipiravir and MIL77, another recombinant humanised monoclonal antibody combination, were used for post-exposure prophylaxis in 1 case series, with no EVD development in 4 HCWs with moderate-risk or high-risk exposures including deep penetrating needlestick injuries.152
primary candidates for further development during an interna-
tional consultation in September 2014. The non-replicating
bivalent (expressing ZEBOV and SUDV GP) cAd3 completed
phase 1 trials in the United States and monovalent
(ZEBOV-GP) in the United Kingdom, United States, and
Mali, and Switzerland with results from Uganda
expected. High levels of specific antibody and T-cell response,
considered essential for protective immunity, were
generated. Fever and malaise occurred in 3% to 60%.
In the study in the US/UK/Mali populations, a modified vaccinia
virus expressing nucleoprotein for several filoviruses (ZEBOV,
SUDV, Thai Forest, and Marburg) (MVA-BN-Filo) was given
vaccine has been used in HIV-negative adults in Sierra
Leone as a single dose, with no vaccine-related serious adverse events
(SAEs) and good immunogenicity data in the initial 28 days,
which fell quickly in longer follow-up. Finally, replication-
incompetent hAd26 expressing ZEBOV-GP, boosted with
MVA-BN-Filo was used in a blinded placebo controlled study in the
United Kingdom, demonstrating high proportion with immune
responses, persisting to 8 months.

The second viral vector vaccine rVSV-ZEBOV employs a
replication-competent VSV expressing GP from ZEBOV
Kikwit 1995 strain. Due to high-level protection of non-
human primates from infection in both pre- and post-exposure
studies, this vaccine had been used in accidentally Ebola-
exposed adults prior to phase 1 studies (ref 169). In phase
1 studies, coordinated by the VSV-Ebola Consortium
(VEBCON) of African and European scientists, the vaccine
demonstrated GP-specific antibody responses and neutralising
antibodies at higher doses in participants in Germany, Kenya,
Switzerland, and Gabon. Transient vaccine viraemia after
1 day and mild-moderate adverse events were detected in most
of the vaccines across countries, but an oligo-arthritis developed
in 22% of 51 Swiss vaccinees with rVSV-ZEBOV in
synovial fluid, as well as in rash samples. No severe adverse
events were reported, and the vaccine went on to a phase 3
study in Guinea: Ebola ca Suffit (‘Ebola, that’s enough’).
This was an open-label cluster-randomised ring vaccination
trial where clusters were contacts around a confirmed case
(rings) and were allocated 1:1 to immediate or 21 days delayed
vaccination. Final results from 19 non-randomised and 98 ran-
domised rings comprising 5837 individuals (5643 adults and
194 children) were published in early 2017 showing a vaccine
efficacy of 100%. Debates around the trial design and criti-
cisms of analysis abounded but only 3 vaccine-attributable
SAEs were noted (anaphylaxis, fever, and influenza-like
illness), none of which were fatal. A second phase 2/3 study of
the same vaccine was initiated in early 2015: Sierra Leone Trial
to Introduce a Vaccine against Ebola (STRIVE). A collabora-
tion between Sierra Leone and United States, this was a ran-
domised individually controlled (immediate versus delayed)
trial, with substudies reporting short-term reactogenicity and
longer term immunogenicity. No vaccine efficacy estimate will
be possible as no cases were reported in the study population,
but no SAEs were reported, and safety, immunogenicity, and
reactogenicity data are expected.

Long-term follow-up of several studies described is awaited,
but many other important vaccine studies remain in phases 1
and 2 including, importantly, in West Africa, and in HIV-
positive adults and in children. Partnership for Research on
Ebola Virus in Liberia (PREVAIL), EBOVAC-Salone, and
the VEBCON collaboration are examining AdV26 and MVA-
BN-Filo boost and rVSV-ZEBOV-GP. Studies of human
parainfluenza 3 with EBOV-GP are underway in the United
States. Finally, a study examining DNA vaccine study with and
without interleukin and electroporation is recruiting partici-
ants in the United States.

The isolated success, despite criticisms, of rVSV-
ZEBOV-GP in Guinea not only offers potential for immediate
response in further outbreaks and hope for prevention outside
epidermics, but an immunological standard in humans to
which other candidate vaccines can also be compared.

**Similarities With the HIV Epidemic**

Many have highlighted the similarities between the West
African EVD outbreak and the early stages of the HIV epi-
dermic, of which there are numerous corollaries. Both are
viruses spread through blood and body fluids to close con-
tacts, and ‘sick relatives are nursed at home by family mem-
ters’. There were ‘strikingly similar’ stigmatising attitudes
wards those with EVD and both survivors and orphans of
parents who died from EVD, with misinformation in the
affected communities that required social mobilisation and
voices from within to counter. Such community awareness
can only be achieved with appropriate financing of messages
and social support, as was achieved with HIV. Access to
novel therapeutic agents and significant debate about the
need for randomised controlled evidence in a rapidly fatal
epidemic were as core to considerations about trial design in
epidemic, of which there are numerous corollaries. Both are
and tuberculosis disease control. Similarly, effective
knowledge of disease transmission and access to appropriate
PPE were as vital to EVD control as they were for HIV
and tuberculosis disease control.

**Summary**

The response to any future EVD will be dependent on local
context as well as the scale of the outbreak. There are several
outstanding questions, such as how best to engage effectively
with local populations on messaging and disease control, how
to best manage the basic aspects of EVD care including fluid
management, and how novel technologies can be used to assist
with diagnostic and surveillance efforts. Regarding vaccination, many important issues remain unanswered including the duration of protection; cross-protection for other strains of EBOV; likelihood of viral escape with possible mutations; who should pay for stockpiling, procurement, and delivery of mass vaccination; and whether at-risk countries should implement preemptive or reactive vaccination strategies. 

Although specific EVD outbreak response strategies are documented in this publication, what is clear is that the magnitude of the West African EVD outbreak can be attributed, at least in part, to the weakness of national health systems. Therefore, any sustainable approach to outbreak control in the region must take a system wide perspective and is reliant on investment in the health systems, human resourcing for health, and surveillance mechanisms, underpinned by appropriate laboratory diagnostics. One recent review of all public health responses highlighted that ‘the weight of evidence suggests that a rapid response to the discovery of new Ebola cases can stop transmission, preventing minor outbreaks from becoming major epidemics in large, mobile populations’.187 What is needed to enact this are clear and immediate systems to assist those countries most in need to have early access to appropriate resources, EVD expertise, augmented public health responses, academic input into novel therapeutic treatment and prevention, rapidly deployable research protocols to test therapeutics, and international support on recognition of any new outbreaks. We have the tools and knowledge to control future outbreaks, all that is required is the provision of timely and proportionate intervention.

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Disclosures and Ethics

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