What Do We Know About Controlling Ebola Virus Disease Outbreaks?

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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

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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 (EBOV) 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 deliveries[8,9] and acute abdominal surgical emergencies,[10] 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 centres[12]: 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

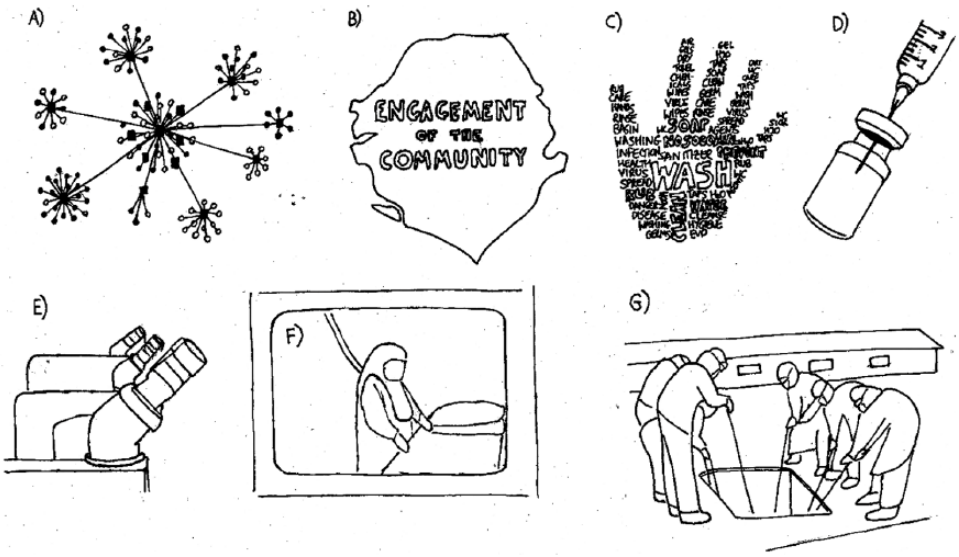

Figure 1. Summary of Ebola virus disease outbreak control measures: (A) surveillance and contact tracing, (B) community engagement, (C) infection prevention and control, (D) vaccines and therapeutics, (E) diagnostics, (F) isolation facilities for suspected cases and quarantine for close contacts, and (G) safe burial.

population, inhibiting adequate contact tracing; and reduced social networks, rendering social mobilisation less effective.[14] 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.[15] 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[16] or smartphone applications that use Global Positioning Systems.[17]

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.[15]

Surveillance and Community Engagement

Initial lack of surveillance mechanisms were a key aspect to allowing EVD to take hold across the region.[18] In the first phase of the response, Ebola surveillance consisted of 2 primary components: case investigation and reporting and contact tracing.[19] 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 [20] 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.[21] 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.[22] 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.[23] 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.[24] 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.[19]

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.[25] 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.[26] King's Sierra Leone Partnership developed a standardised operating procedure that detailed construction, staffing, and troubleshooting of Ebola holding units (EHUs),[27] in addition to suggesting mechanisms for real-time monitoring of bottlenecks in outbreak response, such as bed capacity and utilisation, and laboratory testing.[28] There is recognition that international governance mechanisms need to be strengthened to provide better resilience for future large-scale outbreaks.[29] 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.[30,31]

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.[32,33] Vertical, imposed quarantine was much less accepted than community-led quarantine,[32] and in several areas, increased public mistrust and negatively influenced health seeking behaviour and engagement with EVD response efforts.[34] Logistical problems including the delivery of water, food, and medications to quarantined household compounded these problems, as well as social stigmatisation.[35] This led to reports of individuals fleeing from quarantined households and delays in notification of symptoms.[34] 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.[33]

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.[36] 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.[37]

Whole genome sequencing was used for outbreak investigation[38] as well as phylogenetic analysis to determine genetic drift and mutation with EBOV sequences,[39] including real-time sequencing using portable devices.[40]

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.[41] Several lateral flow assays have shown encouraging results, including those tested in the field with[42] and without[43] the need for cold-chain storage and also within laboratory settings.[44] 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[45] and deployed to rural areas in a mobile field laboratory in Guinea to assist diagnosis in areas without easy access to reference diagnostic services.[46] Deployable field laboratories have also been successfully used in Liberia.[47] Several recent review articles detail the development of EVD-specific diagnostics[48] and the use of biochemical testing to augment care in resource-poor and resource-rich settings.[49]

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.[50] 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.[51] Ways to develop regional responses that are harmonised across porous borders are required for future outbreaks.[52] 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.[53] The development of the WHO's Emerging Diseases Clinical Assessment and Response Network (EDCARN) is one instrument to achieve this.[54] 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.[55]

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.[56] 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.[25] 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 EVD outcomes in the West African outbreak.[51] Royal Sierra Leone Armed Forces worked alongside more traditional haemorrhagic fever response organisations such as Médecins Sans Frontières (who first raised concerns about the epidemic size and slow international response in March 2014[57]) but were able to provide more monitoring and therapeutic interventions.[58] During the height of the West African outbreak, the capacity for care in ETCs could not keep pace with the demand of new cases in the community. Community care centres (CCCs) were community-based structures which were converted into isolation units and staffed by community HCWs, uninfected family members, and survivors. These CCCs were promoted as a strategy for interrupting transmission as an interim measure and were tested in Sierra Leone[59,60] and Liberia.[61] In Sierra Leone, CCCs operated at a standard of many EHUs and what impact they had in interrupting disease transmission is not yet clear.[62] Further reviews of their effectiveness are awaited.

What is clear is that adequate provision of inpatient EVD beds, adequate staffing levels for all aspects of disease control, and integrated detection and messaging in communities are key to reduce transmission. It is estimated that if the isolation bed capacity was available 1 month earlier in Sierra Leone, an extra 12 500 cases would have been averted.[63] Difficult to entangle from this is the contradictory finding that bed capacity rose once the epidemic was already waning in Liberia, with one review concluding that 'much of the decline in the epidemic curve was driven by critical behaviour changes within local communities, rather than by international efforts that came after the epidemic had turned'.[64] Further studies on community behaviours in Liberia suggest that they learnt to adapt behaviour and manage disease response in the absence of national and international intervention.[65]

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.[66] 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.[67] Tuberculosis prevention and control services in all 3 countries were severely disrupted,[68] as were human immunodeficiency (HIV) programmes[69] and malaria services.[70] 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.[70] 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.[71] Where advance contingency planning had been implemented, services were able to be maintained at reasonable levels,[72] and countermeasures such as additional mass drug administration for malaria during the outbreak were effective.[73] 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.[9] 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.[74] This is in keeping with historical outbreaks in the Democratic Republic of the Congo

and Uganda,[75,76] and they remain a vital element in preventing and reducing the impact of future outbreaks.[77]

There is historical evidence that good IPC practices inside ETCs reduce HCW and nosocomial infections during outbreaks.[78,79] 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.[79] 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.[79,80] 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.[81] 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.[82–84]

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.[78,79] 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.[78,79] There is evidence that EBOV RNA has been detected on surfaces in facilities, both before[85] and following routine decontamination,[86] although this was not seen in the single published study examining this prior to the West African outbreak.[87] 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.[78,82]

Isolation of suspected and confirmed patients with EVD is essential to control outbreaks and has been shown to significantly reduce transmission in the community.[88] 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.[89]

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.[90] 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.[91] A detailed open-access book chapter review of IPC measures implemented within one central referral hospital is available.[25]

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.[32,92–97] Viable virus has been isolated from animal tissues or fluids in the laboratory as late as 7 days post-mortem.[98]

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[92] 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,[99] 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.[100–107]

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.[108] Other traditional practices which could lead to EVD transmission include shaving the

head of a wife whose husband has died and covering her head with mud formed from the washings of her husband's corpse,[109] 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.[110] It is possible for dignified funerals to be held without high risk to those attending.[19] 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.[32,107,111,112]

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.[113] Survivors are known to excrete EBOV RNA in many body fluids including urine, stool, sweat, vaginal fluid, cerebrospinal fluid, tears, saliva, and amniotic fluid.[114] Disease recrudescence has been observed within the cerebrospinal fluid in meningoencephalitis[115] and within the ocular cavity as anterior uveitis[116] – immune privileged sites, which have been called a 'paradigm shift' when considering long-term disease control,[117] 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 EBOV RNA in the semen of Sierra Leonean survivors for up to 9 months[118]; however, this was surpassed by evidence of culture-positive virus at day 70 in a US survivor cohort,[119] followed by evidence of sexual transmission at day 450 with detectable RNA at day 500 following contraction of EVD.[120] 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.[121,122] To counter the concerns of onward spread following the outbreak close, national semen testing and counselling programmes have been initiated in Liberia,[123] although operational challenges have been encountered.[124] Recent data from a Guinea cohort demonstrate the fluctuating presence of EVD, complicating such programmes.[38]

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%,[125] although the mothers survived.[126] 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.[127] 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.[128] 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.[129] 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.[130] 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.[131] Initial estimates of bed numbers needed to curtail spread were thought to be higher than what was promised by international agencies[132]; however, subsequent models have demonstrated the increases in bed capacity in Sierra Leone helped avert nearly 60 000 cases.[63] Travel restrictions and airport entry screening were proposed as a method of limiting international spread, with contemporaneous[133] and retrospective[134] models suggesting that curtailing the outbreak at source was the most efficient method of disease control, including screening on exit from affected countries.[135] Early models suggested the likelihood of airborne spread to be much higher than what was observed.[136,137] Models have been used to estimate the added impact of sexual transmission or reintroduction into communities thought to be disease free.[138,139] Finally, modellers have estimated the likelihood of disease recurrence in the region, thought to be within 20 years in the absence of vaccination campaigns.[140]

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.[141] 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

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

TRIAL (REFERENCE)	DESIGN	SITES	PATIENTS	ENROLMENT DATES	END POINT REACHED	OUTCOME
Brincindofovir[144]	Single-arm phase 2 trial	1	4	January 1, 2015 to January 31, 2015	No – trial terminated	All 4 enrolled patients died
Favipiravir – JIKI[145]	Single-arm phase 1 trial	4	126 (540 historic controls)	December 17, 2014 to April 8, 2015	No – reported differently	Nuanced conclusions – limited tolerability
Favipiravir – Jui[146]	Single-arm phase 2 trial	1	39 (85 historic controls)	November 1, 2014 to November 10, 2014	NA	Survival rate (56% [22/39] vs 35% [30/85]; $P = .027$)
TKM-Ebola[147]	Single-arm phase 2 trial	1	14 (3 cohorts, observational)	March 11, 2015 to June 15, 2015	Yes – stopped due to futility	No survival benefit
ZMapp[148]	RCT (non-blinded)	11	36 (35 controls), Guineans had Favipiravir (FVP), unclear if matched	March 1, 2015 to November 1, 2015	No – stopped early due to low EVD numbers	Mortality rate (37% [13/35] vs 22% [8/36]; 91.2% posterior probability).
Convalescent plasma[149]	Non-random comparative study	1	99 (507 controls)	February 17, 2015 to August 3, 2015	No – also uncertain if any neutralising antibody present	Mortality rate (38% [158/418] vs 31% [26/84]); $P = .92$ after age/Cycle Threshold value (CT) adjustment

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

product support[142] 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.[149] The brincidofovir 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 trial[145] 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 Bayesian 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]

Vaccination

Arguably, the greatest medical advance in EVD disease control has been in vaccine development. Safe, effective, and long-lasting vaccination against EVD has long been argued as one of the main methods of controlling or preventing an EVD outbreak. It has been estimated that herd immunity could be established if 42% to 63% of a population were vaccinated with an 80% effective vaccine.[153] Ebola vaccine development has progressed from unsafe and unsuccessful inactivated virus candidates in the early 1980s to multiple current options include DNA, recombinant vector, and virus-like particle (VLP) vaccines, which are addressed in turn below. There are now 50 human vaccine trials in progress or completed (clinicaltrials.gov accessed August 31, 2016), including 2 phase 3 trials in West Africa.

A DNA vaccine encoding wild-type glycoprotein (GP) from Zaire EBOV (ZEBOV) and Sudan EBOV (SUDV) was safe, well tolerated, and immunogenic in healthy adults 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 Kibuuka et al.[155] Virus-like particle vaccines lack the risks of viral replication, elicit both humoral and cell-mediated responses thought desirable for effective protection against Ebola[156,157] and are reportedly rapidly scalable.[158] A nano-particle VLP has been coupled with Matrix-M adjuvant and has shown protective immunity in mice.[159] The manufacturer has released preliminary results which indicated tolerability and immunogenicity in Australian adults of a single dose Novavax Inc.[160] Full publication of results from single and second doses is required to determine its use in an epidemic or as prevention.

Viral vector vaccines have made the biggest advances in EVD vaccine development. Although several have shown promise in phase 1 studies, vesicular stomatitis virus (rVSV) and adenovirus platform vaccines were identified by WHO as

primary candidates for further development during an international consultation in September 2014.[161] The non-replicating bivalent (expressing ZEBOV and SUDV GP) cAd3 completed phase 1 trials in the United States[162] and monovalent (ZEBOV-GP) in the United Kingdom,[163] United States, and Mali,[164] and Switzerland,[165] with results from Uganda expected. High levels of specific antibody and T-cell response, considered essential for protective immunity, were generated.[156,157] Fever and malaise occurred in 3% to 60%.[163–165] 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 and led to an increase in immunogenicity and longer persistence.[164,166] hAd5 has completed phase 1 evaluation in 120 Chinese participants and demonstrated a high rate of adverse events (78 of 110 participants reported at least 1 adverse event) but was highly immunogenic, up to 28 days.[167] The same hAd5 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.[168] 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.[169]

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).[170,171] 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.[172,173] 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.[174] 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').[175] 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 randomised 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 criticisms of analysis abounded[176,177] 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 collaboration between Sierra Leone and United States, this was a randomised 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.[178]

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 participants 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 of epidemics, 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 epidemic, of which there are numerous corollaries. Both are viruses spread through blood and body fluids to close contacts, and 'sick relatives are nursed at home by family members'.[179] There were 'strikingly similar' stigmatising attitudes towards 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.[180] Such community awareness can only be achieved with appropriate financing of messages and social support, as was achieved with HIV.[181] 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 EVD[182–184] as they were with HIV.[185] 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.[186]

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 pre-emptive 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 outbreak. 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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REFERENCES

1. World Health Organization (WHO). *Ebola Situation Report – 30 March 2016*. Geneva, Switzerland: WHO; 2016. http://apps.who.int/ebola/current-situation/ebola-situation-report-30-march-2016. Accessed February 20, 2017.
2. Apostolou A, Bartholomew ML, Greeley R, et al. Transmission of hepatitis C virus associated with surgical procedures – New Jersey 2010 and Wisconsin 2011. *Morb Mortal Wkly Rep*. 2015;64:165–170.
3. Ohuabunwo C, Ameh C, Oduyebo O, et al. Clinical profile and containment of the Ebola virus disease outbreak in two large West African cities, Nigeria, July-September 2014. *Int J Infect Dis*. 2016;53:23–29.
4. Petti S, Messano GA, Vingolo EM, et al. The face of Ebola: changing frequency of haemorrhage in the West African compared with Eastern-Central African outbreaks. *BMC Infect Dis*. 2015;15:564.
5. Lado M, Walker NF, Baker P, et al. Clinical features of patients isolated for suspected Ebola virus disease at Connaught Hospital, Freetown, Sierra Leone: a retrospective cohort study. *Lancet Infect Dis*. 2015;15:1024–1033.
6. Levine AC, Shetty PP, Burbach R, et al. Derivation and internal validation of the Ebola prediction score for risk stratification of patients with suspected Ebola virus disease. *Ann Emerg Med*. 2015;66:285.e1-293.e1.
7. Arranz J, Lundeby KM, Hassan S, et al. Clinical features of suspected Ebola cases referred to the Moyamba ETC, Sierra Leone: challenges in the later stages of the 2014 outbreak. *BMC Infect Dis*. 2016;16:308.
8. Deaver JE, Cohen WR. Ebola virus screening during pregnancy in West Africa: unintended consequences. *J Perinat Med*. 2015;43:649–655.
9. Brolin Ribacke KJ, Saulnier DD, Eriksson A, von Schreeb J. Effects of the West Africa Ebola virus disease on health-care utilization – a systematic review. *Front Public Heal*. 2016;4:222.
10. Bundu I, Patel A, Mansaray A, Kamara TB, Hunt LM. Surgery in the time of Ebola: how events impacted on a single surgical institution in Sierra Leone. *J R Army Med Corps*. 2016;162:212–216.
11. Zachariah R, Harries AD, Lado M, et al. The WHO clinical case definition for suspected cases of Ebola virus disease arriving at Ebola holding units: reason to worry? *Lancet Infect Dis*. 2015;15:989–990.
12. Snyder R, Marlow M, Riley L. Ebola in urban slums: the elephant in the room. *Lancet*. 2014;2:e685.
13. Okware SI, Omaswa F, Talisuna A, et al. Managing Ebola from rural to urban slum settings: experiences from Uganda. *Afr Health Sci*. 2015;15:312–321.
14. Maduka O, Maleghemi S, Komakech W, et al. Effective risk communication and contact tracing for Ebola virus disease prevention and control – experiences from Port Harcourt, Nigeria. *Public Health*. 2016;135:140–143.
15. Olu OO, Lamunu M, Nanyunja M, et al. Contact tracing during an outbreak of Ebola virus disease in the Western Area districts of Sierra Leone: lessons for future Ebola outbreak response. *Front Public Heal*. 2016;4:130.
16. Schafer IJ, Knudsen E, McNamara LA, Agnihotri S, Rollin PE, Islam A. The Epi Info Viral Hemorrhagic Fever (VHF) Application: a resource for outbreak data management and contact tracing in the 2014-2016 West Africa Ebola epidemic. *J Infect Dis*. 2016;214:S122–S136.
17. Sacks JA, Zehe E, Redick C, et al. Introduction of mobile health tools to support Ebola surveillance and contact tracing in Guinea. *Glob Heal Sci Pract*. 2015;3646–659.
18. Wojda TR, Valenza PL, Cornejo K, et al. The Ebola outbreak of 2014-2015: from coordinated multilateral action to effective disease containment, vaccine development, and beyond. *J Glob Infect Dis*. 2016;7:127–138.
19. McNamara LA, Schafer IJ, Nolen LD, et al. Ebola surveillance – Guinea, Liberia, and Sierra Leone. *Morb Mortal Wkly Rep Suppl*. 2016;65:35–43.
20. Stehling-Ariza T, Rosewell A, Moiba SA, et al. The impact of active surveillance and health education on an Ebola virus disease cluster – Kono District, Sierra Leone, 2014-2015. *BMC Infect Dis*. 2016;16:611.
21. Li Z-J, Tu W-X, Wang X-C, et al. A practical community-based response strategy to interrupt Ebola transmission in sierra Leone, 2014-2015. *Infect Dis Poverty*. 2016;5:74.
22. Kpanake L, Gossou K, Sorum PC, Mullet E. Misconceptions about Ebola virus disease among lay people in Guinea: lessons for community education. *J Public Health Policy*. 2016;37:160–172.
23. Lindblade KA, Kateh F, Nagbe TK, et al. Decreased Ebola transmission after rapid response to outbreaks in remote areas, Liberia, 2014. *Emerg Infect Dis*. 2015;21:1800–1807.
24. Ratnayake R, Crowe SJ, Jasperse J, et al. Assessment of community event-based surveillance for Ebola virus disease, Sierra Leone, 2015. *Emerg Infect Dis*. 2016;22:1431–1437.
25. Brown CS, Elsherbiny M, Johnson O, et al. *Ebola and Health Partnerships, Action in a Time of Crisis* (Ebola). Rijeka, Croatia: InTechOPen; 2016. http://www.intechopen.com/books/ebola/ebola-and-health-partnerships-action-in-a-time-of-crisis. Accessed February 20, 2017.
26. Onyeonoro UU, Ekpemiro UC, Abali C, Nwokeukwu HI. Ebola epidemic – the Nigerian experience. *Pan Afr Med J*. 2015;22:17.
27. Youkee D, Johnson O, Amardeep K, Hall A, Lado M. *King's Sierra Leone Partnership Ebola Holding Units Standard Operating Procedure*. Freetown, Sierra Leone: KSLP; 2014. http://kslp.org.uk/wp-content/uploads/2015/05/KSLP-Ebola-Holding-Unit-Guide-FINAL.pdf. Accessed February 20, 2017.

28. Brown C, Kessete Q , Baker P, et al. Bottlenecks in health systems functioning for control of Ebola virus disease in Connaught Hospital, Freetown, Sierra Leone. Presented at: 26th European Congress of Clinical Microbiology and Infectious Diseases; Apr 9-12, 2016; Amsterdam, The Netherlands. Poster P0092.
29. Mackey TK. The Ebola outbreak: catalyzing a 'Shift' in global health governance? *BMC Infect Dis*. 2016;16:699.
30. Forestier C, Cox AT, Horne S. Coordination and relationships between organisations during the civil-military international response against Ebola in Sierra Leone: an observational discussion. *J R Army Med Corps*. 2016;162:156–162.
31. Moll R, Reece S, Cosford P, Kessel A. The Ebola epidemic and public health response. *Br Med Bull*. 2016;117:15–23.
32. Nyenswah TG, Fallah M, Calvert GM, et al. Cluster of Ebola virus disease, Bong and Montserrado counties, Liberia. *Emerg Infect Dis*. 2015;21: 1253–1256.
33. Grigg C, Waziri NE, Olayinka AT, Vertefeuille JF, Centers for Disease Control and Prevention (CDC). Use of group quarantine in Ebola control – Nigeria, 2014. *Morb Mortal Wkly Rep*. 2015;64:124.
34. Pellecchia U, Crestani R, Decroo T, Van den Bergh R, Al-Kourdi Y. Social Consequences of Ebola Containment Measures in Liberia (Braunstein LA, editor). *PLoS ONE*. 2015;10:e0143036.
35. ACAPS. *Ebola Outbreak in West Africa. Lessons Learned from Quarantine – Sierra Leone and Liberia*. Geneva, Switzerland: ACAPS; 2015.
36. Janvier F, Foissaud V, Delaune D, et al. Deployment of the French military field laboratory dedicated to Ebola virus infected patients in Guinea, January-July 2015. *J Infect Dis*. 2016;213:1208–1209.
37. Semper AE, Broadhurst MJ, Richards J, et al. Performance of the GeneXpert Ebola assay for diagnosis of Ebola virus disease in Sierra Leone: a field evaluation study (von Seidlein L, editor). *PLoS Med*. 2016;13:e1001980.
38. Keita AK, Toure A, Sow MS, et al. Extraordinary long term and fluctuating persistence of Ebola virus RNA in semen of survivors in Guinea: implications for public health [published online ahead of print November 17, 2016]. *Clin Microbiol Infect*. doi:10.1016/j.cmi.2016.11.005.
39. Carroll MW, Matthews DA, Hiscox JA, et al. Temporal and spatial analysis of the 2014-2015 Ebola virus outbreak in West Africa. *Nature*. 2015;524:97–101.
40. Quick J, Loman NJ, Duraffour S, et al. Real-time, portable genome sequencing for Ebola surveillance. *Nature*. 2016;530:228–232.
41. Nouvellet P, Garske T, Mills HL, et al. The role of rapid diagnostics in managing Ebola epidemics. *Nature*. 2015;528:S109–S116.
42. Broadhurst MJ, Kelly JD, Miller A, et al. ReEBOV antigen rapid test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study. *Lancet*. 2015;6736:1–8.
43. Walker NF, Brown CS, Youkee D, et al. Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, Western Area, Sierra Leone, January to February 2015. *Euro Surveill*. 2015;20:1–6.
44. Phan JC, Pettitt J, George JS, et al. Lateral flow immunoassays for Ebola virus disease detection in Liberia. *J Infect Dis*. 2016;214:S222–S228.
45. Benzine JW, Brown KM, Agans KN, et al. Molecular diagnostic field test for point-of-care detection of Ebola virus directly from blood. *J Infect Dis*. 2016;214:S234–S242.
46. Kurosaki Y, Magassouba N, Oloniniyi OK, et al. Development and evaluation of reverse transcription-loop-mediated isothermal amplification (RT-LAMP) assay oupled with a portable device for rapid diagnosis of Ebola virus disease in Guinea. *PLoS Negl Trop Dis*. 2016;10:1–12.
47. Cardile AP, Littell CT, Backlund MG, et al. Deployment of the 1st area medical laboratory in a split-based configuration during the largest Ebola outbreak in history. *Mil Med*. 2016;181:e1675–e1684.
48. Broadhurst MJ, Brooks TJG, Pollock NR. Diagnosis of Ebola virus disease: past, present, and future. *Clin Microbiol Rev*. 2016;29:773–793.
49. 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:e0004948.
50. Reece S, Brown C, Dunning J, Chand M, Zambon M, Jacobs M. The UK's multidisciplinary response to an Ebola epidemic. *Clin Med*. In press.
51. Ansumana R, Jacobsen KH, Idris M, et al. Ebola in Freetown area, Sierra Leone – a case study of 581 patients. *N Engl J Med*. 2014;372:587–588.
52. Brown CS, Cropley IM. Ebola virus disease: where are we now and where do we go? *Postgrad Med J*. 2014;90:610–612.
53. Rouse EN, Zarecki SM, Flowers D, et al. Safe and effective deployment of personnel to support the Ebola response – West Africa. *Morb Mortal Wkly Rep Suppl*. 2016;65:90–97.
54. World Health Organization (WHO). *Emerging Diseases Clinical Assessment and Response Network (EDCARN)*. Geneva, Switzerland: WHO; 2016. http://www.who.int/csr/edcarn/en/.
55. Breakwell L, Gerber AR, Greiner AL, et al. Early identification and prevention of the spread of Ebola in high-risk African countries. *Morb Mortal Wkly Rep Suppl*. 2016;65:21–27.
56. Johnson O, Youkee D, Brown CS, et al. Ebola holding units at government hospitals in Sierra Leone: evidence for a flexible and effective model for safe isolation, early treatment initiation, hospital safety and health system functioning. *BMJ Glob Heal*. 2016;1:e000030.
57. Médecins Sans Frontières (MSF). *Guinea: Ebola Epidemic Declared, MSF Launches Emergency Response*. Brussels: MSF; 2014. http://www.msf.org/article/guinea-ebola-epidemic-declared-msf-launches-emergency-response. Accessed February 20, 2017.
58. Lamb LE, Cox AT, Fletcher T, McCourt AL. Formulating and improving care while mitigating risk in a military Ebola virus disease treatment unit. *J R Army Med Corps*. 2017;163:2–6.
59. Olu O, Cormican M, Kamara K-B, Butt W. Community Care Centre (CCC) as adjunct in the management of Ebola Virus Disease (EVD) cases during outbreaks: experience from Sierra Leone. *Pan Afr Med J*. 2015;22:14.
60. Michaels-Strasser S, Rabkin M, et al. Innovation to confront Ebola in Sierra Leone: the community-care-centre model. *Lancet Glob Heal*. 2015;3: 361–e362.
61. Logan G, Vora NM, Nyensuah TG, et al. Establishment of a community care center for isolation and management of Ebola patients – Bomi County, Liberia, October 2014. *Morb Mortal Wkly Rep*. 2014;63:1010–1012.
62. Oosterhoff P, Mokuwa E, Wilkinson A. *Community-Based Ebola Care Centres: A Formative Evaluation*. London, England: Ebola Anthropology Network; 2015.
63. Kucharski AJ, Camacho A, Flasche S, Glover RE, Edmunds WJ, Funk S. Measuring the impact of Ebola control measures in Sierra Leone. *Proc Natl Acad Sci*. 2015;112:14366–14371.
64. Kirsch TD, Moseson H, Massaquoi M, et al. Impact of interventions and the incidence of Ebola virus disease in Liberia – implications for future epidemics. *Health Policy Plan*. 2017;32:205–214.
65. Abramowitz SA, McLean KE, McKune SL, et al. Community-centered responses to Ebola in urban Liberia: the view from below. *PLoS Negl Trop Dis*. 2015;9:e0003706.
66. Oxfam. *Never Again. Building Resilient Health Systems and Learning From the Ebola Crisis*. Oxford, UK: Oxfam; 2015.
67. Bolkan HA, Bash-Taqi DA, Samai M, Gerdin M, von Schreeb J. Ebola and indirect effects on health service function in Sierra Leone [published online ahead of print December 19, 2014]. *PLoS Curr*. doi:10.1371/currents.outbreaks.0307d588df619f9c9447f8ead5b72b2d.
68. Ansumana R, Keitell S, Roberts GMT, et al. Impact of infectious disease epidemics on tuberculosis diagnostic, management and prevention services: experiences and lessons from the 2014-2015 Ebola Virus Disease outbreak in West Africa. *Int J Infect Dis*. 2016;56:101–104.
69. Loubet P, Mabileau G, Baysah M, et al. Likely effect of the 2014 Ebola epidemic on HIV care in Liberia. *AIDS*. 2015;29:2347–2351.
70. Parpia AS, Ndeffo-Mbah ML, Wenzel NS, Galvani AP. Effects of response to 2014-2015 Ebola outbreak on deaths from malaria, HIV/AIDS, and tuberculosis, West Africa. *Emerg Infect Dis*. 2016;22:433–441.
71. Elston JWT, Moosa AJ, Moses F, et al. Impact of the Ebola outbreak on health systems and population health in Sierra Leone. *J Public Health*. 2015;38:673–678.
72. Ortuno-Gutierrez N, Zachariah R, Woldeyohannes D, et al. Upholding tuberculosis services during the 2014 Ebola storm: an encouraging experience from Conakry, Guinea. *PLoS ONE*. 2016;11:e0157296.
73. Aregawi M, Smith SJ, Sillah-Kanu M, et al. Impact of the mass drug administration for malaria in response to the Ebola outbreak in Sierra Leone. *Malar J*. 2016;15:480.
74. Vetter P, Dayer J, Schibler M, et al. The 2014-2015 Ebola outbreak in West Africa: hands on. *Antimicrob Resist Infect Control*. 2016;5:17.
75. Kerstiëns B, Matthys F. Interventions to control virus transmission during an outbreak of Ebola hemorrhagic fever: experience from Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis*. 1999;179:S263–S267.
76. Borchert M, Mutyaba I, Van Kerkhove MD, et al. Ebola haemorrhagic fever outbreak in Masindi District, Uganda: outbreak description and lessons learned. *BMC Infect Dis*. 2011;11:357.
77. Hageman JC, Hazim C, Wilson K, et al. Infection prevention and control for Ebola in health care settings – West Africa and United States. *Morb Mortal Wkly Rep Suppl*. 2016;65:50–56.
78. Kilmarx PH, Clarke KR, Dietz PM, et al. Ebola virus disease in health care workers – Sierra Leone, 2014. *Morb Mortal Wkly Rep*. 2014;63:1168–1171.
79. Senga M, Pringle K, Ramsay A, et al. Factors underlying Ebola virus infection among health workers, Kenema, Sierra Leone, 2014-2015. *Clin Infect Dis*. 2016;63:454–459.
80. Matanock A, Arwady MA, Ayscue P, et al. Ebola virus disease cases among health care workers not working in Ebola treatment units – Liberia, June-August, 2014. *Morb Mortal Wkly Rep*. 2014;63:1077–1081.
81. McLean KE, Abramowitz SA, Ball JD, et al. Community-based reports of morbidity, mortality, and health-seeking behaviours in four Monrovia communities during the West African Ebola epidemic [published online

ahead of print July 27, 2016]. *Glob Public Health*. doi:10.1080/17441692.2016.1208262.
82. Maduka O, Odia O. Ethical challenges of containing Ebola: the Nigerian experience. *J Med Ethics*. 2015;41:917–919.
83. Pathmanathan I, O'Connor KA, Adams ML, et al. Rapid assessment of Ebola infection prevention and control needs – six districts, Sierra Leone, October 2014. *Morb Mortal Wkly Rep*. 2014;63:1172–1174.
84. Bell BP, Damon IK, Jernigan DB, et al. Overview, control strategies, and lessons learned in the CDC response to the 2014-2016 Ebola epidemic. *Morb Mortal Wkly Rep Suppl*. 2016;65:4–11.
85. 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:S145–S152.
86. Youkee D, Brown CS, Lilburn P, et al. Assessment of environmental contamination and environmental decontamination practices within an Ebola holding unit. Freetown: Sierra Leone. *PLoS ONE* 2015;10:e0145167.
87. Bausch DG, Towner JS, Dowell SF, et al. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. *J Infect Dis*. 2007;196:S142–S147.
88. Dzau VJ, Sands P. Beyond the Ebola battle – winning the war against future epidemics. *N Engl J Med*. 2016;375:203–204.
89. Dramowski A, Mehtar S. *Ebola Prevention and Control*. Cape Town, South Africa: Bettercare; 2015.
90. Fu C, Wang S. Nosocomial infection control in healthcare settings: protection against emerging infectious diseases. *Infect Dis Poverty*. 2016;5:30.
91. Tartari E, Allegranzi B, Ang B, et al. Preparedness of institutions around the world for managing patients with Ebola virus disease: an infection control readiness checklist. *Antimicrob Resist Infect Control*. 2015;4:22.
92. Victory KR, Coronado F, Ifono SO, Soropogui T, Dahl BA. Centers for Disease Control and Prevention (CDC). Ebola transmission linked to a single traditional funeral ceremony – Kissidougou, Guinea, December, 2014-January 2015. *Morb Mortal Wkly Rep*. 2015;64:386–388.
93. Dietz PM, Jambai A, Paweska JT, Yoti Z, Ksiazek TG. Epidemiology and risk factors for Ebola virus disease in Sierra Leone-23 May 2014 to 31 January 2015. *Clin Infect Dis*. 2015;61:1648–1654.
94. Faye O, Boëlle P-Y, Heleze E, et al. Chains of transmission and control of Ebola virus disease in Conakry, Guinea, in 2014: an observational study. *Lancet Infect Dis*. 2015;15:320–326.
95. Fitzpatrick G, Vogt F, Gbabai OBM, et al. Describing readmissions to an Ebola case management centre (CMC), Sierra Leone, 2014. *Euro Surveill*. 2014;19:20924.
96. Moreau M, Spencer C, Gozalbes JG, et al. Lactating mothers infected with Ebola virus: EBOV RT-PCR of blood only may be insufficient. *Euro Surveill*. 2015;20:21017.
97. Legrand J, Grais RF, Boelle PY, Valleron AJ, Flahault A. Understanding the dynamics of Ebola epidemics. *Epidemiol Infect*. 2007;135:610–621.
98. Prescott J, Bushmaker T, Fischer R, Miazgowicz K, Judson S, Munster VJ. Postmortem stability of Ebola virus. *Emerg Infect Dis*. 2015;21:856–859.
99. Francesconi P, Yoti Z, Declich S, et al. Ebola hemorrhagic fever transmission and risk factors of contacts, Uganda. *Emerg Infect Dis*. 2003;9:1430–1437.
100. Report of an International Commission. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ*. 1978;56:271–293.
101. Breman J, Piot P, Johnson K, Al E. The epidemiology of Ebola hemorrhagic fever in Zaire. In: Halter S, ed. *Ebola Virus Haemorrhagic Fever*. North Holland: Elsevier; 1978:85–97.
102. Roels TH, Bloom AS, Buffington J, et al. Ebola hemorrhagic fever, Kikwit, democratic republic of the Congo, 1995: risk factors for patients without a reported exposure. *J Infect Dis*. 1999;179:S92–S97.
103. Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179:S87–S91.
104. Roddy P, Thomas SL, Jeffs B, et al. Factors associated with Marburg hemorrhagic fever: analysis of patient data from Uige, Angola. *J Infect Dis*. 2010;201:1909–1918.
105. Wamala JF, Lukwago L, Malimbo M, et al. Ebola hemorrhagic fever associated with novel virus strain, Uganda, 2007-2008. *Emerg Infect Dis*. 2010;16:1087–1092.
106. Blackley DJ, Lindblade KA, Kateh F, et al. Rapid intervention to reduce Ebola transmission in a remote village – Gbarpolu county, Liberia, 2014. *Morb Mortal Wkly Rep*. 2015;64:175–178.
107. Nkoghe D, Kone ML, Yada A, Leroy E. A limited outbreak of Ebola haemorrhagic fever in Etoumbi, Republic of Congo, 2005. *Trans R Soc Trop Med Hyg*. 2011;105:466–472.
108. Richards P, Amara J, Ferme MC, et al. Social pathways for Ebola virus disease in rural Sierra Leone, and some implications for containment. *PLoS Negl Trop Dis*. 2015;9:e0003567.
109. Ferme M. *The Underneath of Things: Violence, History and the Everyday in Sierra Leone*. Berkeley, CA: University of California Press; 2001.
110. World Health Organization (WHO). *How to Conduct Safe and Dignified Burial of a Patient who Has Died From Suspected or Confirmed Ebola Virus Disease*. Geneva, Switzerland: WHO; 2014.
111. Formenty P, Leroy EM, Epelboin A, et al. Detection of Ebola virus in oral fluid specimens during outbreaks of Ebola virus hemorrhagic fever in the Republic of Congo. *Clin Infect Dis*. 2006;42:1521–1526.
112. De Roo A, Ado B, Rose B, Guimard Y, Fonck K, Colebunders R. Survey among survivors of the 1995 Ebola epidemic in Kikwit, Democratic Republic of Congo: their feelings and experiences. *Trop Med Int Health*. 1998;3:883–885.
113. Vetter P, Kaiser L, Schibler M, Ciglenecki I, Bausch DG. Sequelae of Ebola virus disease: the emergency within the emergency. *Lancet Infect Dis*. 2016;16:e82–e91.
114. Vetter P, Fischer WA, Schibler M, Jacobs M, Bausch DG, Kaiser L. Ebola virus shedding and transmission: review of current evidence. *J Infect Dis*. 2016;214:S177–S184.
115. Jacobs M, Rodger A, Bell DJ, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet*. 2016;388:498–503.
116. Varkey JB, Shantha JG, Crozier I, et al. Persistence of Ebola virus in ocular fluid during convalescence. *N Engl J Med*. 2015;372:2423–2427.
117. MacIntyre CR, Chughtai AA. Recurrence and reinfection – a new paradigm for the management of Ebola virus disease. *Int J Infect Dis*. 2016;43:58–61.
118. Deen GF, Knust B, Broutet N, et al. Ebola RNA persistence in Semen of Ebola virus disease survivors – preliminary report [published online ahead of print October 14, 2015]. *N Engl J Med*. doi:151014140118009.
119. Uyeki TM, Erickson BR, Brown S, et al. Ebola virus persistence in Semen of male survivors. *Clin Infect Dis*. 2016;62:1552–1555.
120. Diallo B, Sissoko D, Loman NJ, et al. Resurgence of Ebola virus disease in Guinea linked to a survivor with virus persistence in seminal fluid for more than 500 days. *Clin Infect Dis*. 2016;63:1353–1356.
121. Mate SE, Kugelman JR, Nyenswah TG, et al. Molecular evidence of sexual transmission of Ebola virus. *N Engl J Med*. 2015;373:2448–2454.
122. Christie A, Davies-Wayne GJ, Cordier-Lassalle T, et al. Possible sexual transmission of Ebola virus – Liberia, 2015. *Morb Mortal Wkly Rep*. 2015;64:479–481.
123. Soka MJ, Choi MJ, Baller A, et al. Prevention of sexual transmission of Ebola in Liberia through a national semen testing and counselling programme for survivors: an analysis of Ebola virus RNA results and behavioural data. *Lancet Glob Heal*. 2016;4:e736–e743.
124. Purpura LJ, Soka M, Baller A, et al. Implementation of a national semen testing and counseling program for male Ebola survivors – Liberia, 2015-2016. *Morb Mortal Wkly Rep*. 2016;65:963–966.
125. Bebell LM, Riley LE. Ebola virus disease and Marburg disease in pregnancy: a review and management considerations for filovirus infection. *Obstet Gynecol*. 2015;125:1293–1298.
126. Baggi FM, Taybi A, Kurth A, et al. Management of pregnant women infected with Ebola virus in a treatment centre in Guinea, June 2014. *Euro Surveill*. 2014;19:20983.
127. World Health Organization (WHO). *Ebola Virus Disease in Pregnancy: Screening and Management of Ebola Cases, Contacts and Survivors*. Geneva, Switzerland: WHO; 2015. http://apps.who.int/iris/bitstream/10665/184163/1/WHO_EVD_HSE_PED_15.1_eng.pdf. Accessed February 20, 2017.
128. Meltzer MI, Atkins CY, Santibanez S, et al. Estimating the future number of cases in the Ebola epidemic – Liberia and Sierra Leone, 2014-2015. *Morb Mortal Wkly Rep Surveill Summ*. 2014;63:1–14.
129. Camacho A, Kucharski AJ, Funk S, Breman J, Piot P, Edmunds WJ. Potential for large outbreaks of Ebola virus disease. *Epidemics*. 2014;9:70–78.
130. World Health Organization (WHO). *Statement on the 1st Meeting of the IHR Emergency Committee on the 2014 Ebola Outbreak in West Africa*. Geneva, Switzerland: WHO; 2014. http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/. Accessed February 20, 2017.
131. Kucharski AJ, Camacho A, Checchi F, et al. Evaluation of the benefits and risks of introducing Ebola community care centers, Sierra Leone. *Emerg Infect Dis*. 2015;21:393–399.
132. Lewnard JA, Ndeffo Mbah ML, Alfaro-Murillo JA, et al. Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis. *Lancet Infect Dis*. 2014;14:1189–1195.
133. Mabey D, Flasche S, Edmunds WJ. Airport screening for Ebola. *BMJ*. 2014;349:g6202.
134. Otsuki S, Nishiura H. Reduced risk of importing Ebola virus disease because of travel restrictions in 2014: a retrospective epidemiological modeling study. *PLoS ONE*. 2016;11:e0163418.
135. Cohen NJ, Brown CM, Alvarado-Ramy F, et al. Travel and border health measures to prevent the international spread of Ebola. *Morb Mortal Wkly Rep Suppl*. 2016;65:57–67.

136. Gomes M, Pastore y Piontti A, Rossi L, et al. Assessing the international spreading risk associated with the 2014 West African Ebola outbreak [published online ahead of print September 2, 2014]. *PLoS Curr Outbreaks*. doi:10.1371/currents.outbreaks.cd818f63d40e24aef769dda7df9e0da5.
137. Bogoch II, Creatore MI, Cetron MS, et al. Assessment of the potential for international dissemination of Ebola virus via commercial air travel during the 2014 West African outbreak. *Lancet*. 2015;385:29–35.
138. Vinson JE, Drake JM, Rohani P, Park AW. The potential for sexual transmission to compromise control of Ebola virus outbreaks [published online ahead of print June 8, 2016]. *Biol Lett*. doi:10.1098/rsbl.2015.1079.
139. Abbate JL, Murall CL, Richner H, Althaus CL. Potential impact of sexual transmission on Ebola virus epidemiology: Sierra Leone as a case study. *PLoS Negl Trop Dis*. 2016;10:e0004676.
140. Guo Z, Xiao D, Li D, et al. Predicting and evaluating the epidemic trend of Ebola virus disease in the 2014-2015 outbreak and the effects of intervention measures. *PLoS ONE*. 2016;11:e0152438.
141. Boyles T. Priorities in Ebola research – a view from the field. *Lancet*. 2015;385:23.
142. Leligdowicz A, Fischer WA, Uyeki TM, et al. Ebola virus disease and critical illness. *Crit Care*. 2016;20:217.
143. Uyeki TM, Mehta AK, Davey RT, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med*. 2016;374:636–646.
144. Dunning J, Kennedy SB, Antierens A, et al. Experimental treatment of Ebola virus disease with brincidofovir. *PLoS ONE*. 2016;11:e0162199.
145. 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 (Lipsitch M, editor). *PLOS Med*. 2016;13:e1001967.
146. Bai C-Q, Mu J-S, Kargbo D, et al. Clinical and virological characteristics of Ebola virus disease patients treated with Favipiravir (T-705) – Sierra Leone, 2014. *Clin Infect Dis*. 2016;63:1288–1294.
147. 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:e1001997.
148. PREVAIL II Writing Group Multi-National PREVAIL II Study Team. A randomized, controlled trial of ZMapp for Ebola virus infection. *N Engl J Med*. 2016;375:1448–1456.
149. 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.
150. World Health Organization (WHO). *Use of Convalescent Whole Blood or Plasma Collected From Patients Recovered From Ebola Virus Disease*. Geneva, Switzerland: WHO; 2014.
151. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus*. 2016;14:152–157.
152. Jacobs M, Aarons E, Bhagani S, et al. Post-exposure prophylaxis against Ebola virus disease with experimental antiviral agents: a case-series of healthcare workers. *Lancet Infect Dis*. 2015;15:1300–1304.
153. Gittings K, Matson KL. Establishing herd immunity against Ebola through vaccination. *Vaccine*. 2015;34:2644–2647.
154. Sarwar UN, Costner P, Enama ME, et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial. *J Infect Dis*. 2015;211:549–557.
155. Kibuuka H, Berkowitz NM, Millard M, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b, randomised, double-blind, placebo-controlled clinical trial. *Lancet*. 2015;385:1545–1554.
156. Bradfute SB, Bavari S. Correlates of immunity to filovirus infection. *Viruses*. 2011;3:982–1000.
157. Sullivan NJ, Hensley L, Asiedu C, et al. CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. *Nat Med*. 2011;17:1128–1131.
158. Warfield KL, Aman MJ. Advances in virus-like particle vaccines for filoviruses. *J Infect Dis*. 2011;204:1053–1059.
159. Bengtsson KL, Song H, Stertman L, et al. Matrix-M adjuvant enhances antibody, cellular and protective immune responses of a Zaire Ebola/Makona virus glycoprotein (GP) nanoparticle vaccine in mice. *Vaccine*. 2016;34:1927–1935.
160. Novavax Inc. *Novavax Announces Positive Top-Line Data from Phase 1 Ebola Vaccine Trial on WHO Teleconference* [press release]. Gaithersburg, MD: Novovax, 2015:1–2.
161. World Health Organization (WHO). *Meeting Summary of the WHO Consultation on Potential Ebola Therapies and Caccines*. Geneva, Switzerland: WHO; 2014.
162. Ledgerwood JE, DeZure AD, Stanley DA, et al. Chimpanzee adenovirus vector Ebola vaccine – preliminary report. *N Engl J Med*. 2014;376:928–938.
163. Rampling T, Ewer K, Bowyer G, et al. A monovalent chimpanzee adenovirus Ebola vaccine – preliminary report. *N Engl J Med*. 2016;374:1635–1646.
164. Tapia MD, Sow SO, Lyke KE, et al. Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2016;3099:1–12.
165. De Santis O, Audran R, Pothin E, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *Lancet Infect Dis*. 2016;16:311–320.
166. Ewer K, Rampling T, Venkatraman N, et al. A monovalent chimpanzee adenovirus Ebola vaccine boosted with MVA. *N Engl J Med*. 2016;374:1635–1646.
167. Li J-X, Hou L-H, Meng F-Y, et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Glob Heal*. 2017;5:e324–e334.
168. Zhu F-C, Wurie AH, Hou L-H, et al. Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2017;389:621–628.
169. Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia Ankara-vectored Ebola vaccines: a randomized clinical trial. *JAMA*. 2016;315:1610–1623.
170. Gunther S, Feldmann H, Geisbert TW, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J Infect Dis*. 2011;204:785–790.
171. Lai L, Davey R, Beck A, et al. Emergency postexposure vaccination with vesicular stomatitis virus-vectored Ebola vaccine after needlestick. *JAMA*. 2015;313:1249–1255.
172. Agnandji ST, Huttner A, Zinser ME, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe – preliminary report. *N Engl J Med*. 2015;347:1647–1660.
173. Regules JA, Beigel JH, Paolino KM, et al. A recombinant vesicular stomatitis virus Ebola vaccine. *N Engl J Med*. 2017;376:330–341.
174. Huttner A, Dayer JA, Yerly S, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. *Lancet Infect Dis*. 2015;15:1156–1166.
175. 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;389:505–518.
176. Krause PR. Interim results from a phase 3 Ebola vaccine study in Guinea. *Lancet*. 2015;386:831–833.
177. Rid A, Miller FG. Ethical rationale for the Ebola 'ring vaccination' trial design. *Am J Public Health*. 2016;106:432–435.
178. Widdowson M, Carr W, Gibson L. Implementing an Ebola vaccine study – Sierra Leone background to trial conception trial design and ethical considerations. *Morb Mortal Wkly Rep*. 2016;65:98–106.
179. Brown C, Arkell P, Rokadiya S. Ebola virus disease: the 'Black Swan' in West Africa. *Trop Doct*. 2015;45:2–5.
180. Davtyan M, Brown B, Folayan MO. Addressing Ebola-related stigma: lessons learned from HIV/AIDS. *Glob Health Action*. 2014;7:26058.
181. Wainberg MA, Kippax S, Bras M, Sow PS. HIV and Ebola: similarities and differences. *J Int AIDS Soc*. 2014;17:19896.
182. Adebamowo C, Bah-Sow O, Binka F, et al. Randomised controlled trials for Ebola: practical and ethical issues. *Lancet*. 2014;384:1423–1424.
183. Cox E, Borio L, Temple R. Evaluating Ebola therapies – the case for RCTs. *N Engl J Med*. 2014;371:2350–2351.
184. Shaw D. Randomisation is essential in Ebola drug trials. *Lancet*. 2014;384:1667.
185. Byar DP, Schoenfeld DA, Green SB, et al. Design considerations for AIDS trials. *N Engl J Med*. 1990;323:1343–1348.
186. Drain PK. Ebola: lessons learned from HIV and tuberculosis epidemics. *Lancet Infect Dis*. 2015;15:146–147.
187. WHO Ebola Response Team. After Ebola in West Africa – unpredictable risks, preventable epidemics. *N Engl J Med*. 2016;375:587–596.