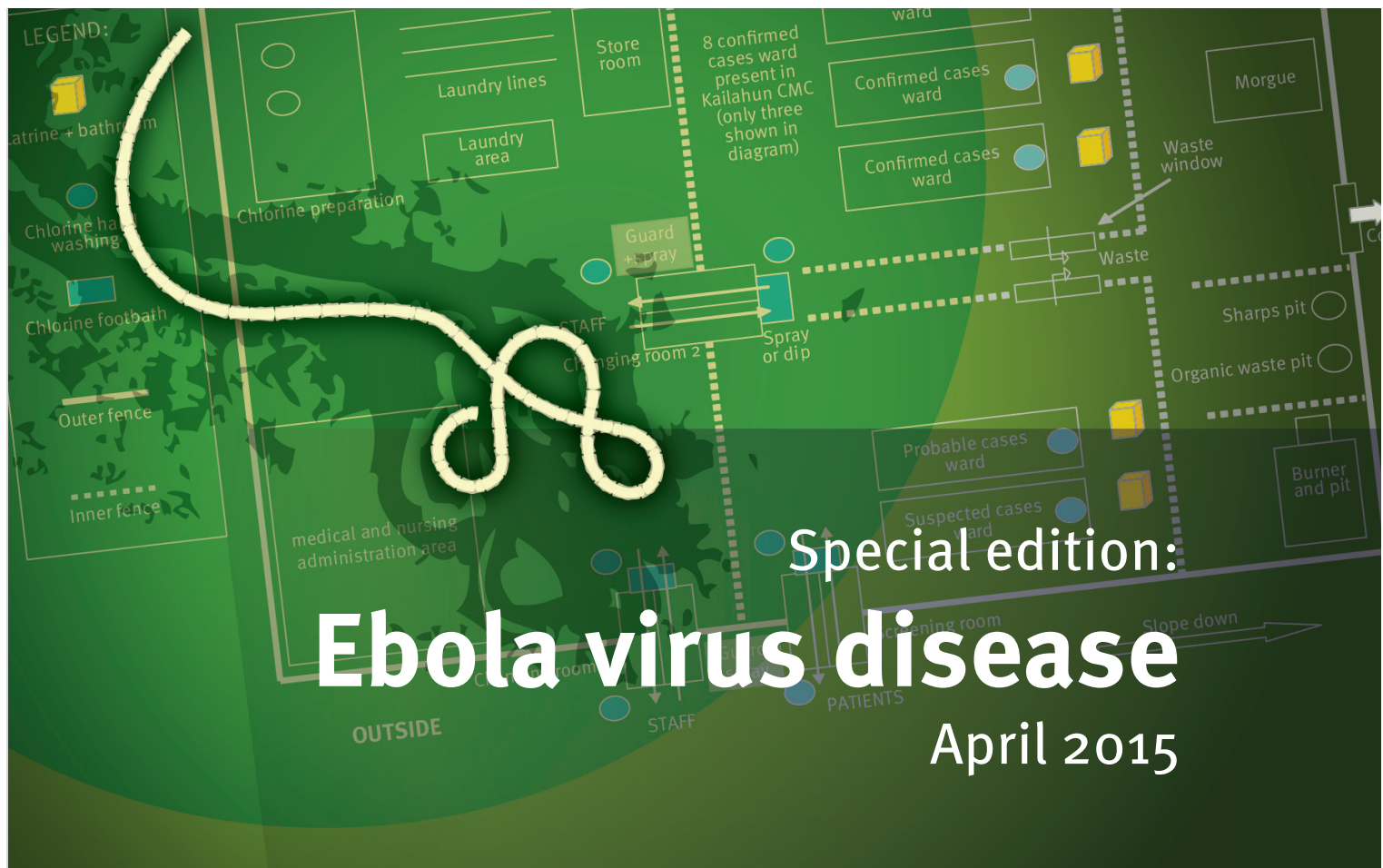




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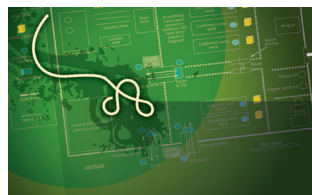
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Illustration of Ebola virus

The tail of the epidemic and the challenge of tracing the very last Ebola case

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One year ago, on 23 March 2014, the World Health Organization (WHO) announced that it had been notified 'of a rapidly evolving outbreak of Ebola virus disease (EVD) in forested areas of south-eastern Guinea'. At that time, 49 cases, including 29 deaths had been reported. In the following months and weeks, the outbreak spread to the two neighbouring countries Sierra Leone and Liberia and peaked six months later, in October 2014, with up to 1,500 cases reported on a weekly basis. It was then when several scientific publications presented forecasts for the coming months that ranged from 60,000 EVD cases for the most conservative estimates, up to several hundred thousands of EVD cases [1-4] for the more forthcoming ones. As of 22 March 2015, the toll of the epidemic has been 24,907 reported cases including 10,326 deaths [5]. Despite these far too high numbers, the even higher forecasts were fortunately not attained. This can be partly attributed to the unprecedented mobilisation of resources generated by these high estimates.

In the past eight weeks, the number of new confirmed, probable and suspected EVD cases has been stabilising at around 365 notifications per week [6,7]. However, this trend results from the combination of heterogeneous patterns: while Liberia has almost interrupted human-to-human transmission, and the 'historical' epicentre of the epidemic in the forested area at the border of Sierra Leone and Guinea reports few new cases, there has been a shift of the epidemic towards the capital cities of Freetown and Conakry and their surrounding districts where there is sustained and even increasing transmission [8].

The elimination of human-to-human transmission of the Ebola virus in the affected countries is achievable. Liberia has shown that strict and comprehensive implementation of control measures are effective to interrupt this form of transmission [9]. This can be achieved since sufficient Ebola treatment units and laboratory capacity are currently available in the region [10]. It should also be feasible because the mobilisation of field epidemiologists trained in the various

field-training programmes around the world has dramatically increased in recent months.

Upon entering what seems to be the tail of the epidemic and, as in any such moment, the 'Ebola endgame' strategy requires adaptation to the heterogeneity of the epidemiological situation. The tools for EVD control need to be fine-tuned and the commitment from the teams supporting local authorities in affected countries needs to be sustained. While the pressure on clinical and laboratory expertise gradually decreases, the demand shifts towards field epidemiologists to assist local public health experts and support community workers to engage in active surveillance and to monitor remaining transmission chains in affected communities. The priority at this stage of the epidemic is the early detection of possible re-emergence of transmission, in relation with importation of cases from areas still experiencing active transmission. Other contributing factors to re-emergence of transmission could be delayed secondary transmission, as suspected recently through sexual contact in Liberia and Macenta, Guinea or new primary zoonotic transmission from the animal reservoir given the long duration of the present outbreak [11,12]. However, no conclusive evidence is available for sexual transmission of the disease by convalescent EVD-negative individuals [13]. Moreover, no new primary zoonotic transmission has been documented in the affected countries.

A paper by Rexroth et al. in this issue of *Eurosurveillance*, presents results from a survey of European infectious disease epidemiologists and microbiologists about their decisions to apply for Ebola response missions in West Africa [14]. It sheds light on the motivation and concerns of experts with regards to apply for deployment in affected countries. The need to deploy larger number of international experts to support the local outbreak response became evident when the epidemic went out of control in West Africa during the autumn of 2014. At the same time, limited secondary transmission occurred from an imported case in the United States and a medically evacuated case in Spain [15,16]. This

gave rise to fear of the possibility that more imported cases and secondary transmission could occur, anywhere in our globally connected world [17]. Along with the dramatic forecasts, this led to concerns about the evolution of the epidemic and its potential spread, and an increase in deployed resources to the affected region.

The main concern for deployment of experts enrolled in the study was the concerns of their family and the lack of support from their employers. The study covers the period from 19 November to 7 December 2014. From March 2014 until 7 December, the European Centre for Disease Prevention and Control (ECDC) had facilitated the mobilisation of 13 experts to the affected countries through the WHO Global Outbreak And Response Network (GOARN) mechanism, all but three from the various field epidemiological training programmes in the European Union. In the three and half months since the study end, an additional 33 staff were mobilised. Currently, 19 experts mobilised through ECDC are deployed to West Africa: 14 in Guinea and five in Sierra Leone.

The paper by Walker et al. on a point-of-care blood test for identification of EVD, highlights the fact that the availability of a rapid diagnostic bedside test would be of great value in isolation facilities, especially when the proportion of patients infected with Ebola virus among suspected cases will have decreased as the epidemic is fading out [18]. The study shows that a 100% predictive negative value can probably be achieved with the presented rapid test, which would greatly reduce the amount of PCR tests necessitating considerable laboratory infrastructure and personnel. As discussed in the paper, applying the rapid test to safely discard suspected patients not infected with Ebola virus would dramatically reduce the burden on isolation unit beds and the need for confirmatory diagnostic PCR tests. For example, of 100 suspected EVD patients that would have to be tested and among which only 10 would be infected with Ebola virus, the rapid test, using a CT score of 6 as a threshold, would safely identify 87 persons as non-EVD patients and only require 13 diagnostic PCR tests to correctly identify these 10 EVD patients. Furthermore, as the epidemic continued to fade out, and if there would be only one Ebola virus infected patient among the 100 tested, the rapid test would identify 96 of the non-EVD patients and the PCR test would only need to be applied to the four remaining ones to identify the single case of EVD.

Complementing the considerations on the need for affordable and sustained field epidemiology and laboratory support, the paper by Fähnrich et al. reminds us that after one year into the epidemic, most affected areas still have no access to an appropriate information system to document the extent of the epidemic and to support the control. An information system able to monitor the epidemiological situation and the performance of the control measures is however, crucial

for efficient outbreak response and should be implemented as early as possible. While such systems are still desirable at the current stage of the outbreak, they should eventually cover other epidemic-prone diseases also. Interestingly, the unavailability of computers in the field to register data can be effectively overcome by an approach relying on smart phone technology and cloud platforms [19].

The backbone of good surveillance is the timely provision of quality data to those who need it to steer interventions. Information systems such as the one presented will certainly improve processes involved in data acquisition. However, much still needs to be done to ensure the correct application of case definitions, the appropriate investigation of cases, and the exhaustiveness of reporting across affected districts and countries, in order to improve the ability to effectively depict the epidemiological situation and fully assess the progress and performance of the control programmes.

The paper by Alqahtani et al. on the perception of the risk and protective means regarding EVD among pilgrims from Australia to the Hajj, reports that one in six pilgrims thinks that Ebola transmits by air, one in five that they are at high risk of acquiring EVD during the Hajj, one in two that the use of masks would protect them [20]. These results remind us that misconception affecting pilgrims to the Hajj is certainly also true for members of EVD affected communities. While health advice to travellers should be strengthened in the context of epidemics, the mobilisation of anthropologists should support the surveillance and response teams in the affected communities and contribute to alleviate the fears of the community members towards the required control measures.

Finally, the article by Goodfellow et al. in this issue highlights the importance of the legacy of the international support to respond to the epidemic [21]. The authors stress that most of the laboratory technology now used in the affected countries may not be set up in a sustainable way and thus new strategies are required to ensure that in the aftermath of the epidemic there will be enough capacity to recognise and handle a future probable resurgence of EVD early. The paper calls for an extension of laboratory activities to cover essential clinical and microbiology services. The support activities should be extended beyond laboratory activities in the tail of the epidemic. They should ensure that EVD targeted activities are maintained until the last case of the last chain of transmission is controlled, while ensuring that surveillance and control of other epidemic-prone diseases are reactivated. This is particularly important during the rainy season that may lead to a dramatic increase in diseases such as measles, infectious diarrhoea, malaria, yellow fever or Lassa fever. Considering the low immunisation coverage overall, prior to the EVD epidemic [22], and the interruption of immunisation programmes during the

epidemic, all those involved in the control of the EVD outbreak should work hard to ensure that no devastating outbreak of a vaccine-preventable disease, such as measles, will be part of the legacy of the international support to the response to the Ebola outbreak. risk of leptospirosis exposure among these groups.

Conflict of interest

None declared.

Authors' contributions

Denis Coulombier has drafted the editorial, Kaja Kaasik-Aaslav provided epidemiological background.

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Preparedness is crucial for safe care of Ebola patients and to prevent onward transmission in Europe – outbreak control measures are needed at its roots in West Africa

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Recent events related to the current outbreak of Ebola virus disease (EVD) in West Africa seemingly indicate inevitable problems that Europe has to face: an individual became symptomatic from Ebola virus disease only after having arrived in a non-affected country [1], and healthcare workers became infected with Ebola while caring for patients, either in West Africa or in non-affected countries where they had been medically evacuated [2–4]. Moreover, media enquiries and reports reveal concern among the general public.

All this follows the dramatic development of the epidemic in West Africa over the past months, and forecasts unanimously agree that it will take weeks if not months before the trend in the affected region can be inverted and the epidemic be controlled [5–6]. Therefore, European countries will have to cope with more cases arriving from affected areas while being well prepared to prevent secondary transmission.

While infections in the dedicated healthcare settings in Europe will probably remain single and unfortunate events, they need to be investigated thoroughly in order to incorporate the lessons learnt from them into improved standards and procedures as well as consider them in training activities.

There are three possible scenarios that may result in patients infected with Ebolavirus to present in healthcare settings in Europe and healthcare workers or support staff coming into contact with them.

The first scenario is related to a patient in an affected country with a confirmed Ebolavirus infection who is medically evacuated to Europe. This scenario should not result in further transmission in Europe and thus constitute a rather low risk as preparations are possible for such planned situations. However, as pointed out above, and whenever humans are involved, occasions may occur where unfortunate events may lead to infection of a healthcare worker contact. While caring

for Ebola patients in European settings should remain safe when appropriate procedures are in place, a 100 per cent elimination of risks can never be expected.

The second scenario refers to a symptomatic patient boarding a commercial flight, possibly to seek medical care in Europe. Upon declaring the Ebola outbreak in West Africa a public health event of international concern, the World Health Organization (WHO) International Health Regulations Emergency Committee also recommended exit screening in the affected countries [7]. To render this seemingly easy and not too cost intensive measure effective, it needs to be applied systematically to all travellers departing from affected countries. Where this is the case, the risk of exportation can be minimised to a great extent. The support provided by the United States in the affected countries should have helped in the current situation in this respect [8]. Additional screening at the point of entry (entry screening) may complement exit screening, as it may detect the few symptomatic cases that could have been missed by the exit screening or those who may have become symptomatic during the flight. However, entry screening is complex to implement because of the indirect routes that may be taken by travellers.

The third scenario consists of a person travelling to Europe from an affected country while incubating the virus and developing symptoms only after arrival, as experienced recently in Dallas, United States [1]. This situation constitutes the greatest risk to Europe and predisposes to limited secondary transmission to close contacts at the early stage of the disease, when the patient becomes infectious and before being isolated. Efforts are made by all countries in the European Union to minimise this risk through a set of measures namely (i) to provide information about the disease and advice in case of symptoms to all travellers coming from affected areas, (ii) to sensitise front-line healthcare providers about possible EVD symptoms and the need to enquire about recent travel to the affected region

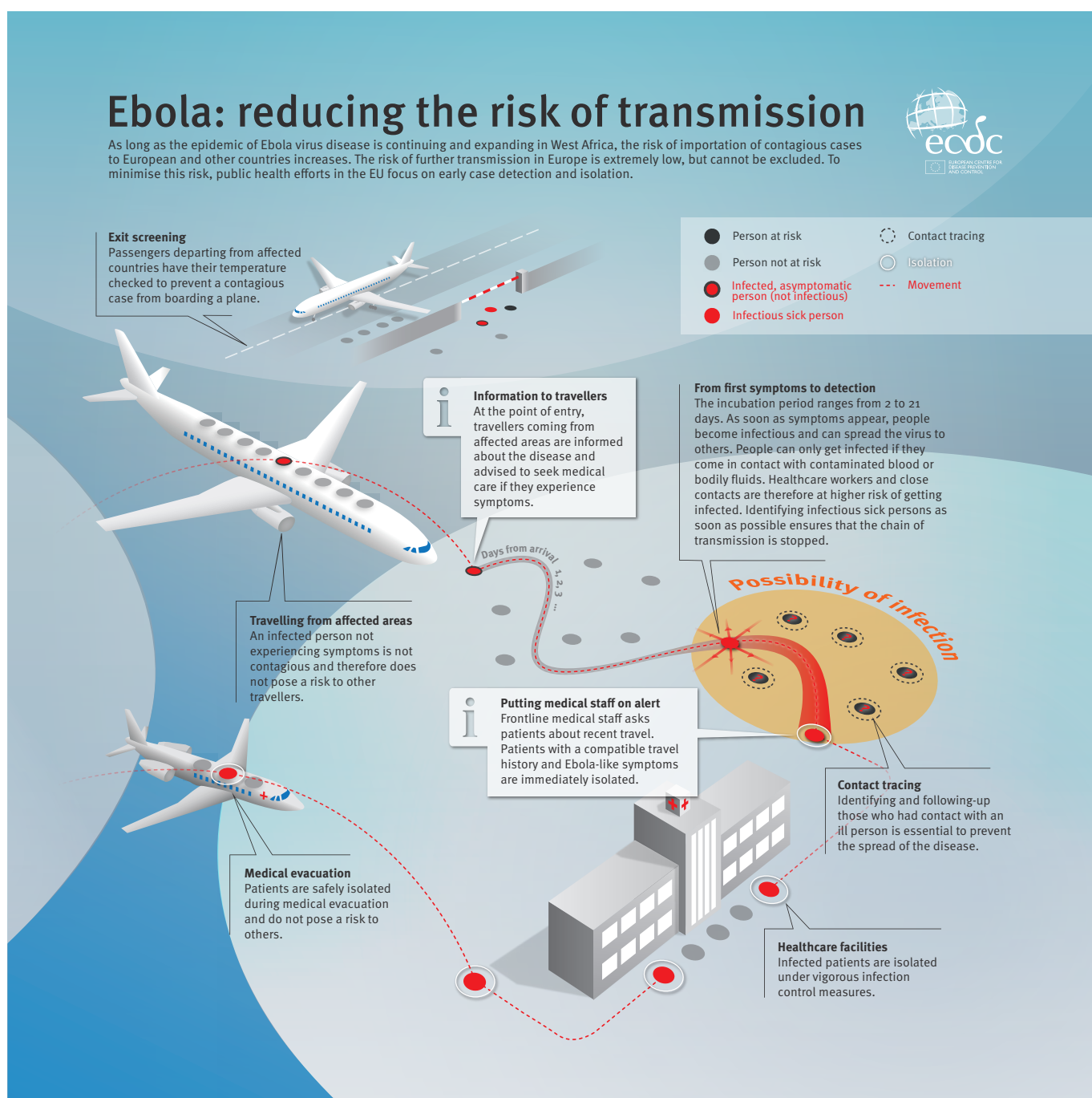
while ascertaining patients, and to ensure their timely isolation when EVD is considered, and (iii) to provide guidance for investigating cases and for infection control measures that should allow to care safely for such patients.

The infographic presents in a simplified way three scenarios described above (Figure).

Medical evacuations to Europe remain particularly safe when infection control measures are applied by experienced, well trained professionals. Despite the envisaged increase in such evacuations that will eventually result in treatment of Ebola cases in European hospitals, transmission to healthcare personnel should

remain the unfortunate sporadic exception. More cases as seen in Dallas will be seen in Europe. Any such situation could happen as well in other regions of the world.

Above all, however, the cases of recently evacuated infected healthcare workers to Europe who were involved in responding to the outbreak in affected countries, should remind us about the important work of those who work in West Africa where the burden of EVD weighs heavily on the population and has affected local healthcare structures and other services considerably. The risk of further spread associated with the ongoing Ebola outbreak in West Africa can only be mitigated by controlling the epidemic at its roots in the affected countries.



We are in tune with voices raising concern about the current situation and calling for strong leadership within the international community to ensure that adequate measures are implemented in this critical situation [9]. The European Centre for Disease Prevention and Control (ECDC) strongly supports respective initiatives from WHO as far as possible within its mandate. As pointed out in the Lancet [9], currently, the international community needs to further strengthen its support to affected countries. While it is still unclear when the outbreak will end, it will be important to analyse this event carefully and learn from it in order to be better prepared for similar events in the future. This we owe to those who suffer and who lost their lives as well as those who are working to save lives and trying to contain this unprecedented Ebola outbreak in the affected countries.

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Containing Ebola virus infection in West Africa

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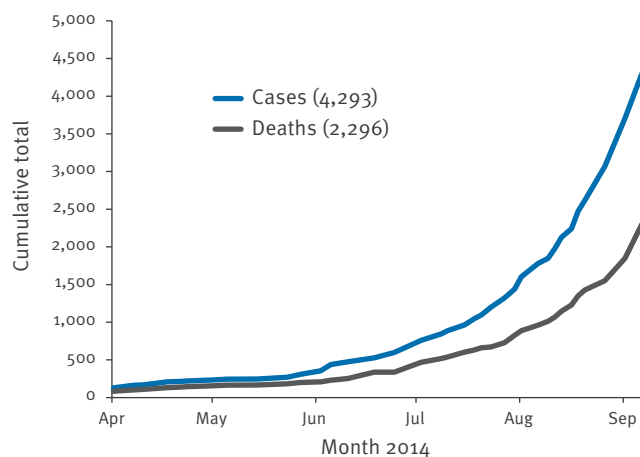
Ebola virus disease (EVD) is leaving a mark deeper and wider than ever before. The current outbreak now spans five countries in West Africa – Guinea, Liberia, Nigeria, Senegal and Sierra Leone – with over 4,200 cases and 2,200 deaths reported to the World Health Organization (WHO) as of 6 September 2014 (Figure 1) [1]. Unfortunately, with many cases either not reported or yet to show symptoms, the true number of infections is likely to be considerably higher. The first countries affected were among the world's poorest, areas where long periods of civil wars have battered health services and eroded public trust. As a result, the outbreak has spread to other countries, and continues to expand. What began as a local problem has turned into an international crisis.

Challenges for control in Africa

Past Ebola outbreaks have never risen beyond a few hundred reported cases, and even these events have been comparatively rare. When EVD spills over from its animal host into human populations, it typically generates dozens rather than hundreds of infections [2].

FIGURE

Cumulative number of Ebola virus disease cases and deaths in West Africa, April to 6 September 2014



Source: World Health Organization [1]

Chance events in the early stages of an outbreak can have a large impact on its final size. Infected individuals' movement patterns, social interactions, beliefs about disease causation and trust in authorities can all influence the extent of transmission, and hence the scale of control measures required to stop the infection.

In theory, Ebola is easily containable. It has a long incubation period – around a week on average – and cases are typically infectious only after displaying symptoms [3,4]. This means that isolation of symptomatic patients, contact tracing and follow-up surveillance of all contacts should be sufficient to stop transmission. Contrast this with pandemic influenza, which has a much shorter incubation period and can generate numerous cases who may be asymptomatic yet infectious [5]. For isolation to be effective during an Ebola outbreak, however, there must be rapid identification of cases and follow-up of contacts. Several factors can hinder this. In settings with limited testing facilities, cases that are not tested can be misdiagnosed. Not all EVD patients display distinctive hemorrhagic symptoms: the 1994 Ebola outbreak in Gabon was originally attributed to yellow fever [6], and early cases in the 1995 Kikwit outbreak were mistaken for dysentery and typhoid fever [7].

The exponential growth in case numbers during an outbreak also makes resource-intensive activities like contact tracing and surveillance increasingly difficult. Recent studies, including the one by Nishiura et al. in this issue, suggest that the reproduction number of Ebola (the average number of secondary cases generated by a typical case) is between 1.5–2 in some countries [8,9]. Based on the durations of incubation and infectiousness of EVD [3], it is plausible that the number of cases could therefore double every fortnight if the situation does not change. There are currently hundreds of new EVD cases reported each week; with the number of infections increasing exponentially, it could soon be thousands. Following up contacts and monitoring them for symptoms has already become unfeasible in areas where health authorities are stretched to the limit.

Disease control efforts in West Africa have been further hampered by cases not attending healthcare facilities, and instead remaining in the community. Fear and mistrust of health authorities has contributed to this problem, but increasingly it is also because isolation centres have reached capacity. As well as creating potential for further transmission, large numbers of untreated – and therefore unreported – cases make it difficult to measure the true spread of infection, and hence to plan and allocate resources. Even if patients are isolated, however, and their close contacts successfully traced, efforts can be undermined by unpredictable behavior. This was exemplified by the outbreak reported last week in Port Harcourt, Nigeria, which started after a contact of the index case in Lagos broke quarantine and left the capital [10].

Fear and mistrust are not unique to the current Ebola outbreak. During the 2000-1 outbreak in Uganda, health authorities faced similar challenges, including public protests, lack of co-operation from followed-up contacts, and shortages of staff willing to work in Ebola isolation units [11]. To control the infection, authorities needed to provide leadership and build trust. Interventions included education in various settings: in the community, educators strived to instill confidence, explaining how to avoid infection and recognise symptoms, while in hospitals, healthcare workers were provided with additional training, support and protection [12].

Education can also help address cultural practices that fuel outbreaks. The initial chain of Ebola virus transmission in Guinea in early 2014 included two funerals [13], and in May, another funeral introduced the epidemic to Sierra Leone [14]. Again, this is not just a feature of the present outbreak in West Africa. Funeral practices contributed to previous outbreaks in Central Africa too, but in many instances, it was possible to change people's behaviour. With support from health educators, communities altered the way burials were conducted, reducing transmission [12,15].

Need for an international response

Introducing control measures requires substantial resources, and there is a limit to what a local response can achieve alone. Yet as the current outbreak has grown, neighboring countries have closed borders and introduced travel restrictions. Similar actions were taken during past outbreaks, such as the one in Uganda in 2000-1 [16]. Such restrictions can hinder control efforts, making it harder to bring in personnel and resources.

Ebola cannot be ignored in the hope it will burn itself out. It is true that outbreaks of acute infections will generally decline once a large number people have been infected, because there are no longer enough susceptible individuals to sustain transmission. But if Ebola indeed has a reproduction number of 2 in some

locations as described by Nishiura et al. [8], the susceptible pool – which likely includes most individuals – would have to shrink by at least half before the outbreak declined of its own accord [17]. Given the vast populations in affected areas and the disease's high fatality rate, this is clearly not an acceptable scenario.

Stopping transmission will instead require stronger control measures. On 28 August, the WHO issued a road map to provide a plan for the Ebola response [18]. It had three main objectives: (i) to achieve full coverage of control measures in countries with widespread transmission; (ii) to introduce emergency interventions in countries with an index case or small outbreak; and (iii) to strengthen Ebola preparedness in other countries, especially those connected to affected areas.

The scale of the current outbreak means an international response is needed. The threat to Europe and other continents remains low – in countries with strong health systems, an imported case should be straightforward to contain [19] – but without containment the devastation in West Africa will continue. Much of the damage is now coming from knock-on effects on basic healthcare. Not just EVD patients are affected by the outbreak; in cities like the Liberian capital Monrovia, the presence of the infection has led to the closure of most health facilities. As a result, untreated injuries and illnesses are leading to further loss of life.

In collaboration with affected countries, the international community must commit the resources required to control the outbreak. A week ago, Médecins Sans Frontières announced an urgent need for expertise and equipment [20]. As well as financial support, affected countries require experienced healthcare workers and specialists in biological disasters. The response must also include additional protective clothing and isolation units, and diagnostic tools and laboratory testing facilities. Health authorities will need food for those in quarantine too, plus vehicles to transport patients and trace their contacts, and air support to move resources between affected areas.

The scientific community can also support control efforts. Mathematical modelers can help quantify transmission in different areas, and provide short-term forecasts. Researchers are also working on potential drugs and vaccines. On 4 and 5 September 2014, WHO held a meeting to discuss what treatments are currently in development [21]. Testing of these experimental therapies and vaccines will soon start and must be fast-tracked to establish their safety and efficacy.

The effort required to control EVD will inevitably vary by country. In some locations, it has been suggested that the reproduction number could already be near 1; in others it could still be as high as 2 [8]. As pointed out above, the size of the transmission and the reproduction number will be influenced by multiple factors, including the level of public trust in authorities

and health services, as well as behaviours and beliefs shaped by social and cultural traditions. Transmission is also likely to be setting-specific. The reproduction number is an average value: some individuals and interactions will contribute more to transmission than others. The infection will be easier to control if it is possible to identify and target these crucial links in the transmission chain.

Over the past 38 years, there have been more than twenty Ebola outbreaks, and all of them have been successfully contained. Many of the issues currently facing West Africa – from lack of trust in health authorities to poor infection control – have surfaced before, and have been overcome. However, the current outbreak is unprecedented both in size and scale. It will require a response to match.

Conflict of interest

None declared.

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Lactating mothers infected with Ebola virus: EBOV RT-PCR of blood only may be insufficient

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We describe two Ebola virus (EBOV) RT-PCR discordant mother–child pairs. In the first, blood from the breast-feeding mother, recovering from EBOV infection, tested negative twice but her urine tested positive. Her child became infected by EBOV and died. In the second, the breastfed child remained EBOV-negative, although the mother’s blood tested positive. We highlight possible benefits of EBOV RT-PCR testing in urine and breast milk and the need for hygiene counselling when those fluids are EBOV-positive.

We report two Ebola virus (EBOV) RT-PCR discordant mother-child pairs that illustrate that EBOV RT-PCR testing of relevant fluids in addition to blood, such as urine and breast milk, may be useful, in certain instances.

Background

The current West African Ebola virus disease (EVD) epidemic is different from all previous EVD outbreaks [1]. Because of its regional and international distribution, the massive strain on the local health systems in the affected countries and the very large number of persons infected, the current outbreak has evolved into a major humanitarian crisis [2].

Offering patient care to breastfeeding Ebola virus (EBOV) infected women and their children in such a setting can be particularly challenging because evidence-based guidelines about breastfeeding are lacking. This

report of two EBOV RT-PCR discordant mother-child pairs illustrates possible benefits of EBOV RT-PCR testing in urine and breast milk, not just in blood.

Case 1: mother-child pair

In early October 2014, a woman in her late 30s was referred to the Ebola Treatment Centre (ETC) of Médecins Sans Frontières (MSF) in Guéckédou, Guinea because of general malaise and myalgia. She was accompanied by her asymptomatic, almost exclusively breastfed, six-month-old infant.

The patient had taken care of a relative who had developed symptoms compatible with EBOV in early September and had died 12 days after symptom onset. The patient had also organised the funeral. Two days after the relative’s death, she developed high fever, intense fatigue, headache, muscle and abdominal pain, vomiting and diarrhoea. She was admitted to a local hospital where she received oral and intravenous empirical anti-malaria treatment and antibiotics for three days. The diagnosis was unclear. Although she had symptoms compatible with EBOV infection, she was not tested for EVD as EBOV RT-PCR tests were not available.

After three days in hospital, 13 days after the onset of her symptoms, the patient was referred to the ETC of MSF for persistent malaise and myalgia. Upon admission, she was afebrile. Given the clinical history and

the high-risk contact, the patient was admitted to the ETC in the 'suspect' zone of the 'high-risk' area. Her asymptomatic child was housed in a nursery next to the ETC and breastfeeding was stopped. On day 14 of illness, the patient's EBOV RT-PCR blood test (Realstar Filovirus Screen, RT-PCR Kit 1.0, Altona Diagnostics, Hamburg) as well as a rapid malaria test (SD BIOLINE Malaria Ag P.f, Standard Diagnostics Inc.) were negative.

On the same day (day 14 of illness of the mother), the child developed fever (39.1°C), diarrhoea and severe weakness; a malaria rapid test was negative but EBOV RT-PCR test was positive (cycle threshold (CT) value 19.80; CT values <20 are highly positive whereas >35 are weakly positive).

A second EBOV RT-PCR blood test of the mother, 16 days after symptom onset, remained negative but the urine EBOV RT-PCR test from the same day was positive (CT value 29.09). EBOV RT-PCR test of breast milk performed on day 17 after symptom onset was negative and breastfeeding was restarted. The patient had recovered well and was discharged on the same day but the child passed away three days later.

Case 2: mother-child pair

A woman in her mid-20s developed a febrile syndrome four days after having given birth to a healthy baby and was admitted to an MSF ETC in Guéckédou five days later. We note that a close relative of the patient who was present during the delivery, developed symptoms compatible with EVD on the day following the delivery and died one week later. The patient had taken care of this relative.

Upon admission, the patient's temperature was 39°C and she had severe weakness, myalgia, arthralgia, anorexia, dysphagia, hiccups, abdominal pain and diarrhoea. Minor bloody vaginal discharge was noted. An oral antibiotic (cefixime) and anti-malaria treatment were started empirically. On day 6 after onset of illness, a rapid malaria test was negative but an EBOV RT-PCR blood test was positive (CT value 23.92). The clinical course of the patient was favourable and she was declared cured 12 days later (day 18 after onset of illness). After two negative EBOV RT-PCR blood tests, 24 hours apart, she was discharged from hospital. No EBOV RT-PCR of the breast milk was performed.

Upon admission, her infant was 10 days old and had been breastfed since birth. The child was immediately separated from the mother and breastfeeding was stopped. Six days later, the child developed fever (38.9°C). Ceftriaxone and gentamicin were started. Artesunate was also given but stopped after a negative malaria test. EBOV RT-PCR blood tests were negative on day 1 and 3 after onset of fever. Gentamicin was stopped after two days but ceftriaxone continued for eight days with a favourable clinical outcome. The infant rapidly became asymptomatic and was followed

up for 21 days after the last contact with the sick mother. The child did not develop EVD.

Discussion

We describe two EBOV RT-PCR discordant mother-child pairs that illustrate the complexity of taking care of patients with EBOV infection.

If a lactating mother's blood is EBOV RT-PCR negative and has an EBOV-positive breastfed child (Case 1), healthcare workers should investigate whether the mother recently recovered from a confirmed or suspected EBOV infection. The mother's urine and breast milk should be tested by EBOV RT-PCR for shedding of EBOV even after the virus becomes undetectable in the blood [3,4]. The child in Case 1 described, was most likely infected by the mother, however, whether the child became infected through breast milk or through contact with another bodily fluid, remains unknown. We cannot fully rule out the possibility that the source of the child's infection was the relative who was taken care of by the child's mother but this would mean the incubation period of the child was at least 16 days which is long given the average incubation period of 8 to 10 days [5].

Data on how long infective EBOV can be present in other body fluids such as saliva, tears, urine, stool, breast milk, vaginal and amniotic fluid and seminal fluids, are still limited [4]. We do know that in the 36-year-old patient with EVD who was evacuated in August 2014 to an isolation facility in Hamburg, Germany, infective EBOV was still isolated from urine samples on day 26 of his illness, nine days after the clearance of EBOV from plasma [3]. We also know that EBOV can be isolated from convalescent patients in semen up to 82 days after disease onset [6]. However, in a study by Bausch et al., EBOV could not be cultured from the urine in 11 cases, but this might have been caused by virus degradation from breaks in the cold chain during sample collection, storage and shipping [4].

Detection for long periods of time in urine is known for other viruses, such as the West Nile virus [7] but poorly documented for EVD. The added value of EBOV testing of the urine of convalescent patients remains to be determined. Indeed, a positive PCR test does not mean the urine is still infectious and it would be impossible to keep patients with positive EBOV RT-PCR urine or semen tests for months in isolation.

EBOV has been detected in breast milk previously [4] but the timing of EBOV appearance, how long it remains in breast milk in an EBOV-infected lactating mother and the exact risk for a child to become infected through breastfeeding, remain poorly understood. EBOV was isolated from the breast milk of one lactating woman 15 days after disease onset, and after EBOV was already cleared from the blood [4]. We will need prospective studies of mother and child pairs, combining PCR testing with virus culture of breast milk to finally come

up with evidence-based recommendations regarding breastfeeding in cases of lactating mothers with EVD. Although high levels of actively produced IgA in breast milk have been shown to provide limited local mucosal protection for breastfed children against influenza virus infection [8], further studies are needed to determine the cellular and immunologic effects of breast milk-secreted antibodies in EVD patients.

These two cases demonstrate that when caring for mother-child pairs, healthcare workers should consider the potential role of testing relevant body fluids in addition to blood, such as urine and breast milk.

In case of discordant RT-PCR results between an EBOV-positive mother and her EBOV-negative breastfed child, ideally, breastfeeding should be stopped if safe replacement for breastfeeding is available [9]. Otherwise, feeding the child with heat-treated expressed breast milk [10] could be considered. Where a mother has survived EVD, ideally, her breast milk should be confirmed negative for EBOV before resuming breastfeeding. If EBOV RT-PCR diagnostic is not available, it is advised to avoid breastfeeding by EVD-surviving mothers [9].

The possibility of prolonged EBOV shedding in urine and breast milk means that counselling about hygiene in handling those fluids should be an important component of health promotion at the time of discharge from the ETC.

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Conflicts of interest

None declared.

Authors' contributions

Michel Moreau, Craig Spencer, Julia Garcia Gozalbes, Alseny Modey Camara were involved in the care of patients at the ETC in Guéckédou. Sophie Gryseels and Benny Borremans performed the PCR testing. Michel Moreau and Robert Colebunders wrote the first draft. Michel Van Herp, Tom Decroo, Annabelle Lefevre, Antonino Di Caro, Roman Wölfel, Dirk Becker, Stephan Günther, Joseph Bore, Raymond Koundouno, Leentje Peetermans, all reviewed the paper, and their comments were incorporated.

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First secondary case of Ebola outside Africa: epidemiological characteristics and contact monitoring, Spain, September to November 2014

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On 6 October 2014, a case of Ebola virus disease (EVD) acquired outside Africa was detected in Madrid in a healthcare worker who had attended to a repatriated Spanish missionary and used proper personal protective equipment. The patient presented with fever $38.6\text{ }^{\circ}\text{C}$ without other EVD-compatible symptoms in the days before diagnosis. No case of EVD was identified in the 232 contacts investigated. The experience has led to the modification of national protocols.

Introduction

The current Ebola virus disease (EVD) epidemic affecting countries in West Africa is the largest ever registered outbreak of this disease [1]. Ongoing intensive transmission in the community and in healthcare facilities associated with weak health systems including limited human and material resources hinder adequate outbreak control and case management. Healthcare workers (HCW) in these areas have been significantly affected during this epidemic [2-5].

On 7 August 2014, the Spanish government decided to repatriate a Spanish missionary healthcare worker at the St. Joseph's hospital in Monrovia (Liberia) who had tested positive for Ebola virus. On arrival, the person was admitted to the infectious diseases isolation unit at the reference hospital (La Paz-Carlos III Hospital Complex in Madrid). The patient remained hospitalised until his death on 12 August. On 22 September, a second Spanish missionary healthcare worker who had worked at a hospital in Lunsar (Sierra Leone) and who was also suffering from Ebola virus infection was repatriated under the same procedure. This patient was admitted to the same reference hospital where he died on 25 September. One of the HCW who was caring

for the second repatriated Ebola case was diagnosed with EVD on 6 October. This was the first secondary case of this disease outside Africa.

In this paper we describe the epidemiological characteristics and public health control measures adopted after the identification of this first transmission outside the epidemic area. The information and lessons learnt in Spain may contribute to improving preparedness and response guidelines and protocols in non-affected countries. The risk of transmission of Ebola virus to healthcare professionals associated with repatriated patients needs to be reassessed and considered for future surveillance and control measures in these settings [5-7].

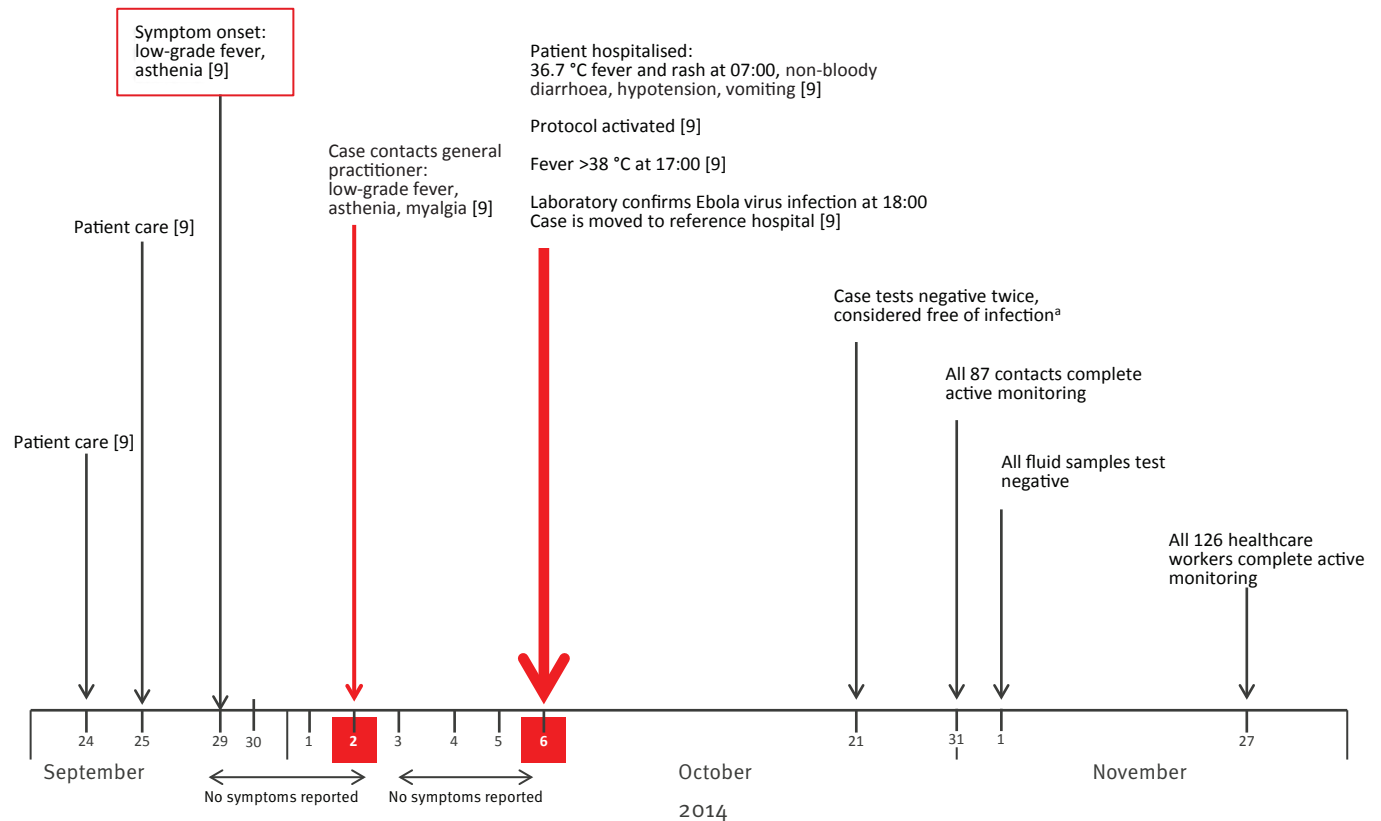
Epidemiological investigation and contact monitoring

Case description

The secondary case of EVD diagnosed in Spain on 6 October was one of the 117 HCW who had participated in the care of the two repatriated EVD cases. The HCW completed the 21-day monitoring period after caring for the first case on 30 August. On 21 and 25 September, she was exposed to the second patient and presumably contaminated fomites. She was classified as a low-risk contact and was therefore self-monitoring for symptoms, in accordance with the protocol [8]. The HCW had used appropriate personal protective equipment (PPE), i.e. waterproof long-sleeved clothing covering the feet, waterproof footwear, hood, face mask or goggles, double layer of gloves, and FP3 respirator [8], and she did not recall any incident during its use.

FIGURE 1

Timeline of events for secondary Ebola case, Madrid, 24 September–27 November 2014



^a Culture results for all body fluids taken on 21 October were negative

Following the established procedures for HCW caring for EVD patients [8], the hospital recommended self-monitoring for 21 days from 25 September onwards. According to these procedures, the HCW was supposed to inform the monitoring official at the hospital in case of fever >38.6 °C and any of the symptoms of the disease: severe headache, vomiting, diarrhoea, abdominal pain or bleeding. On the following day, 26 September, she was off duty. She contacted the monitoring official for the first time on 2 October.

Symptoms started on 29 September. She presented malaise and low-grade fever <38 °C. The grade fever remained at this level for three days and increased to 38 °C in the three following days [9]. Figure 1 shows the evolution and timeline of events.

On 6 October at 04:00, she called the public health officials to report a temperature of 37.3°C, general malaise, nausea and cough. These symptoms led the public health officer to request medical evaluation at home and to refer her to the closest hospital. On admission at 07:00, she had a temperature of 36.7 °C, blood pressure of 90/60 mm Hg, 95% oxygen saturation measured by means of pulse oximetry, and a maculopapular rash. She reported that she had not

received antipyretic agents [9]. At 08:00 on 6 October, the hospital contacted the public health services and they decided to classify the case as under investigation for EVD and send blood samples to the national reference laboratory. The patient's condition worsened in the following hours [9] and at 18:00, the reference laboratory confirmed the diagnosis of EVD. The patient was transferred to the reference hospital under strict isolation measures. The patient received antiviral treatment and convalescent serum from a recovered Ebola patient. On 21 October, the case tested EVD-negative in two samples taken 48 hours apart and, according to protocols, was considered free of Ebola virus infection on 1 November when a PCR test of all body fluid samples yielded negative results. The isolation measures were suspended on the same day, and the patient was finally discharged on 5 November 2014.

Contact monitoring

The epidemiological investigation began at the time of diagnosis. Information on the patient's possible exposure was requested and contact identification, risk classification and monitoring began at the same time. A committee of experts was established for the classification of contacts. High- and low-risk classification criteria and the action taken for each group are

TABLE 1

Classification of contacts and public health measures adopted for the secondary Ebola case, Madrid, 6 October–27 November 2014

CLASSIFICATION OF CONTACTS	PUBLIC HEALTH MEASURES FOR CONTACTS
Low-risk contact	
A person who, with appropriate PPE and without incidences in the use of PPE, had direct contact with a confirmed case, with his/her body fluids or any material that has potentially been contaminated in the course of healthcare;	Active monitoring: professionals responsible for monitoring contacts have daily contact with the monitored individual, measure his/her axillary temperature twice a day and record the presence of any symptom;
A person who has stayed in a closed physical space in which there could have been fomites with biological remains from the case and who does not comply with high-risk contact criteria (e.g. seats in the waiting room, the same surgery, the same ambulance, etc)	The identity of contacts for monitoring is sent to health centres and hospitals (alerts in electronic clinical records) for early detection in case they consult for Ebola-related symptoms. The Blood Donors Centres of the Madrid Region also receive electronic alerts in the clinical records to avoid any incident related to possible blood donations by these individuals.
High-risk contact	
Close contact (distance <1 m), without appropriate PPE or with incidences in the use of PPE, with a confirmed case who was coughing, vomiting, bleeding or had diarrhoea;	Quarantine is indicated. In order to facilitate the compliance with the quarantine, hospital quarantine is offered to these contacts. All contacts included in this group (15 people) agreed to be admitted voluntarily.
Unprotected sexual relation with a confirmed case three months after the onset of symptoms;	
Direct contact with clothing, bedclothes or fomites contaminated with the blood, urine or body fluids of a confirmed case, without appropriate PPE or with incidences in the use of PPE;	
Percutaneous wound (e.g. needle-stick injury) or mucosal exposure to body fluids, tissues or laboratory samples of a confirmed case;	
Healthcare given to a case or handling of his/her samples, without the appropriate PPE or with incidences in the use of PPE.	

TABLE 2

Number of contacts of the secondary Ebola case by exposure place, relationship with case and risk category (high risk contacts in brackets), Madrid, Spain, 29 September–27 November 2014 (n=232)

Relation with case/ place of exposure	Cleaner	Patient/patient's aid	Spouse	HCW	Dog sacrifice	Ambulance technicians	Other	Total
Transport by ambulance ^a	4	12	0	3	0	10	0	29
Primary care	2 (1)	22	0	4 (1)	0	0	0	28 (2)
Home	8 ^b	0	1 (1)	1 (1)	6	0	1	17 (2)
Hospital	2	0	0	7 (7)	0	0	3 (1)	12 (8)
Other activities	0	0	0	2	0	0	7 (3)	9 (3)
Subtotal	16 (1)	34	1 (1)	17 (9)	6	10	11 (4)	95 (15)
HCW at reference hospital	11	0	0	113	0	0	2	126
Reference laboratory	0	0	0	0	0	0	11	11
Total contacts	27 (1)	34	1 (1)	130 (9)	6	10	24 (4)	232 (15)

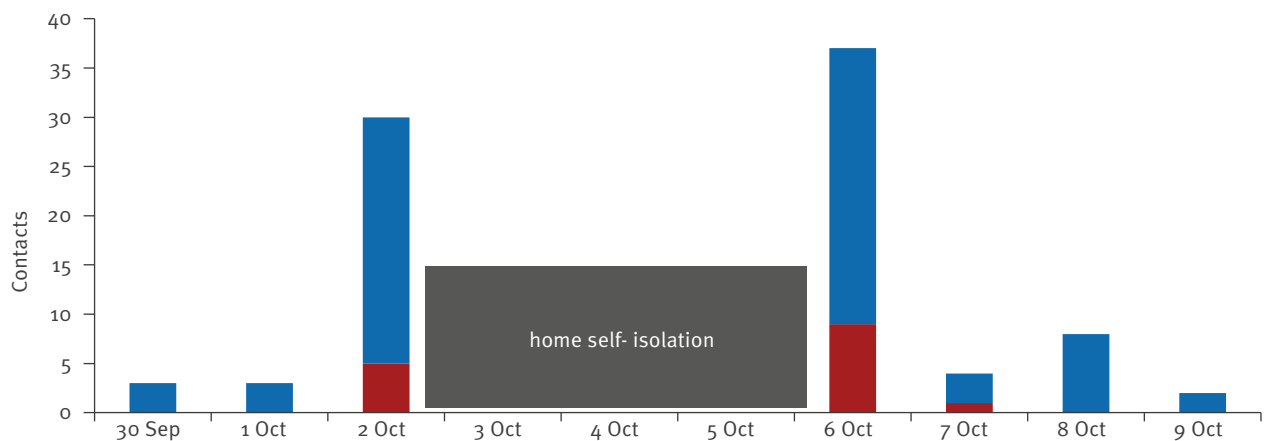
HCW: healthcare worker who attended to the secondary case.

^a Two ambulances: from home to first hospital and from first hospital to reference hospital.

^b The home cleaning was performed on the day after the patient was discharged from hospital.

FIGURE 2

Number of contacts of the secondary Ebola case, by exposure date and risk category^a, Madrid, Spain, 29 September–9 October 2014 (n=87)



	30 Sep	1 Oct	2 Oct	3 Oct	4 Oct	5 Oct	6 Oct	7 Oct	8 Oct	9 Oct
Low risk	3	3	25	0	0	0	28	3	8	2
High risk	0	0	5	0	0	0	9	1	0	0

^a Excluded healthcare workers at the reference hospital, laboratory workers and home cleaners.

presented in Table 1. These actions were adapted from those established in the current protocol [8]. The first epidemiological information was provided by a family member of the patient at the hospital and was completed with available health and administrative records and the locations the patient reported to have visited from onset of symptoms until hospitalisation.

A total of 232 contacts were identified, of whom 15 were classified as high-risk and 217 as low-risk (Table 2). Most contacts, excluding HCW at reference hospital, occurred on the day of diagnosis at the hospital where the diagnosis was established (Figure 2). The 15 contacts classified as high-risk were informed of the risks associated with their contact with the case and were recommended a quarantine, at a hospital facility if possible. All of them voluntarily agreed to undergo hospital quarantine for 21 days after the last exposure day.

One of the low-risk contacts presented fever during the monitoring, but EVD was ruled out.

A total of 126 hospital employees were in contact with the patient during her stay at the hospital. Follow-up ended on 27 November, 21 days after the final exposure of the hospital cleaning staff. By that time, none of the contacts monitored had presented EVD.

Discussion

Action protocols are based on the evidence obtained in the outbreak in Africa [9-11]. Early detection of cases for minimising the probability of transmission is the key aim of contact monitoring. However, when the first

secondary case was diagnosed in Spain, the case definition provided in the existing national protocol and in most international protocols (European Centre for Disease Prevention and Control [12], United States (US) Centers for Disease Control and Prevention [13,14]) required a fever of >38.6 °C and symptoms compatible with the disease. This definition was not sensitive enough to detect this case in the first stages of disease. The non-specific clinical presentation of Ebola also makes early case detection difficult. This situation was also observed in the two secondary cases diagnosed a few days later in the US [15-17].

We would like to draw attention to the ‘paucisymptomatic’ presentation of EVD in infected contacts closely monitored after exposure to confirmed cases outside of the epidemic area in Africa not described up to now.

The public health measures applied immediately to the contacts of the secondary case in Madrid included active monitoring of low-risk contacts and quarantine for high-risk contacts. All contacts accepted these measures. However, in the future it may be necessary to apply the quarantine to more people or to contacts who refuse to be quarantined. In our opinion, it is necessary to develop procedures and laws which would establish and help apply the quarantine.

The experience with the repatriated cases in several non-epidemic countries and the secondary transmissions identified in Spain and in the US have resulted in proposals to modify existing protocols. These proposals [18] include increased sensitivity of the case

definitions for persons under investigation in order to detect possible cases in the initial phases of the disease, particularly for contacts of confirmed cases, and a revision of contact classification and monitoring measures.

The Spanish experience highlights that the generation of secondary cases among HCW caring for repatriated EVD patients represents the currently main risk for Europe as has happened also in US [8,13-15]. The risk is very low, however it can not be excluded [19].

Despite the existence of preparedness and response plans, trained professional teams, 24/7 alert systems and contingency plans for control and response of communicable diseases in both hospitals, the number of exposed contacts among HCW was high. After the secondary case was diagnosed, training and assessment was reinforced for all healthcare professionals involved in the treatment and care of EVD and a committee was set up to classify incidents. This alert shows the need for constant updating and training of professionals in the use of PPE and strict application of donning and doffing procedures in order to minimise the risks. Hence it is necessary to provide adequate risk communication and create awareness in HCW who care for these patients.

Despite the rapid activation of the protocols and control measures, this first case of secondary transmission of EVD outside Africa has represented an unprecedented challenge for the health services and public health authorities in Spain [9,12-14] and has highlighted the need to strengthen continuous preparation and training in order to respond properly to this type of emergency.

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Conflict of interest

None declared.

Authors' contributions

Jenaro Astray and M^a Ángeles López wrote the first draft of the manuscript. M^a Ángeles López managed the Ebola outbreak alert system, Jenaro Astray coordinated the Ebola response team of the Community of Madrid and acted as a liaison to the reference hospital, Maria Ordobás was responsible for contact monitoring, Felicitas Dominguez managed the alert information system, Carmen Álvarez and Manuel Martínez led the Ebola Crisis Committee. Carmen Amela, M^a José Sierra and Fernando Simón coordinated the Ebola response at the national level, and Carmen Amela also participated in the regional Ebola response team. Josep Jansa and Diamantis Plachouras participated in the contact classification and assessment. The working group participated in the fieldwork, conducting epidemiological survey, classifying

cases and contact monitoring. All authors critically read and revised the drafts of the manuscripts.

Members of the working group of the Ebola outbreak investigation team of Madrid

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Management of pregnant women infected with Ebola virus in a treatment centre in Guinea, June 2014

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We report two cases of confirmed Ebola virus disease in pregnant women, who presented at the Médecins Sans Frontières Ebola treatment centre in Guéckédou. Despite the very high risk of death, both pregnant women survived. In both cases the critical decision was made to induce vaginal delivery. We raise a number of considerations regarding the management of Ebola virus-infected pregnant women, including the place of amniocentesis and induced delivery, and whether certain invasive medical acts are justified.

We report two cases of confirmed Ebola virus disease (EVD) in pregnant patients who presented and were treated at the Médecins Sans Frontières (MSF) Ebola treatment centre in Guéckedou. We also raise a number of considerations regarding the role of amniocentesis and induced delivery in the management of pregnant women with EVD.

Description of the cases

Case one

Initial presentation

At the beginning of June 2014, a woman in her late 20s at seven months gestation presented at the Ebola treatment centre in Guéckedou, Guinea, with a history of seven days of asthenia, fever (self-reported), and vomiting. Her past obstetrical history included six vaginal deliveries and no abortions. On admission, physical examination revealed a temperature of 37.1 °C, mild dehydration and the patient reported fetal movement. The Ebola virus (EBV) test (real-time reverse transcription-polymerase chain reaction (RT-PCR)) was positive.

Clinical course and management

On the same day (day 0), the woman was admitted to the EBV treatment/isolation unit where she

immediately started receiving supportive treatment, including Ringer's lactate, antipyretics, ceftriaxone (2 g/day), metoclopramide and omeprazole. The woman responded well to this supportive treatment and by day six of her admission, she was free from symptoms, and reported continuously fetal movements. On day eight and 10, the results of the EBV tests came back negative, and the woman was considered cured. The woman remained in the unit for further monitoring.

On day 11, the woman's temperature rose to 38 °C, and further examination revealed that fetal movements and heartbeat had stopped. Cervical examination showed no uterine contractions, no cervical dilation, no blood or other discharge. Intravenous metronidazole was added for suspected chorioamnionitis. To evaluate the possibility of maternal-to-fetal EBV transmission, an amniocentesis was performed. The clear-coloured amniotic fluid contained a high Ebola viral load (corresponding to a real-time RT-PCR cycle threshold (CT) value of 21.29).

On day 15, the patient was afebrile. An assisted delivery was organised to take place in the high-risk zone of the treatment centre. Labour induction with misoprostol resulted in a vaginal delivery of a stillborn male fetus (first degree maceration). The placenta was complete. No episiotomy was required, uterine bimanual massage, oxytocin (10 Units intravenous) and ergometrine (one vial of 0.2 mg intramuscular) helped obtaining normal uterine retraction and prevented any excessive post-partum bleeding. The samples from the placenta (maternal and fetal side), meconium, and the fetus (intra-cardiac aspiration, throat swab, ear swab, umbilical cord) were EBV positive (Table). The patient was afebrile after delivery, and was discharged on day 18. A seven-days post-natal consultation (PNC) showed a normal evolution.

TABLE

Test results from maternal and fetal samples taken from two pregnant patients during their stay at the Ebola treatment centre, Guéckédou, Guinea, June 2014

Timeline	Specimen type	Ebola virus load result (CT value)	Semi-quantitative viral load result	Other results
Patient 1				
Day 0 (admission)	Blood (mother)	Positive (21.29)	+++	Malaria negative
Day 8	Blood (mother)	Negative (-)	-	IgG positive ($\geq 1:1,280$) IgM positive ($\geq 1:320$)
Day 10	Blood (mother)	Negative (-)	-	-
Day 12	Amniotic fluid (amniocentesis)	Positive (23.31)	+++	-
Day 15	Amniotic fluid (fetal mouth swab)	Positive (21.41)	+++	-
Day 15	Amniotic fluid (fetal ear swab)	Positive (24.78)	+++	-
Day 15	Placenta (fetal side)	Positive (24,12)	+++	-
Day 15	Placenta (maternal side)	Positive (19,23)	+++	-
Day 15	Fetal blood – sample 1	Positive (16,13)	+++	-
Day 15	Fetal blood – sample 2	Positive (23.6)	+++	-
Day 15	Fetal meconium (anus swab)	Positive (20,32)	+++	-
Day 18	Blood (mother)	Negative (-)	-	-
Patient 2				
Day 1 ^a	Blood (mother)	Positive (26.46)	++	Malaria positive
Day 7	Blood (mother)	Positive (25,43)	++	-
Day 11	Amniotic fluid (mouth swab)	Positive (24.10)	+++	-
Day 11	Amniotic fluid (fetal ear swab)	Positive (28.82)	++	-
Day 11	Placenta (fetal side)	Positive (14.22)	+++	-
Day 11	Placenta (maternal side)	Positive (19.98)	+++	-
Day 11	Fetal meconium (anus swab)	Negative (-)	-	-
Day 16	Blood (mother)	Negative (-)	-	-
Day 18	Blood (mother)	Negative (-)	-	-

CT: cycle threshold; NA: not available; RT-PCR: reverse transcription-polymerase chain reaction.

^a Patient 2 first presented at the treatment centre in the afternoon (day 0) so the result of Ebola virus testing was available the next day (day 1).

Real-time RT-PCR was performed with the Smart Cycler. The obtained CT values correspond with the accumulation of the fluorescent signal and are inversely proportional with the viral load. CT values are classified in subsequent categories of 0–25, 25–35 and 35–40 and correspond with + + +, + + and + results.

When the real-time RT-PCR was negative this is indicated for the viral load by a – result.

Case two

Initial presentation

In mid-June 2014 a primipara in her early 20s at seven months gestation presented with a history of five days of arthralgia, asthenia, diarrhoea, fever (self-reported) and headache. The patient presented with a history of grade III female genital mutilation (FGM). On admission, the patient had a temperature of 38.4 °C, and reported fetal movements and no contractions.

Clinical course and management

On the next day (day 1), the EBV test and malaria rapid test were positive. The patient's fever worsened (39.5 °C), and she had an onset of haematuria and cough. The patient reported fetal movements had

stopped. Supportive treatment included intravenous ampicillin and metronidazole for a possible chorioamnionitis, as well as intravenous artesunate (malaria treatment) and Ringer's lactate.

On day five, the patient's systolic blood pressure dropped to 60 mmHg (norm: 90–119) and additional fluids were intravenously administered. On day eight, the patient presented with symmetrical oedema of the lower extremities. Obstetrical examination revealed a hypertonic uterus, transverse or breech presentation, no fetal heartbeat, cervical dilation of one centimeter in diameter, and no discharge. Despite the risk, ketamine anaesthesia was provided, external version manoeuvres were performed, and the fetus was rendered in cephalic presentation.

On day 10, the patient was disoriented and presented with anasarca. On the morning of day 11, the patient was found unconscious, with the fetal head intra-vaginal. Ketamine was administered, an episiotomy was performed, and a male stillborn fetus was delivered vaginally. The placenta was complete. Urinary retention complicated uterine retraction, and uterine bi-manual massage was employed together with the administration of oxytocin (10 U) and ergometrine (1 vial of 0.2mg). Post-partum haemorrhage only stopped after repeatedly (five times) packing the uterus with gauze. Due to the FGM, bladder catheterisation was unsuccessful. Urine was aspirated through a supra-pubic bladder paracentesis (the urine was not tested for EBV). A final vaginal and uterine exploration showed no further complications. The samples from the placenta (maternal and fetal side) and the fetus (throat swab, ear swab) were EBV positive. The sample from the meconium was negative (Table). No pericardial puncture was performed.

On day 12, the patient regained consciousness, and spontaneous diuresis resumed after a single dose dexamethasone injection. The patient had a temperature of 40 °C. Gentamicin was added to the treatment. Over the next six days the patient improved clinically. On day 17, the patient was afebrile. On day 16 and 18, EBV tests were negative and the patient was considered cured. The patient was discharged on day 19. She did not attend her scheduled appointment seven-days PNC.

Ebola virus outbreak in West Africa

In March 2014, an EVD outbreak was declared in Guéckedou, Guinea, following which it spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali [1,2]. The viral strain responsible for the current outbreak has been identified as the Zaire strain, a particularly virulent strain associated with mortality rates as high as 90% [1]. Overall, by 21 November 2014, 15,351 individuals have become infected and 5,459 of these have died. Among those infected, 588 were healthcare workers and 377 of these have died [2]. Patients with EVD generally present with a history of contact with another person with EVD and an abrupt onset of a non-specific febrile syndrome. A systemic inflammatory response can cause multiple organ failure and shock [3,4]. Pregnant women are reported to be at higher risk to die [5].

Since the onset of the outbreak in Guinea, MSF has set up and is running six Ebola treatment centres – including one in Guékédou where the outbreak began.

Discussion

There are very few studies reporting on maternal and fetal outcomes of pregnant women infected with EBV. We report on two cases of pregnant women infected with EBV in Guinea. Despite pregnant women being at higher risk of more severe disease and mortality [5],

both women survived. Both fetuses unfortunately died in utero. This case report raises a number of important points for discussion regarding the management of pregnant women infected with EBV.

Although our findings are based on two cases only, they depict a more positive picture of the maternal outcomes of EVD during pregnancy. In both cases the delivery occurred during the healing phase, when the EBV viraemia in the pregnant woman was controlled, and when clotting had probably returned to normal. During previous outbreaks also caused by the Zaire strain, such as in the Democratic Republic of the Congo (DRC) 1976 Yambuku outbreak, only nine (11%) of 82 EBV infected pregnant women were reported to have survived [6]. Similarly, during another EBV outbreak in the DRC 20 years later (1995 in Kikwit) only one (7%) of 15 pregnant women was reported to have survived, and EBV-infected pregnant women had a notably higher mortality rate (93%) than non-pregnant EBV-infected women (70%) [5]. For the current outbreak, data on pregnancy are not routinely reported so overall figures on the survival of pregnant women and their unborn children or neonates are not available at this point.

Despite the two women described in this report surviving, in both cases the fetus died in utero. There is not much chance for the fetus to survive EBV infection. A massive infection of the fetus is likely to occur through the placenta. Furthermore maternal immunoglobulins M are poorly transported through placental villi and the fetal secretory immune system starts producing immunoglobulin M around the 20th week of gestation [7]. Fetal and neonate mortality was equally reported high in other outbreaks. In Yambuku, 11 live neonates were born to EBV-infected women and all died within 19 days [6]. In Yambuku and Kikwit, abortion occurred among 19 of 82 (23%) and 10 of 15 (67%) infected pregnant women respectively [5,6]. In Kikwit the only surviving pregnant patient had an abortion [5]. In Yambuku, one of the nine survivors aborted in the treatment centre. Abortions occurred spontaneously, likely because of fetal death due to EBV infection. Unfortunately the pregnancy outcomes of the other pregnant EVD survivors were not reported [6].

This is the first description of the use of amniocentesis to determine the presence of intrauterine EBV infection. In the case of the first patient, despite her having an undetectable viral load and declared cured before the demise of the fetus, a subsequent amniocentesis revealed a high viral load in the amniotic fluid. For this reason, a vaginal delivery was arranged to take place in the high-risk zone of the EVD treatment centre. In the absence of the amniocentesis, the recovered EBV negative patient might have been referred to the local maternity for delivery, exposing the maternity staff to a very high risk of EBV infection. Alternatively, she might have had a spontaneous abortion at home with potential risk of subsequent transmission of EBV to household contacts. In the second case, an emergency

delivery was required and performed at the EVD treatment centre after the patient was found in shock, with intra-vaginal fetal head. This delivery also took place in the high-risk zone of the centre and episiotomy was justified due to the grade III FGM. Post-partum, an amniotic fluid sample was taken from the dead fetus through an oral swab and yielded a high EBV viral load.

For both cases, the assisted delivery occurred a few days after fetal movement had reportedly stopped. As these were the first induced deliveries of EBV infected pregnant women, careful planning had to be considered as well precautionary measures, given the high risk of nosocomial transmission to healthcare workers [3]. Moreover, based on previous reports [5,6], it was also taken into account that spontaneous abortions could occur shortly after fetal death, limiting the need for invasive procedures, and reducing the risk to healthcare staff.

During both deliveries, strict barrier nursing techniques were used. Full protective equipment included scrubs, waterproof overall, apron, boots, N95 masks, head cover, goggles, a double pair of gloves and arm-length gynaecological gloves (three layers of gloving). Absorbent pads were laid underneath the patients to absorb a maximal amount of fluids. Two pads were laid over the abdomen and the perineal region to limit splashing. Biomedical waste was gathered in the immediate proximity of the patient, and regularly sprayed with 0.5% chlorine solution. None of the five healthcare workers who were present during the deliveries reported here became infected.

These two case presentations raise a number of considerations regarding the management of pregnant women infected with EBV including the role of amniocentesis and induced delivery, and whether certain invasive medical procedures are justified, despite the inherent risk for healthcare workers.

In conclusion, our case report adds to the scarce body of literature on the outcomes of pregnant women infected with EBV. We also highlight some important considerations in the management of such patients and describe, for the first time, the use of amniocentesis to detect fetal infection with EBV.

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Conflict of interest

None declared.

Authors' contribution

Fernanda Mendez Baggi, Aicha Taybi, Andreas Kurth, and Sylvie Jonckheere collected data in the MSF Ebola treatment centre in Guékédou, and wrote the first draft. Michel Van Herp, Antonino Di Caro, Roman Wölfel, Stephan Günther, Hilde Declerck, and Tom Decroo all reviewed the first draft and final version of the paper, and their comments were incorporated.

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Describing readmissions to an Ebola case management centre (CMC), Sierra Leone, 2014

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Case management centres (CMCs) are part of the outbreak control plan for Ebola virus disease (EVD). A CMC in Sierra Leone had 33% (138/419) of primary admissions discharged as EVD negative (not a case). Fifteen of these were readmitted within 21 days, nine of which were EVD positive. All readmissions had contact with an Ebola case in the community in the previous 21 days indicating that the infection was likely acquired outside the CMC.

Between 26 June and 1 September 2014, 138 patients were discharged from the Kailahun Ebola case management centre (CMC) in Sierra Leone, as non-Ebola virus disease (EVD) cases, because they tested negative for the virus by polymerase chain reaction (PCR). Of these, 15 returned to the CMC within 21 days of their first admission and subsequently nine tested positive for Ebola virus. This raised the question as to whether CMCs could be acting as potential amplifiers of infection even though appropriate infection control measures are being followed. Such a question is of public health importance to the overall future control of the EVD outbreak, which is ongoing in West Africa [1]. To our knowledge, there is no literature available which describes the evolution of readmissions to Ebola CMCs during an outbreak and this paper addresses that deficit.

Ebola virus disease outbreak in West Africa

The current EVD outbreak in West Africa commenced in Guinea in December 2013 [1] and since then has spread to Sierra Leone, Liberia, Nigeria and Senegal [2]. It is the largest EVD outbreak recorded in history [2] with 6,553 (suspected, probable and confirmed) cases and 3,083 deaths reported as of 23 September 2014 in affected countries [2]. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 8 August 2014 [3].

During EVD outbreaks transmission via infected body fluids occurs in three settings: (i) community, through

contact with an infected person or contaminated fomites, (ii) burials, due to touching dead bodies, and (iii) nosocomial, via lack of infection control measures within healthcare facilities. In particular, the latter two settings [4] can quickly amplify an Ebola epidemic [5,6]. The incubation period of the virus ranges from two to 21 days [5,7].

Description on the Kailahun Ebola case management centre

Médecins Sans Frontières (MSF) have six Ebola CMCs operational in West Africa, one of which is based in Kailahun, Sierra Leone. Suspected, probable and confirmed case definitions are equivalent to those used by the WHO [8]. In brief, a suspected case is any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a person with suspected, probable or confirmed EVD or with a dead or sick animal; any person with sudden onset of high fever and at least three of the following symptoms: abdominal pain, anorexia, arthralgia, diarrhoea, dysphagia, dyspnoea, headache, hiccups, lethargy, myalgia, or vomiting; or any person who had unexplained haemorrhagic symptoms or who died suddenly from an unexplained cause. A probable case is any person suspected to have EVD who was evaluated by a physician or any person who died from suspected EVD and had an epidemiological link with a confirmed case but was not tested and did not have laboratory confirmation of the disease. Suspect or probable cases are classified as confirmed when they had a positive laboratory test for EVD.

The Kailahun CMC (KCMC) is divided into a high risk zone and a low risk zone (Figure 1). The low risk zone includes the medical and nursing administrative tents, laundry area, storage area and other necessary facilities to support the high risk zone. Within the high risk zone personal protective equipment (PPE) must be worn at all times. The high risk zone comprises: a suspected cases ward, a probable cases ward and eight confirmed cases wards. A barrier fence separates the

confirmed cases wards from the suspected and probable cases wards preventing patient interaction between these two types of wards.

Following medical assessment in triage, patients are referred to the suspected or probable cases ward depending on their case classification. An EVD PCR test (developed in-house by the Public Health Agency of Canada) on a blood sample is then performed. If this is positive the patient is transferred to the confirmed cases ward for further medical support while a negative result allows the patient to be discharged from the CMC. When a patient has a negative PCR result but symptom duration of less than 72 hours, a repeat PCR test is performed at 72 hours or more of symptoms to rule out a false negative result [9]. A patient can spend from less than 24 hours up to three days in the suspect/probable section of the CMC while awaiting the exclusion or confirmation of EVD. When PCR negative patients are discharged, they are considered exposed, and are added to the contact list. Patients who are discharged negative for EVD (not a case) from the suspect/probable wards have the potential to be readmitted at a later date, and test either positive or negative for EVD. When readmissions test positive, they can cause anxiety among medical staff as they try to decipher if the patients have had any other EVD contact history apart from their previous primary assessment in the CMC.

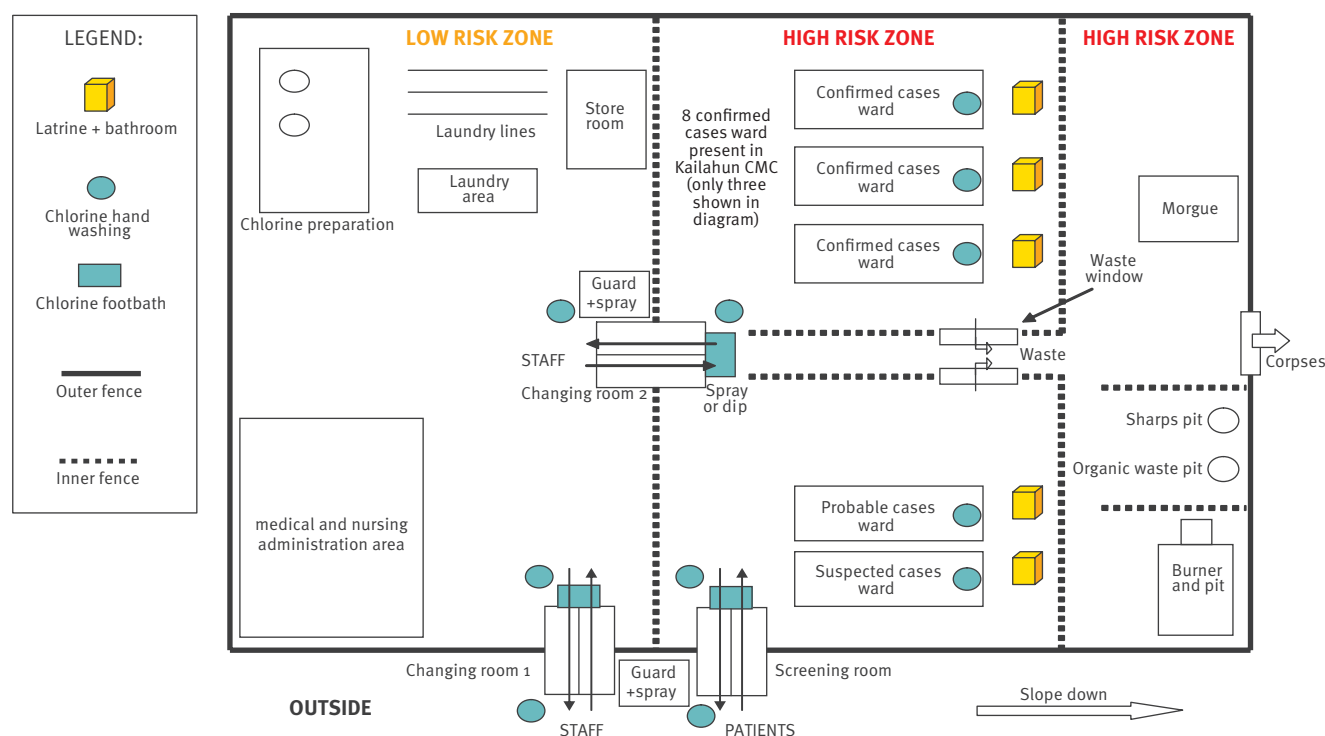
Collection of readmission data at the Kailahun Ebola case management centre and data analyses

A patient register is maintained at the KCMC. It contains basic demographic, epidemiological, medical, laboratory and outcome data for each patient admitted to the facility in Excel 2010 format. All data are stored in a secure manner. To be classified as a readmission a patient must have at least two admission episodes to the CMC that have identical first name, surname, age, sex and address information. All patient readmissions since 26 June 2014 with their corresponding original admissions were extracted from the database. No time limit was imposed on the interval between admission and corresponding readmission when selecting cases. Outcomes for patients were classified as one of the following: cured, dead or not a case. Cured patients had been admitted with a positive EVD PCR and ultimately discharged alive with a negative EVD PCR. Patients classified as dead, had a positive EVD PCR at admission and subsequently died in the CMC from EVD-related complications. The not a case outcome referred to patients who were admitted to the suspect or probable wards, tested negative for the virus by EVD PCR and were then discharged from the CMC.

The crude readmission ratio (CRR) was calculated as the total number of readmissions as a proportion of all 'not a case' primary discharges. Furthermore, the positive readmission ratio (PRR) was defined as the number

FIGURE 1

Outline map of Médecins Sans Frontières (MSF) Ebola case management centre (CMC)



Source: Sterk E. Filovirus haemorrhagic fever guideline. Geneva: Médecins Sans Frontières; 2008.

of readmissions with a positive EVD PCR as a proportion of all 'not a case' primary discharges.

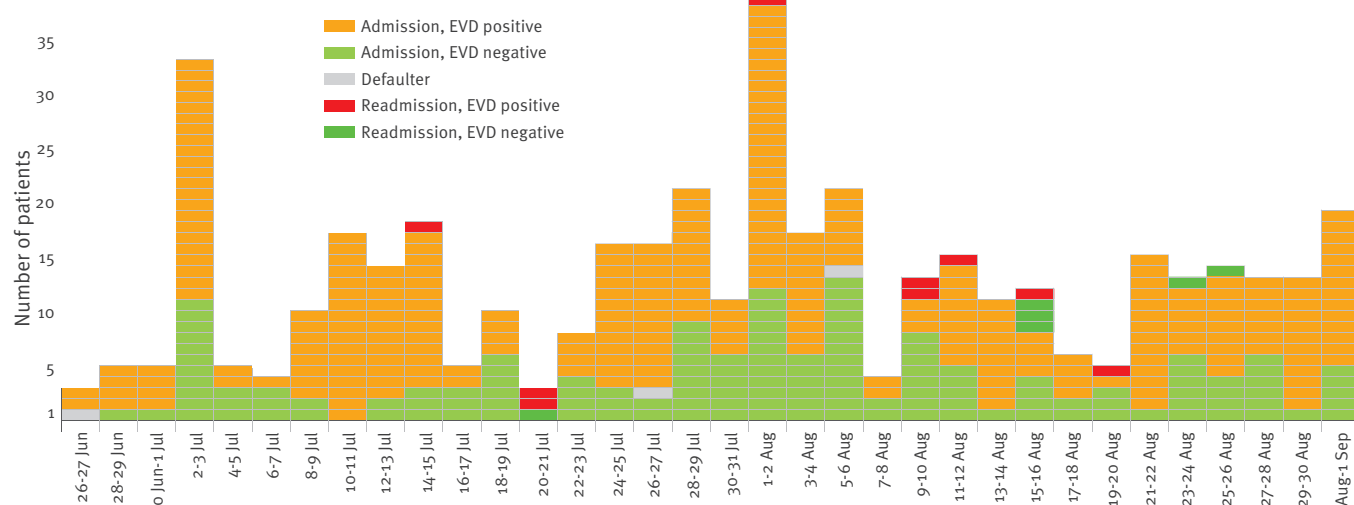
This study fulfilled the MSF Ethics Review Board (Geneva, Switzerland) approved criteria for analysis of routinely collected anonymous programme data. All activities conducted by MSF were approved by the national authorities of Sierra Leone.

Results

Between 26 June and 1 September 2014 (study period), there were 419 primary admissions at the KCMC. Of these, 278 (66%) were EVD PCR positive and 138 (33%) were EVD PCR negative. Three (<1%) admitted patients did not stay long enough in the centre to be tested for EVD (defaulters). During the same period there were 16 readmissions at KCMC. One readmission was

FIGURE 2

Distribution of readmissions to the Ebola case management centre (CMC), Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15 readmissions)



EVD: Ebola virus disease.

TABLE 1

Primary admission and corresponding readmission outcomes, Ebola case management centre (CMC), Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15)

Patient number	Primary admission				Secondary admission (readmission)			
	Time between symptom onset and admission	LOS	EVD PCR result	Outcome	Time between symptom onset and admission	LOS	EVD PCR result	Outcome
1	Unknown	2 days	Negative	Not a case	Unknown	22 days	Positive	Cured
2	0 day	3 days	Negative	Not a case	2 days	5 days	Positive	Death
3	1 day	2 days	Negative	Not a case	1 day	3 days	Negative	Not a case
4	1 day	2 days	Negative	Not a case	1 day	7 days	Positive	Death
5	8 days	1 day	Negative	Not a case	1 day	4 days	Negative	Not a case
6	2 days	2 days	Negative	Not a case	1 day	14 days	Positive	Death
7	3 days	1 day	Negative	Not a case	3 days	21 days	Positive	Cured
8	1 day	3 days	Negative	Not a case	3 days	2 days	Positive	Death
9	9 days	3 days	Negative	Not a case	2 days	23 days	Positive	Cured
10	0 day	2 days	Negative	Not a case	6 days	2 days	Negative	Not a case
11	3 days	1 day	Negative	Not a case	4 days	Current inpatient	Positive	Current inpatient
12	3 days	1 day	Negative	Not a case	1 day	7 days	Positive	Death
13	5 days	6 hours	Not performed	Defaulter	4 days	1 day	Negative	Not a case
14	1 day	3 days	Negative	Not a case	3 days	1 day	Negative	Not a case
15	1 day	2 days	Negative	Not a case	1 day	3 days	Negative	Not a case

EVD: Ebola virus disease; LOS: length of stay; PCR: polymerase chain reaction.

discordant for age (14 years versus 24 years) when compared with the original corresponding admission and was excluded from the analysis. The remaining 15 met the criteria to be defined as readmissions as described in the methodology. Taking these 15 readmissions into account, the KCMC had a total of 434 admissions during the study period, of which 239 (55%) were male. The mean age of admissions was 29.9 years and 106 (24%) were aged 18 years or less.

All 15 readmissions had only one previous admission. One patient did not have an EVD PCR result upon the first admission, as this person left the centre before testing could be done. The 14 remaining readmissions were all related to a prior admission whereby the PCR result was negative for EVD. The distribution of readmissions among all admissions to the KCMC is presented on the epidemiological curve in Figure 2. It shows that four readmissions occurred during the first half of the outbreak while the remaining 11 presented in the second half.

Of the 15 readmissions, seven were male and four were aged 18 years or less. The mean age of readmissions was 27.9 years (range: 1.75–48 years).

A positive EVD PCR test was obtained for nine readmissions of which five died, three were cured and one is a current inpatient at KCMC (Table 1). The crude readmission ratio (CRR) for KCMC was 11% (15/138) while the positive readmission ratio (PRR) was 7% (9/138). The average length of stay (LOS) at the KCMC for primary admissions linked to any readmission was 1.9 days (28/15) whereas the average LOS for primary admissions with corresponding EVD PCR positive and negative readmissions was 2 (18/9) and 1.7 (10/6) days respectively. Regarding the three readmissions who were cured, they had an average LOS after readmission of 22 days (66/3) while the five readmissions who died and six who were not a case had an average LOS of seven (35/5) and 2.3 (14/6) days respectively (Table 1).

The interval between discharge from primary admission and follow-up readmission to the KCMC for all readmissions was an average of 9.4 days with a range from four to 21 days (Table 2). Cases 1 to 15 also had a documented epidemiological contact with a suspected or confirmed case of Ebola (excluding their primary admission to the KCMC) within the prior 21 days to their readmission to the KCMC (Table 2). The majority (10/15) of these epidemiological contact types were household followed by occupational (3/15) and funeral (2/15) (Table 2).

Discussion

In response to the current EVD outbreak in West Africa, numerous Ebola CMCs are operating concurrently in the region [3]. MSF has previously set the standard for constructing and managing these centres in remote African settings [9,10]. The literature indicates that hospitals with inadequate infection control procedures

have previously augmented filovirus outbreaks while appropriately run CMCs help contain them [4]. The emerging situation in Sierra Leone of patients who were initially discharged as non-cases from the KCMC and then returning as EVD PCR positive cases within 21 days has caused medical staff to question if CMCs are acting as potential amplifiers of infection during this outbreak even though appropriate infection control measures are being followed. Such a question is of public health importance to the overall future control of the outbreak.

This study has demonstrated that 7% of patients who were originally discharged as non-cases were readmitted as EVD PCR positive cases. Notably all readmissions occurred within 21 days of primary admission discharge, which is equivalent to the incubation period of EVD. This readmission's timeframe raises the possibility of nosocomial infection having occurred during the primary admission. The average LOS for primary admissions linked to positive readmissions was two days, during which time patients were admitted to the suspect and probable wards of the CMC. Infection control measures are strictly enforced in these wards, which are separated by barrier fencing from the confirmed wards in order to minimise the risk of nosocomial infection. Patients in the suspect/probable wards are encouraged to maintain a minimum distance from other patients at all times and not to touch or use items belonging to other patients. The number of cases per ward is capped to prevent overcrowding. Chlorine solution hand washing facilities are located at multiple points for patient and staff use. Patients can only be transferred from suspect/probable to confirmed wards and not vice versa to prevent spread of infection within the CMC. Hygienist staff regularly disinfects all areas within both the low and high risk zones. The implementation of strict infection control protocol in the suspect/probable wards and the wider CMC in general reduces but can never eliminate the hazard of nosocomial EVD infection.

Importantly, all readmissions to the KCMC had documented epidemiological contacts with suspected or confirmed Ebola cases within the previous 21 days that did not include the original admission to the KCMC. This is a relatively reassuring finding as it acts as a counter weight to the fact that all readmissions occurred within the incubation period of EVD. The source of infection for positive readmissions is as likely to be the household, funeral and occupational contacts documented, as the primary admission to the KCMC. Positive readmissions partly reflect the continuous intense transmission of the virus in the surrounding community.

It is notable that patients who were discharged as not a case had an average LOS of almost two days in the suspect or probable wards. Unfortunately, it was not possible to distinguish between suspect and probable admissions and readmissions, as this information was not sufficiently recorded on the case investigation

TABLE 2

Epidemiological contact information for readmissions to the Ebola case management centre, Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15 readmissions)

Patient number	Interval (days) between primary admission discharge and readmission	Presence of an epidemiological contact explaining readmission (excluding primary admission to KCMC)	Type of epidemiological contact prior to readmission (excluding primary admission to KCMC)	Interval (days) between most recent epidemiological contact (excluding primary admission to KCMC) and symptom onset prior to readmission	Epidemiological contact information
1 ^a	4	Yes	Household	6	Patient 1 lived with two family members who were both admitted to KCMC six days before patient 1 was readmitted to KCMC. The two family members (EVD positive) respectively died three and four days after their admission.
2 ^a	6	Yes	Funeral	9	Patient 2 lived with respective spouse who died of suspected EVD 11 days before patient 2 was readmitted to KCMC. Patient 2 had touched the body during the funeral.
3	4	Yes	Household	5	Patient 3 lived with three persons and patient 4. The first of these three persons was admitted to KCMC eight days before patient 3 was readmitted to KCMC and the two others six days before. All were EVD positive, two died and one was cured. Patient 4 was admitted to KCMC the same day as patient three.
4 ^a	4	Yes	Household	5	Patient 4 lived with three persons and patient 3. The first of these three persons was admitted to KCMC eight days before patient 4 was readmitted to KCMC and the two others six days before. All were EVD positive, two died and one was cured. Patient 3 was readmitted to KCMC the same day as patient 4 but never developed EVD.
5	21	Yes	Occupational	Continual exposure	Patient 5 worked for the Ministry of Health burial team, a high risk occupation for developing EVD.
6 ^a	6	Yes	Funeral	9	Patient 6 lived with respective mother who died of suspected EVD 10 days before patient 6 was readmitted to KCMC. Patient 6 touched the body during the funeral.
7 ^a	12	Yes	Household	12	Patient 7 lived with five extended family members who were all admitted (all EVD positive) to KCMC 15 days before this patient was readmitted to KCMC. All were cured subsequent to medical care.
8 ^a	14	Yes	Household	2	Patient 8 lived with two family members. One was admitted to KCMC (EVD positive) 17 days before patient 8 was readmitted to KCMC and was subsequently discharged as cured five days later, the other was admitted to KCMC five days before patient 8 was readmitted to KCMC and then discharged as cured 23 days later.
9 ^a	9	Yes	Household	10	Patient 9 lived with two family members. One was admitted (EVD positive) to KCMC 12 days before patient 9 was readmitted to KCMC and subsequently discharged as cured five days later. The other was admitted to KCMC five days after patient 9 was readmitted to the KCMC. This person died three days after being admitted.
10	12	Yes	Household	8	Patient 10 lived with five family members, who were admitted (all positive for EVD) to KCMC 14 days before patient 10 was first admitted to the KCMC. Three of the family members died and two were subsequently discharged as cured.
11 ^a	14	Yes	Occupational	Continual exposure	Patient 11 worked as a nurse, a high risk occupation for developing EVD.
12 ^a	5	Yes	Household	3	Patient 12 lived with a family member who was admitted to KCMC the same day than patient 12 was readmitted to KCMC and who died five days later.
13	9	Yes	Household	11	Patient 13 lived with a family member and two children. The two children were admitted to KCMC 16 days before patient 13 was readmitted to the KCMC. One child died four days later and the other was discharged as cured 16 days after admission.
14	16	Yes	Occupational	Continual exposure	Patient 14 worked as a laboratory technician, a high risk occupation for developing EVD.
15	5	Yes	Household	10	Patient 15 lived with respective spouse who was admitted to KCMC (EVD positive) 11 days before patient 15 was readmitted to KCMC. The spouse died four days after respective admission.

EVD: Ebola virus disease; KCMC: Kailahun Ebola case management centre.

^a Patient who tested positive for EVD after readmission.

forms. Efforts are ongoing to collect this information in a more systematic manner in the field. There are multiple reasons for the LOS of almost two days including the lack of availability of a 24 hour laboratory service on-site to process blood samples and the restriction of the phlebotomy service to morning times only due to staff workload and safety concerns regarding performing venesection at night time. A proportion of newly admitted patients will require a repeat EVD PCR test if symptom duration has been less than 72 hours to rule out a false negative result [9]. In such cases the symptomatic patient will have to spend additional time in the suspect or probable ward until a repeat test is performed at the appropriate time. However, for newly arrived patients who already had a minimum of three days of symptoms, it is imperative that phlebotomy and laboratory analysis be performed as quickly as reasonably possible in order to prevent the risk of potential nosocomial EVD infection to patients who could be non-cases staying overnight in the suspect or probable wards. Ideally, phlebotomy and laboratory analysis at the CMC should be provided on a 24 hour basis where feasible. Furthermore, new bedside rapid diagnostic tests (RDT) for EVD that do not require phlebotomy are urgently needed. Such technology improves the timeliness of diagnosis for patients and reduces the risk of infections for healthcare staff.

The epidemiological curve showed that the majority of readmissions occurred during the second half of the outbreak to date. Readmissions can only develop from the pool of discharged non-cases because EVD positive cases have immunity to the specific strain if they survive to discharge [11,12]. On further inspection of the epidemiological curve it appears that positive readmissions have clustered following peaks in primary admissions. The clustering of three positive readmissions between 15 and 21 July and five positive readmissions between 10 and 19 August occurred within 21 days of the primary admissions peaks on 2 and 3 July and on 1 and 2 August respectively. The clustering of readmissions following primary admission peaks within the EVD incubation period suggests the possibility of the presence of superspreaders of the virus.

This study has shown the importance of analysing CMC readmissions to understand what exposures contribute to positive readmissions and to detect potential nosocomial EVD infection when no other sources of infection can be identified. For all positive readmissions described in this study an exposure, in addition to the primary admission, was identified within the EVD incubation period.

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Conflict of interest

None declared.

Author's contributions

Gabriel Fitzpatrick collected data in the MSF CMC in Sierra Leone and wrote the first draft of the paper and incorporated all co-authors comments into the final draft of the paper. Florian Vogt, Osman Bamba Moi Gbabai, Benjamin Black, Maud Santantonio, Elin Folkesson, Tom Decroo and Michel Van Herp all reviewed the paper and submitted their comments, which were included in the final draft of the paper.

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Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014

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We analyse up-to-date epidemiological data of the Ebola virus disease outbreak in Nigeria as of 1 October 2014 in order to estimate the case fatality rate, the proportion of healthcare workers infected and the transmission tree. We also model the impact of control interventions on the size of the epidemic. Results indicate that Nigeria's quick and forceful implementation of control interventions was determinant in controlling the outbreak rapidly and avoiding a far worse scenario in this country.

Outbreak details

The largest Ebola virus disease (EVD) outbreak to date is ongoing in West Africa, particularly in Guinea, Sierra Leone and Liberia, with a total of 7,178 reported cases including 3,338 deaths as of 1 October 2014 [1]. A total of 20 EVD cases (19 laboratory confirmed, one probable) have been reported in Nigeria, with no new cases reported since 5 September 2014. All 20 cases stemmed from a single importation from a traveller returning from Liberia on 20 July 2014 [2]. The Nigerian index case had visited and cared for a sibling in Liberia who died from the disease on 8 July 2014 [2,3]. Despite being aware of his exposure to Ebolavirus in Liberia, the index case flew from Liberia to Lagos, Nigeria, on a commercial airplane on 20 July 2014, with a stopover in Lomé, Togo. The case became symptomatic while flying and collapsed at Lagos airport upon landing, which prompted him to seek medical attention and led to a number of people being exposed to Ebolavirus. Epidemiological investigation revealed that the index case had contracted Ebolavirus in Liberia; the patient died on 25 July 2014 [4].

A total of 894 contacts were subsequently linked to this index case, including the primary, secondary and tertiary contacts [2].** Importantly, one of the primary contacts of the index case had travelled to Port Harcourt, the capital of Rivers State, at the end of July 2014 and was cared for by a healthcare professional who subsequently became infected and died on 22 August 2014. This deceased healthcare worker was in turn linked to a total of 526 contacts in Port Harcourt [2]. As of 1 October 2014, all contacts had completed the 21-day surveillance follow-up, including those under surveillance in Rivers State, with no new report of incident cases [2]. The World Health Organization is soon to officially declare Nigeria free of active Ebolavirus transmission [2].

Here we assess the epidemiological data for the EVD outbreak in Nigeria from 20 July to 1 October 2014, and use a dynamic disease transmission model to illustrate the effect of forceful interventions in rapidly containing the EVD outbreak in Nigeria. The interventions included timely implementation of careful contact tracing and effective isolation of infectious individuals.

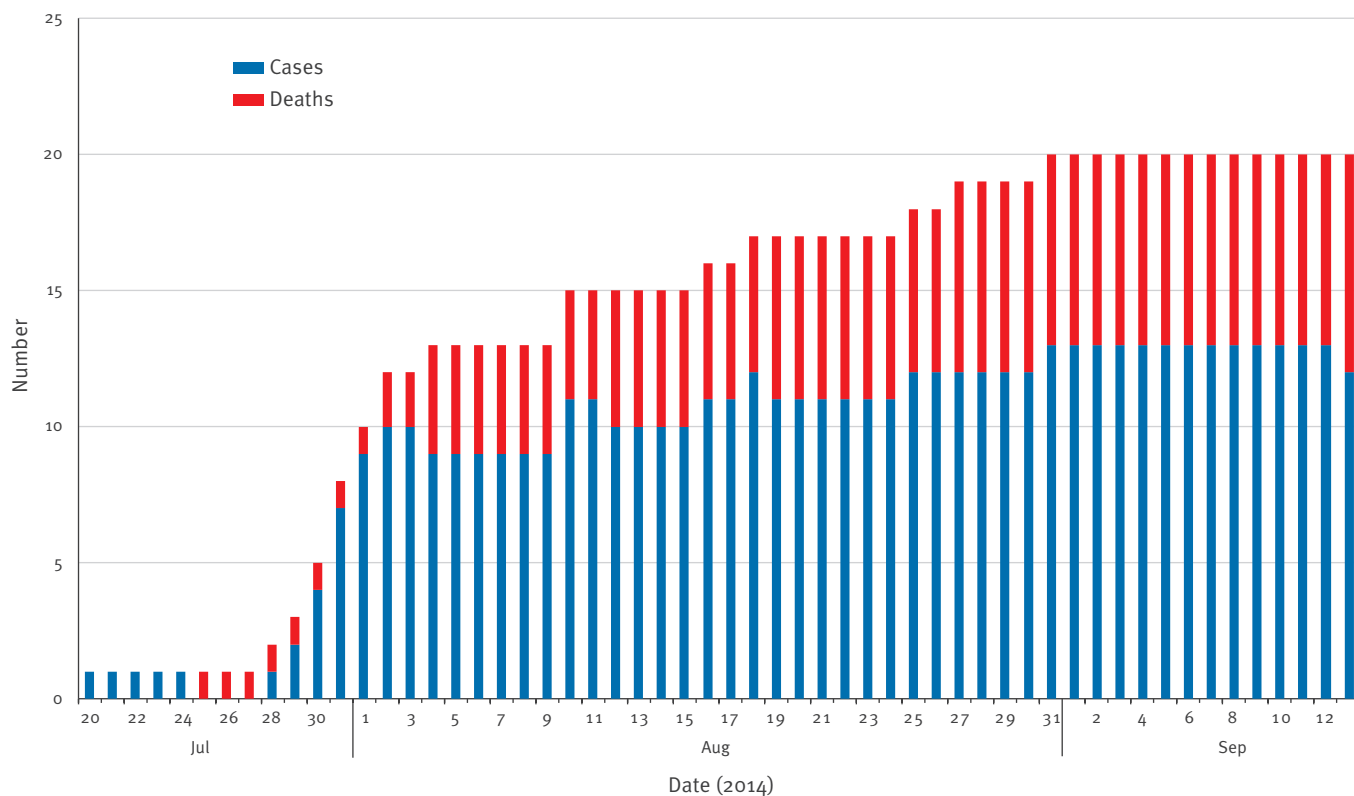
Data sources

We used up-to-date epidemiological data for the EVD outbreak in Nigeria available from public sources as of 1 October 2014 [1,5-32].

The 19 laboratory-confirmed cases were diagnosed by reverse transcription (RT)-PCR at Lagos University Teaching Hospital and Redeemer University in Lagos. Probable cases are suspected cases evaluated by a clinician or any deceased suspected case with an epidemiological link with a confirmed EVD case [1,2].

FIGURE 1

Cumulative reported cases and deaths of Ebola virus disease in Nigeria, July–September 2014***



A total of 19 laboratory-confirmed cases, one probable case and eight deaths among the cases have been reported as of 1 October 2014. The index case entered Nigeria on 20 July 2014 and the onset of outbreak is taken from that date.

To build the Ebola virus disease epidemic curve, we reviewed all relevant information published in *Morbidity and Mortality Weekly Report* [2] and World Health Organization Ebola situational reports and updates for Nigeria published during July to September 2014 [1,5-31] and categorised the 20 reported Ebola virus disease patients by reporting date and discharge status (dead/alive).

The diagnosis of the index case took approximately three days, while results of the tests for the other confirmed cases were typically available within 24 hours. Samples were also sent to the World Health Organization Reference Laboratory in Dakar, Senegal, for confirmation.

All symptomatic contacts were initially held in an isolation ward. Following laboratory confirmation of EVD, all positive symptomatic contacts were immediately moved to an EVD treatment centre. Asymptomatic suspected contacts were separated from symptomatic contacts. Negative asymptomatic individuals were discharged immediately [2].

Modelling Ebolavirus transmission and control

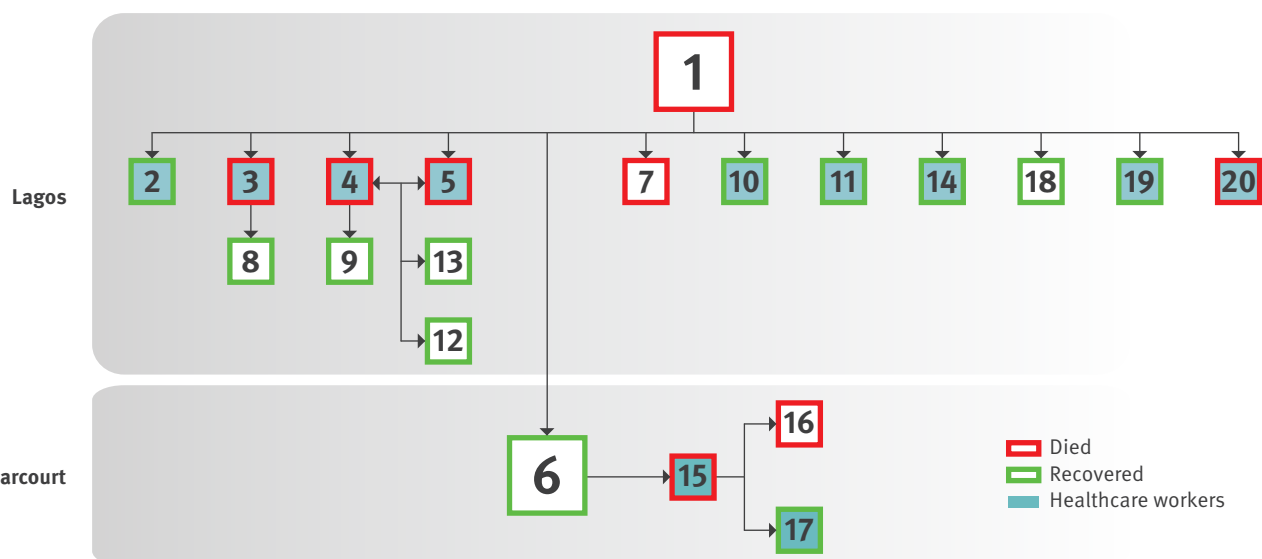
We estimated the case fatality rate (number of reported deaths/number of reported cases), the proportion of infected healthcare workers, and the mean number of secondary cases by generation of the disease by analysing a transmission tree. We employed

two compartments to differentiate between infectious individuals who were in the community and those who had been identified and placed in isolation in hospital. Using epidemic modelling, we also projected the size of the outbreak in Nigeria if control interventions had been implemented at different dates, and hence estimate how many cases were prevented by early start of interventions.

We carried out stochastic EVD outbreak simulations based on a simplified version of the model proposed by Legrand et al. [33], which was developed to classify the contribution of community, funeral and healthcare settings to the total force of infection. Although the model also accounts for transmission stemming from burial practices that involve touching the body of the deceased, this feature is believed to have less influence on transmission in the EVD outbreak in Nigeria [34]. For the sake of simplicity, we only classified transmission in the community and in healthcare settings by adjusting baseline transmission rates, diagnostic rates and enhancement of infection-control measures (e.g.

FIGURE 2

Transmission tree of the Ebola virus disease outbreak in Nigeria, July–September 2014 ***



To develop a detailed transmission tree for the patients included in Figure 1, we built on a published tree [2], cross-referencing the information in the tree with that in World Health Organization reports [1,5–31], as well as information from local newspaper reports (e.g. [32]) that provided details on individual patient’s infection links and their occupation. We categorised each patient according to the transmission setting (Ebola virus acquired in a healthcare setting or the community), patient’s geographical location (Lagos or Port Harcourt) and discharge status (dead/alive).

strict use of protective equipment by healthcare workers and effective isolation of infectious individuals).

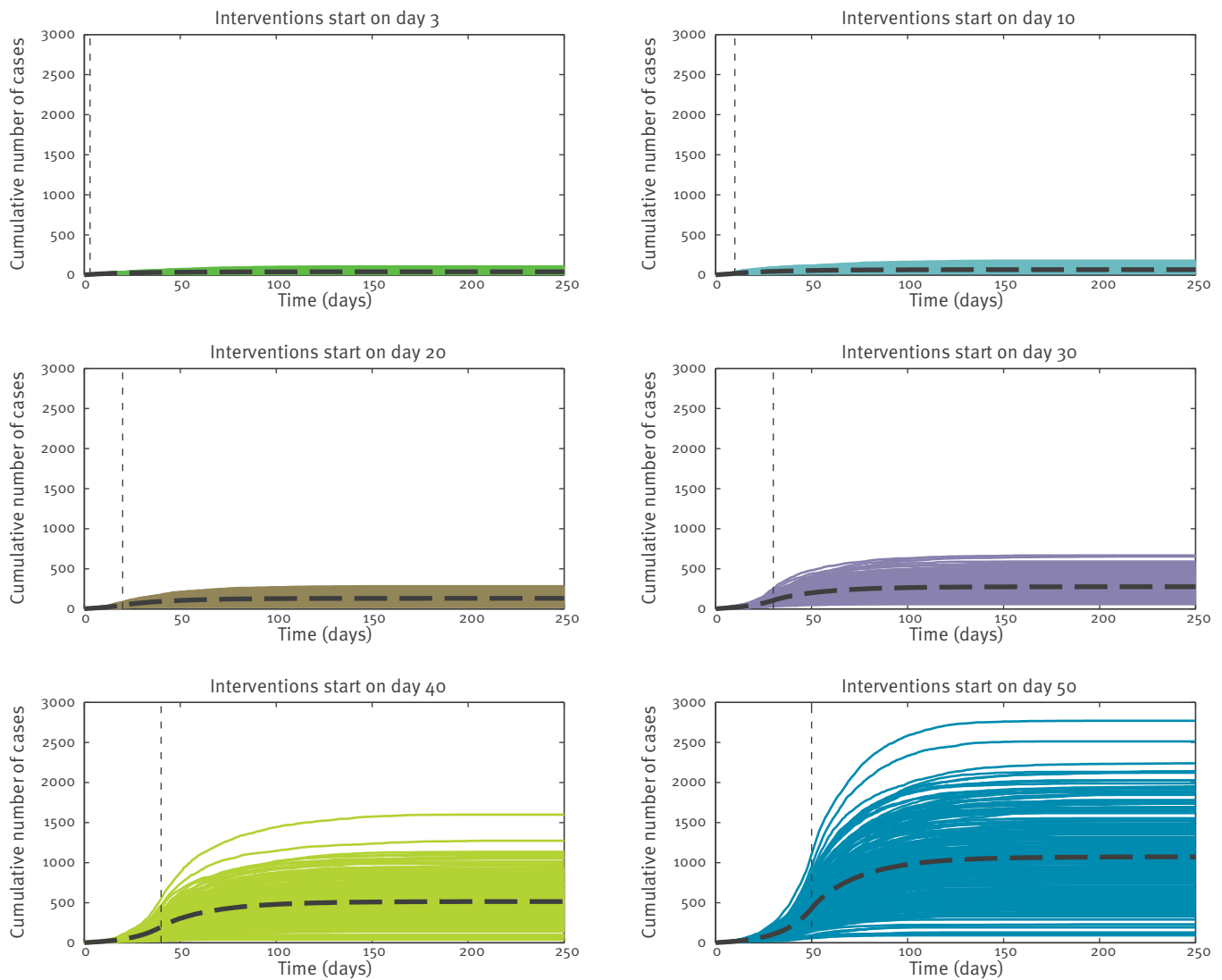
The modelled population was divided into five categories: susceptible individuals (S); exposed individuals (E); Infectious and symptomatic individuals (I); hospitalised individuals (H); and individuals removed from isolation after recovery or disease-induced death (P). Susceptible individuals infected through contact with infectious individuals (secondary cases) enter the latent period at mean rate $\beta(t) (I + l(t) H) / N(t)$ where $\beta(t)$ is the mean human-to-human transmission rate per day, $l(t)$ quantifies the mean relative transmissibility of hospitalised patients compared with that in symptomatic patients in the community, and $N(t)$ is the total population size at time t . Thus, values of this parameter between 0 and 1 measure the effectiveness of the isolation of infectious individuals that decrease Ebola virus transmission probability below that seen in the community. Values close to 0 illustrate ‘near-perfect’ isolation, while values closer to 1 illustrate ‘imperfect’ isolation strategies. Symptomatic infectious individuals I are hospitalised at a time-dependent mean rate $\gamma_a(t)$ or else recover without being hospitalised, at the mean rate γ_r . Individuals in the ‘removed’ category do not contribute to the transmission process. For simplicity, it can be assumed that the time-dependent transmission rate $\beta(t)$, the mean relative transmissibility of hospitalised patients $l(t)$, and the mean diagnostic rate $\gamma_a(t)$, remain constant with values at β_o , l_o , and γ_{a0} before the implementation of intervention

measures. Once control interventions are instituted at time τ , the transmission rate decreases to $\beta_1 (\beta_1 < \beta_o)$, the mean relative transmissibility of hospitalised patients decreases to $l_1 (l_1 < l_o)$ by enhancing infection control measures in healthcare settings, while the diagnostic rate increases to $\gamma_{a1} (\gamma_{a0} < \gamma_{a1})$ through contact tracing activities.

We carried out stochastic simulations of this transmission model to project the size of the outbreak in Nigeria if interventions (index case identification, contact tracing and isolation of those infected) had been started at different dates (range of 3 to 50 days after the index case arrived in Nigeria), and hence estimate how many cases were prevented by an early start of interventions. Baseline epidemiological parameters were set according to the epidemiology of EVD (i.e. incubation period of 6–12 days [35,36], infectious period of 5–7 days [37,38], case fatality rate: 35–50% [36]). Moreover, the mean time from symptom onset to diagnosis (γ_{a0}) was set at five days before the implementation of interventions [11]. Without loss of generality, we set the effective population size at 10,000,000 (assuming larger population sizes, for example, did not affect our conclusions). R_o (the basic reproduction number) denotes the transmission potential before the start of interventions in a completely susceptible population [39], while we refer to R , the reproduction number, when transmission is affected by control interventions. We varied R_o in the range 1.5–2.0 before the start of interventions, based on estimates from other affected countries [40–43]. R_o

FIGURE 3

Simulation results from calibrating the transmission model to assess the timing of control interventions on the size of the Ebola virus disease outbreak in Nigeria



l : mean relative transmissibility of hospitalised patients; R_0 : basic reproduction number.

Baseline epidemiological parameters were set according to the epidemiology of Ebola virus disease and $R_0=2$ before the start of interventions. Moreover, the mean time from symptom onset to diagnosis ($1/\gamma_{ad}$) was set at five days before the implementation of interventions, and the effective population size was set at 10,000,000. After the start of interventions, the mean time from onset to diagnosis was reduced from five days to one day, and the relative infectiousness of hospitalised individuals was reduced by 80% (i.e. $l=1$, $l=0.2$) to reflect the strict enhancement in infection control measures in hospital settings. Day 0 corresponds to the day when the index case was introduced in the population. We analysed 200 stochastic model simulations.

was set by adjusting the baseline transmission rate. After the start of the interventions, only two parameters were adjusted: (i) the mean time from symptom onset to diagnosis was reduced from five days to one day; and (ii) the infectiousness of hospitalised individuals was reduced by 80% to reflect the tightening of infection control measures in hospital settings relative to levels before the identification of the index case (i.e. $l_0=1$, $l_1=0.2$).

We ran 200 stochastic simulations starting with the introduction of an index case and 12 local individuals exposed by the index case at the start of the outbreak

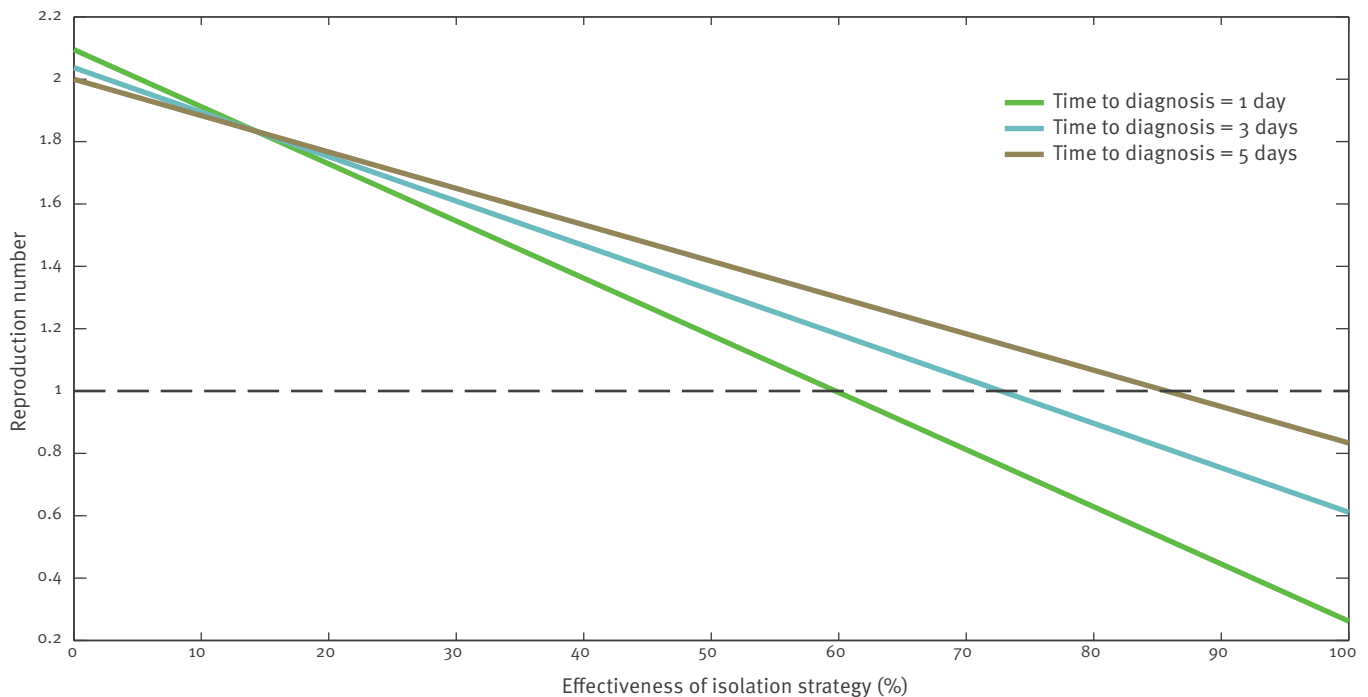
(i.e. $I(0)=1$, $E(0)=12$). We set the timing of start of interventions τ at day 3 of the simulated outbreak (in line with the Nigerian outbreak response), as well as 10, 20, 30, 40 and 50 days, and compared the predicted final epidemic size with that of the outbreak in Nigeria (i.e. 20 EVD cases (laboratory-confirmed and probable)). Simulation code in Matlab is available upon request from the authors.

Results

Eight of the 20 reported EVD cases reported in Nigeria have died, giving an estimated case fatality rate of 40% (95% CI: 22–61) (Figure 1). Of the 20 cases, 11

FIGURE 4

Effects of the effectiveness of isolation of infectious individuals on the reproduction number for three values of the diagnostic rate, Ebola virus disease outbreak, Nigeria



l : mean relative transmissibility of hospitalised patients; R : reproduction number.

There is a critical level of isolation effectiveness of infectious individuals estimated at about 60% with a mean time from symptoms onset to diagnosis of one day, which is necessary to reduce the reproduction number below the epidemic threshold at $R=1.0$ and halt the spread of Ebola virus disease.

The baseline R_0 was set at 2.0 with $l_0 = 1$ and the mean time from symptom onset to diagnosis ($1/\gamma_{av}$) was five days before the implementation of interventions.

were healthcare workers; nine of whom acquired the virus from the index case before the disease was identified in the country [1].

We built the transmission tree of the EVD outbreak, which provides information on the history of each case (Figure 2). The index case generated 12 secondary cases in the first generation of the disease. Five secondary cases were generated in the second generation and two secondary cases in the third generation. This leads to a rough empirical estimate of the reproduction number according to disease generation decreasing from 12 during the first generation, to approximately 0.4 during the second and third disease generations.

The projected effect of control interventions on the transmission of Ebolavirus in Nigeria is illustrated in Figure 3.

The effect of the effectiveness of isolation of infectious individuals on the reproduction number is shown in Figure 4 for three values of the diagnostic rate. There is a critical level of isolation effectiveness of infectious individuals estimated at about 60% with a mean time from symptom onset to diagnosis of one day, which is necessary to reduce the reproduction number below

the epidemic threshold at $R=1.0$ and halt the spread of EVD (Figure 4).

Discussion

We have analysed epidemiological data of what appears to be a limited outbreak of EVD in Nigeria based on data available as of 1 October 2014, with no new EVD cases reported since 5 September 2014. The swift control of the outbreak was likely facilitated by the early detection of the index entering Nigeria from a country where disease is widespread, in combination with intense contact tracing efforts of all contacts of this index case and the subsequent isolation of infected secondary cases [2]. In contrast, the initial outbreak in Guinea remained undetected for several weeks [44]. This detection delay facilitated the transnational spread of the virus to Sierra Leone and Liberia, while difficulties and at times inability to track and contain infectious individuals compounded the situation and resulted in an as yet uncontrolled epidemic in these countries.

We estimated a mean case fatality rate of 40% (95% CI: 22–61) for the EVD outbreak in Nigeria. This estimate based on a small sample size is at the lower end of estimates from previous outbreaks, ranging from 41% to 89% [33] and is likely a result of supportive care

offered in dedicated facilities put in place in a timely fashion by the Nigerian authorities. In comparison, the EVD case fatality rate in the ongoing outbreak in Guinea, Sierra Leone and Liberia has been estimated at 70% (range: 61– 89) [36]. As is the case for any emerging infection, these estimates have to be considered with caution as they are prone to many biases, including under-reporting of milder symptomatic cases (affecting the denominator) and censoring effects related to the unknown final outcome of the most recent infections.

The toll on healthcare workers in the EVD outbreak has been substantial, as they account for 11 of the 20 EVD cases in Nigeria. Past EVD outbreaks have been amplified in healthcare settings, e.g. [45,46], including in the ongoing epidemic in West Africa, with about 5% of the total number of reported EVD cases being healthcare workers based on data available as of 1 October 2014 [20,47].

Fortunately, past experience with the Zaire Ebolavirus strain also indicates that early, intense and sustained infection control measures in healthcare settings can substantially reduce the size and geographical scope of EVD outbreaks [48], which is consistent with the recent Nigerian experience.

The number of secondary cases decreased over subsequent disease generations in Nigeria, reflecting the effects of interventions, in particular the intense and rapid contact tracing strategy, the continuous surveillance of potential contacts, and the largely effective isolation of infectious individuals. Indeed, the mean reproduction number among secondary cases in Nigeria (i.e. excluding the contribution from the imported traveller) was 0.4 in the presence of control interventions. This number is below the epidemic threshold for disease spread, while a recent estimate of R derived from the growth rate pattern for Nigeria straddled the epidemic threshold of 1.0 [36]. In contrast, recent estimates of the reproduction number for the ongoing EVD epidemic in Sierra Leone and Liberia range between 1.5 and 2 [40-43], indicating that the outbreak is yet to be brought under control [43]. Moreover, the size of the outbreak in Nigeria is in agreement with our model simulation results when we assume that interventions were quickly instituted on day 3 of the outbreak. Our model simulations of delayed interventions, in accordance with large outbreaks in the broader West African region, demonstrate the necessity of rapid and forceful control measures. The Nigerian experience offers a critically important lesson to countries in the region not yet affected by the EVD epidemic, as well as to countries in other regions of the world that risk importation of EVD and that must remain vigilant. As a case in point, the recent importation of an EVD case in the United States from Liberia [49] proves that no country is immune to the risk of EVD in a globally connected world, but that rapid case identification and forceful interventions can stop transmission.

* Addendum

To build the EVD epidemic curve (Figure 1), we reviewed all relevant information published in Morbidity and Mortality Weekly Report [2] and WHO Ebola situational reports and updates for Nigeria published during July to September 2014 [1,5-31] and categorised the 20 reported EVD patients by reporting date and discharge status (dead/alive). To develop a detailed transmission tree for these patients (Figure 2), we built on a published tree [2], cross-referencing the information in the tree with that in the WHO reports, as well as information from local newspaper reports (e.g. [32]) that provided details on individual patient's infection links and their occupation. We categorised each patient according to the transmission setting (Ebola virus acquired in a healthcare setting or the community), patient's geographical location (Lagos or Port Harcourt) and discharge status (dead/alive). The addendum was added on 30 April 2015, at the request of the authors, following comments from colleagues involved in the outbreak response in Nigeria.

** Authors' correction

The following corrections were made on 30 April 2015 at the request of the authors, following comments from colleagues involved in the outbreak response in Nigeria and facilitated by the editors of Eurosurveillance: the number of contacts investigated through contact tracing was changed from 898 to 894 and unnecessary information regarding contact type was removed; individual-level patient information provided in Figure 2 was removed, as was a sentence in the text providing details of a nurse who cared for the index patient, for confidentiality purposes. The reference list was expanded to include additional supporting documents and the citations were amended accordingly throughout the article. Finally, a sentence pertaining to the management of contacts that tested negative for Ebola virus was removed in response to comments from colleagues involved in the outbreak response in Nigeria. These changes do not have any bearing on the results or conclusions of the study.

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Conflict of interest

None declared.

Authors' contributions

FOF, AS, DL and OT gathered data; FOF and GC-P conducted statistical analyses and modelling; FOF, GC-P, CV, LS, OT critique the manuscript. All authors contributed to the drafting and approval of the manuscript for submission.

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Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014

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The effective reproduction number, R_t , of Ebola virus disease was estimated using country-specific data reported from Guinea, Liberia and Sierra Leone to the World Health Organization from March to August, 2014. R_t for the three countries lies consistently above 1.0 since June 2014. Country-specific R_t for Liberia and Sierra Leone have lied between 1.0 and 2.0. $R_t < 2$ indicate that control could be attained by preventing over half of the secondary transmissions per primary case.

Introduction

The largest and first regional outbreak of Ebola virus disease (EVD) has been unfolding in West Africa since approximately December 2013, with the first cases traced back to southern Guinea [1]. However, the outbreak was not recognised until March 2014 [1], which facilitated the spread to neighbouring Sierra Leone and Liberia through porous borders as well as Nigeria via a commercial airplane on 20 July [2]. The World Health Organization (WHO) declared this EVD epidemic a Public Health Emergency of International Concern on 8 August 2014 [3]. According to phylogenetic analyses, the causative Ebola virus strain is closely related to a strain associated with past EVD outbreaks in Central Africa, and could have been circulating in West Africa for about a decade [4].

A total of 3,707 cases (including 2,106 confirmed, 1,003 probable and 598 suspected cases, respectively) and 1,848 deaths (concerning 1,050 confirmed and 557 probable cases, as well as 241 suspected cases and deaths, respectively) have been reported in Guinea, Sierra Leone, Liberia, Nigeria, and Senegal as of 31 August 2014 [5]. The total number of cases in Guinea, Sierra Leone, Liberia, Nigeria and Senegal have been 771, 1,216, 1,698, 21 and one, respectively. By contrast, the great majority of past outbreaks have been associated with small numbers of reported cases and have been confined to isolated rural areas in Central Africa. For reference, the largest outbreaks in Central

Africa generated 315 cases in Congo in 1976 and 425 cases in Uganda in 2000 [6,7].

The effective reproduction number, R_t , which measures the average number of secondary cases generated by a typical primary case at a given calendar time, can be helpful to understand the EVD transmission dynamics over time in affected countries as well as gauge the effect of control interventions [8]. Values of $R_t < 1$ indicate that the epidemic is in a downward trend. By contrast, an epidemic is in an increasing trend if $R_t > 1$. The mean reproduction number for EVD has been estimated at 1.83 for an outbreak in Congo in 1995 and 1.34 in Uganda in 2000 prior to the implementation of control interventions [9]. Here we sought to estimate the R_t in real time in order to assess the current status of the evolving outbreak across countries affected in 2014. We also compare our estimates of the reproduction number for the current outbreak with those previously published for the largest outbreaks in Central Africa and discuss our findings from a public health perspective.

Methods

Case data

We analysed the cumulative case counts reported by the WHO [10] as of 26 August 2014. Case counts are classified into three categories, i.e. confirmed, probable and suspected cases. Confirmed cases are laboratory diagnosed by polymerase chain reaction (PCR), positive IgM antibody or viral isolation while suspected cases correspond to individuals presenting fever ($\geq 38.5^\circ\text{C}$ (101°F)) and no favourable response to treatment for usual causes of fever in the area, and at least one of the following clinical signs: bloody diarrhoea, bleeding from gums, bleeding into skin (purpura), bleeding into eyes and urine. Probable cases are suspected cases of EVD with an epidemiological link to a confirmed EVD case [11]. We analysed two different sets of grouped data, i.e. (i) confirmed plus probable

cases and (ii) the total number of reported cases (i.e. confirmed, probable and suspected cases).

Because case counts were reported in irregular time intervals, we estimated daily incidence curves of EVD cases in order to estimate R_t . For this purpose, we first fit a smoothing spline to country-specific cumulative curves of reported cases. Next we took the daily difference of the cumulative counts to obtain daily incidence time series. Of note, the cumulative case series reflects the diagnostic process (among suspected and probable cases) and sometimes declined as a function of time (e.g. 5 April and 12 July in Guinea and Sierra Leone, respectively). When the difference was negative, we replaced it by 0. The smoothing spline was chosen to obtain a coefficient of determination R^2 at 0.995. Data from Nigeria and Senegal have been omitted due to a limited number of cases recorded in these countries thus far.

Mathematical model

We employed mathematical modelling together with time- and country-specific incidence data to estimate the R_t . Thus, here we model the transmission dynamics of EVD using a country-specific next-generation matrix $\{k_{ij,t}\}$ representing the average number of secondary cases in country i at time t generated by a single primary case in country j . Let g_τ represent the probability density function of the generation time of length t days for EVD. Hence, the expected value of EVD incidence in country i at time t is modelled as

$$E(c_{i,t}) = \sum_j k_{ij,t} \sum_{\tau=1}^{\infty} c_{j,t-\tau} g_\tau$$

The univariate version of Equation 1 has been employed by White and Pagano [12,13] in order to jointly estimate R_0 and the generation time distribution of EVD. Assuming that EVD incidence follows a Poisson distribution, the likelihood to estimate $\{k_{ij,t}\}$ is

$$\prod_t \prod_i \frac{(\sum_j k_{ij,t} \sum_{\tau=1}^{\infty} r_{j,t-\tau} g_\tau)^{r_{i,t}} \exp[-(\sum_j k_{ij,t} \sum_{\tau=1}^{\infty} r_{j,t-\tau} g_\tau)]}{r_{i,t}!}$$

where $r_{i,t}$ is the estimated daily incidence in country i on day t derived from the difference of the smoothing spline fit to the cumulative data as explained above.

Each element of the next-generation matrix is interpreted as the average number of secondary cases generated by a single primary case at time t . We assume that the per-contact probability of infection and the average generation time do not differ by country. Thus, the contact matrix regulates the relative difference between each pair of entries of the next-generation matrix, and because the contact patterns within and between countries cannot be directly observed, we made a qualitative assumption for the matrix $\{k_{ij,t}\}$ to approximately capture the pattern of (domestic and transnational) transmission [14], i.e.

$$M_t = \begin{pmatrix} k_{g,t} & \alpha & \alpha \\ \alpha & k_{s,t} & \alpha \\ \alpha & \alpha & k_{l,t} \end{pmatrix}$$

The matrix M_t qualitatively assumes that there are more frequent within-country transmissions (denoted by $k_{g,t}$, $k_{s,t}$ and $k_{l,t}$, where the subscripts g , s and l represent Guinea, Sierra Leone and Liberia, respectively) compared with transnational spread. The transnational spread is modelled by a single parameter α . We employed a piecewise constant model and change the parameters for the above-mentioned elements every seven days. Maximum likelihood estimates of the parameters were obtained by minimising the negative logarithm of Equation 2. Using the most recent incidence estimate i_0 and the exponential growth rate r as calculated from $r=(R-1)/12$ (where R is the most recent reproduction number and 12 is the mean generation time), the expected number of additional cases in 2014 was calculated as

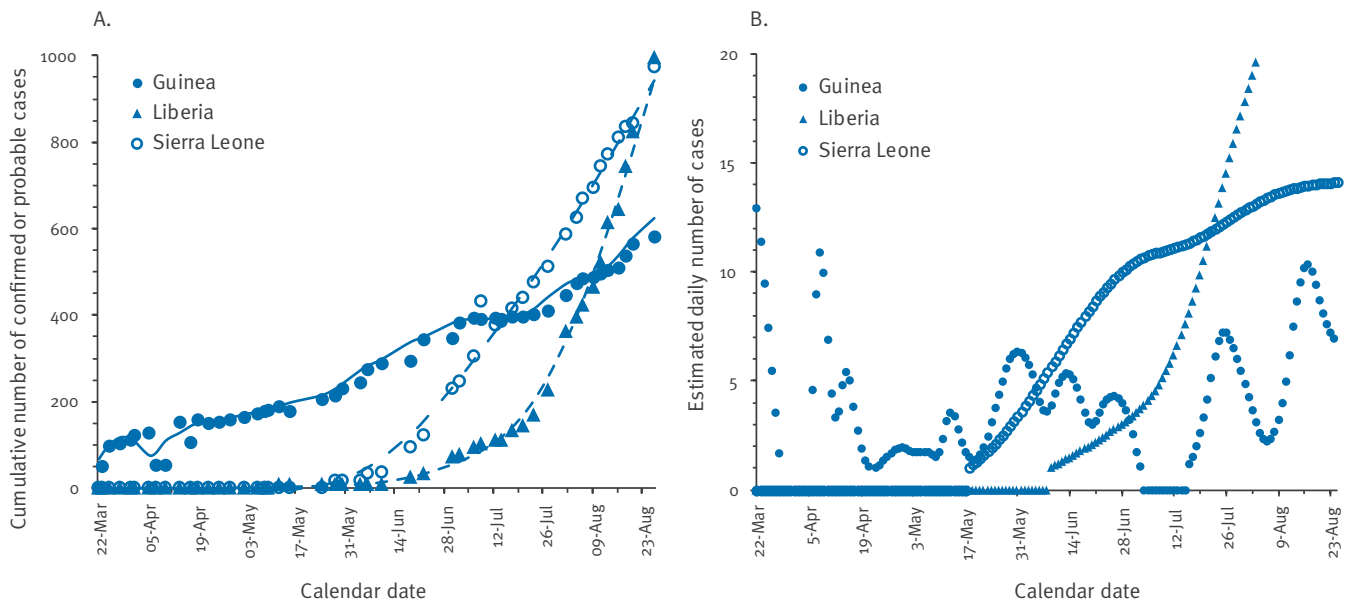
$$I = i_0 \int_0^{120} \exp(rt) dt$$

. The expected cases represent a ‘worst-case’ scenario based on the current situation by assuming a fixed reproduction number R for the remainder of the year (i.e. approximately 120 days remaining in 2014).

We also computed the R_t for all countries (hereafter referred to as the ‘global’ estimate of the reproduction number) by calculating the dominant eigenvalue of the estimated next-generation matrices. Moreover, we calculated column sums of the matrices to estimate the average number of secondary transmissions arising in and from a specific country and also extracted estimates of 2α , the value that governs the transnational spread generated by a single primary case. Although White and Pagano achieved the joint estimation of R_0 and generation time distribution [12,13], we assumed that the generation time is known, because our analysis relies solely on the cumulative number of reported cases with irregular reporting intervals. The generation time was assumed to follow an exponential distribution with a mean of 12 days [15], which is known to be close to the mean incubation period [16]. Based on empirical data of the serial interval distribution [15], we also carried out a sensitivity analysis of reproduction numbers by varying the mean generation time between nine and 15 days. The 95% confidence intervals of the R_t can be computed via bootstrapping methods. However, our study focused on examining model uncertainty associated with the transnational mixing patterns and the mean generation time as model uncertainty in our study is likely more influential on R_t compared to uncertainty relating to measurement error. In sensitivity analyses, we also examined the impact of varying specified time interval on R_t . For this purpose, we also

FIGURE 1

Cumulative and daily epidemic curves of Ebola virus disease (EVD) in Guinea, Liberia, and Sierra Leone, 23 March–26 August 2014



A) Cumulative number of confirmed or probable cases of EVD reported to the World Health Organization [10]. Solid lines are the smoothing spline fits to cumulative curves for each country with a coefficient of variation R^2 at 0.995.

B) Estimated daily incidence curves based on the smoothing spline model. Data from Nigeria and Senegal have been omitted due to the limited number of cases recorded in these countries thus far.

analysed the piecewise constant model for every six and eight days instead of seven days.

Results

Figure 1 illustrates the process of deriving daily EVD incidence curves by country from cumulative curves of reported cases. Multiple fluctuations are evident from the incidence curve for Guinea (Figure 1). In Liberia, the early transmission phase did not appear to exhibit sustained growth and was probably driven by case importations during first epidemic month. Exponential growth was subsequently seen, reflecting self-sustaining transmission. Similarly, the incidence curve for Sierra Leone also displayed steady growth since early June. Most recent EVD incidence data for Guinea also showed an increasing pattern.

Our weekly maximum likelihood estimates of the R_t for each affected country and for the global system in West Africa are displayed in Figure 2. Results indicate that the reproduction number for all countries reached levels below unity in April and May, but has appeared to be continuously above one since early June (Figure 2A). This pattern was robust when using two different datasets (including and excluding suspected cases). Estimates of R_t using total case reports from June to July 2014, a period during which exponential growth of cases has been observed in Sierra Leone and Liberia, ranged from 1.4 to 1.7, respectively. In the hypothetical worst-case scenario that the current situation with an

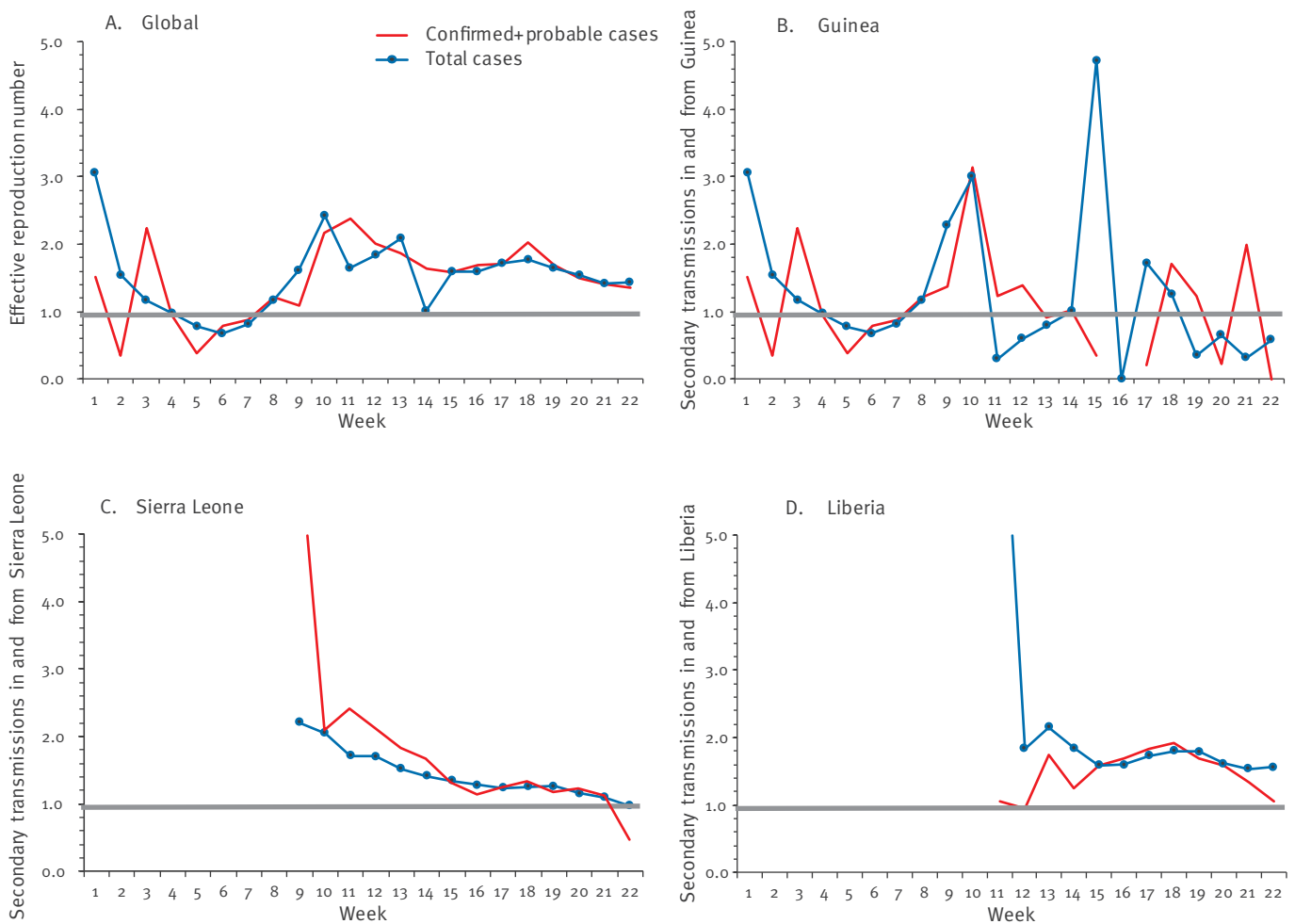
estimated reproduction number R ranging from 1.4 to 1.7 continues for the remainder of the year, we would expect to observe a total of 77,181 to 277,124 additional cases within 2014.

Maximum likelihood estimates of R_t in Guinea appeared to have fluctuated around 1.0 (Figure 2B), which reflects the observed variation in the corresponding incidence curve. Importantly, R_t in this country has not been continuously below 1.0, which supports the view that in this country the outbreak is not yet under control. Estimates of R_t in Sierra Leone and Liberia appeared to be consistently above 1.0 up to week 22 (i.e. the week starting on 18 August) (Figure 2C and 2D). Although R_t in Sierra Leone has been declining with the highest estimates obtained for early June, R_t has not been consistently below 1.0 in this country, including estimates for the latest reporting week (Figure 2). The pattern of R_t in Liberia shows values well above 1.0 since July 2014. In this country, the estimates of R_t reaching values up to 2.0 indicate that the outbreak could only be brought under control if more than half of secondary transmissions per primary case were prevented.

Figure 3A shows the estimated average number of transnational transmissions per single primary case as a function of time (calculated by 2a). α has been high in early June, but has declined dramatically since late June. Nevertheless, most recent model estimates still suggest a non-negligible number of cross-border

FIGURE 2

Effective reproduction number of Ebola virus disease (EVD) estimated for Guinea, Sierra Leone, Liberia, and for the global system in West Africa, 23 March–26 August 2014



A) Global (maximum likelihood) estimates of the effective reproduction number of EVD based on data from all affected countries (Guinea, Sierra Leone and Liberia) were derived from the dominant eigenvalue of the next generation matrix.

B-D) The average number of secondary transmissions arising from Guinea, Sierra Leone and Liberia, was calculated from the corresponding column sum of the next generation matrix. The horizontal grey solid line indicates the reproduction number at 1.0 for reference, below which the epidemic follows a declining trend. Estimates were derived using either confirmed cases plus probable cases or the total reported case counts (confirmed, probable plus suspected cases). Data from Nigeria and Senegal have been omitted due to limited number of cases recorded thus far. Epidemic week 0 corresponds to the week that includes 22 March 2014.

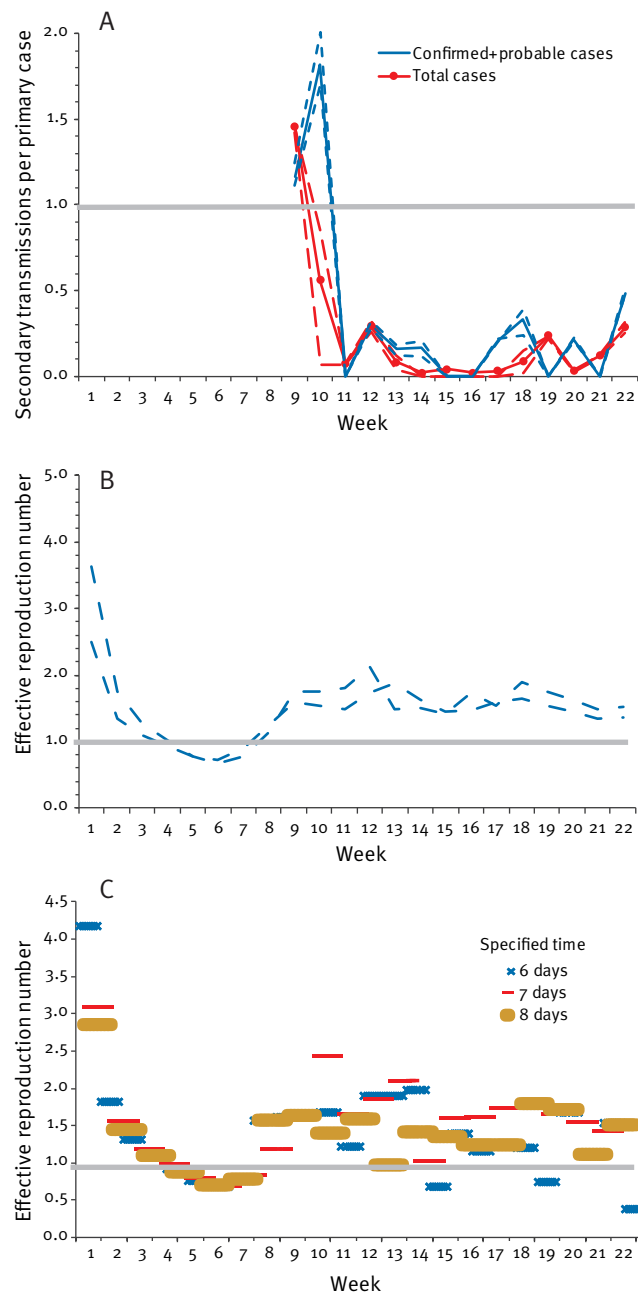
transmissions. Figure 3B examines the sensitivity of R_t for all countries to changes in the mean generation time. Although the absolute values of R_t are positively correlated with the mean generation time, the above-mentioned qualitative patterns of R_t are preserved, which indicates that the ongoing EVD epidemic has yet to be brought under control. Figure 3C examines the sensitivity of R_t to a specified time interval of the piecewise constant model. Perhaps not surprisingly, as the interval is shortened, fluctuations in R_t tend to increase, perhaps due to stochastic effects. Nevertheless, all models roughly provide qualitatively similar patterns in R_t .

Discussion

We have derived global and country-specific estimates of the R_t of EVD for the ongoing outbreak in West Africa. Our global estimates of the R_t appear to be continuously above one since early June, indicating that the epidemic has been steadily growing and has not been brought under control as of 26 August 2014. The country-specific estimates for Sierra Leone and Liberia were also above one, perhaps reflecting the increasing trend in cases in these countries since June. Our estimated reproduction numbers, broadly ranging from one to two, are consistent with published estimates from prior outbreaks in Central Africa [9,17]. Our estimates of $R_t < 2$ indicate that the outbreak could

FIGURE 3

Sensitivity analysis of the effective reproduction number of Ebola virus disease (EVD), West Africa, 23 March–26 August 2014



- A) The estimated average number of secondary cases per single primary case arising from transnational spread. Solid lines represents estimates derived from the mean generation time of 12 days, while dashed lines correspond to estimates derived using nine and 15 days as the mean generation time.
- B) Upper and lower bounds of the effective reproduction number (R_t) for the global dynamics in West Africa are shown assuming a mean generation time of EVD ranging from nine to 15 days. The horizontal grey line is shown as a reference for the reproduction number at 1.0 below which the epidemic follows a declining trend.
- C) Sensitivity of R_t to varying specified time intervals of the piecewise constant model. Estimates in B and C were derived using the total number of reported EVD cases (confirmed, probable plus suspected cases). Epidemic week 0 corresponds to 22 March 2014. Of note, estimates overlap at week 9 as these were derived from epidemiological data for a single country (i.e. Guinea).

be brought under control if more than half of secondary transmissions per primary case are prevented.

Our statistical analysis of the reproduction number of EVD in West Africa has demonstrated that the continuous growth of cases from June to August 2014 signalled a major epidemic, which is in line with estimates of the R_t above 1.0. Moreover, the timing of R_t reaching levels above one is in line with a concomitant surge in cases in Sierra Leone and Liberia. In a worst-case hypothetical scenario, should the outbreak continue with recent trends, the case burden could gain an additional 77,181 to 277,124 cases by the end of 2014. Although such numbers must be interpreted with caution (as they rest on an assumption of continued exponential growth within 2014, which is unlikely), our study supports the notion that the ongoing EVD epidemic must be regarded as a Public Health Emergency of International Concern [3]. This finding also implies that transnational spread of EVD might have hindered control efforts, suggesting that preparedness plans for potential case introductions is critical particularly for countries at high risk of EVD case importations [18] with suboptimal public health systems. The transnational spread per person appears to have been reduced over time, but our most recent model estimates still suggest a non-negligible number of secondary cases arising from transnational spread. Uncontrolled cross-border transmission could fuel a major epidemic to take off in new geographical areas (e.g. as seen in Liberia). Unaffected countries at risk of transnational spread should be on high alert for potential EVD introductions and be ready to launch comprehensive and timely containment responses to avert outbreaks.

Our analysis is not exempted of limitations. First, the epidemic is ongoing in multiple geographical locations, and no simple mixing matrix can capture the complex geographical patterns of spread in the region. Second, cases may be under-ascertained, and hence reported cases may represent only a portion of the total number of infected individuals. However, our estimates of the reproduction number are not affected whenever the diagnosis and reporting rates have not dramatically changed over time. Third, the reporting delays are known to induce a downward bias in incidence in the latest observation, which can complicate real-time analyses. Several studies have successfully addressed this bias [19–22], but we were unable to incorporate this delay into our analyses due to a lack of empirical data to characterise the reporting delay distribution.

Despite the above-mentioned limitations, we believe that our findings are useful to demonstrate that the cases have been steadily growing in the last three months with an R_t above one. Close monitoring of this evolving epidemic should continue in order to assess the status of the outbreak in real time and guide control interventions in the region. Reviewing possible countermeasures for countries at risk of transnational

spread [18] would be of utmost importance to confront the ongoing propagation of cases over time and space.

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Conflict of interest

None declared.

Author contributions

HN conceived mathematical modeling method and analyzed the data. HN and GC drafted and revised the manuscript.

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Assessing the impact of travel restrictions on international spread of the 2014 West African Ebola epidemic

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The quick spread of an Ebola outbreak in West Africa has led a number of countries and airline companies to issue travel bans to the affected areas. Considering data up to 31 Aug 2014, we assess the impact of the resulting traffic reductions with detailed numerical simulations of the international spread of the epidemic. Traffic reductions are shown to delay by only a few weeks the risk that the outbreak extends to new countries.

Introduction

The 2014 Ebola outbreak currently involves three countries with widespread and intense transmission in the West African region (Guinea, Liberia and Sierra Leone) and four others where initial case(s) or localised transmission have been reported (Nigeria, Senegal, Spain and the United States), reaching a total of 8,997 cases and 4,493 deaths in the official report of 15 October 2014 [1].

With the number of cases exponentially increasing in the affected area, several agencies and governments are calling for massive coordinated interventions aimed at the surveillance and containment of the epidemic [2]. Scaling up the international response appears necessary for providing financial support, supply of technical resources and expertise, and delivery of essential services to the affected area [2]. The need to consider an international framework lies also in the possible further international spread of the epidemic [3]. In response to such concerns and in an attempt to reduce the risk of case importation, several countries and airlines have adopted travel restrictions to and from the affected area. These include the suspension of flights by a number of carriers, air/sea/land border closures,

restrictions for non-residents, suspension of visa issuance, and entry screening. Travel bans could potentially hamper the delivery of medical supplies and the deployment of specialised personnel to manage the epidemic [4]. Although international public health and relief agencies and representatives have been urgently calling for lifting such travel bans [4-6], these disease-avoidance mechanisms remain in place at the time of writing, and more are being considered. In light of their potentially harmful effects, the benefits of travel restrictions need to be carefully evaluated.

Air travel data is a critical source of information that has been recently analysed to characterise the degree of connectivity of the affected area to the rest of the world [7,8]. Air travel and human mobility data have also been integrated in large-scale computer micro-simulations that, taking explicitly into account the local evolution of the epidemic in the affected countries, quantify the risk for international spread of Ebola virus disease (EVD) out of Africa in the short term [9]. Hypothetical simulation scenarios considering an 80% reduction of passenger traffic flow out of the region indicate that further international spread is delayed by only a few weeks. Here, we use the model to quantify the effect that the travel restrictions implemented during August 2014 by countries and airlines have on the global spread of Ebola. By comparing the differences between simulations with and without travel restrictions, we can make quantitative estimates of the effectiveness of such restrictions on reducing the importation of new Ebola cases to countries outside of West Africa. Our goal is to inform the debate over the utility of travel bans to slow the spread of Ebola.

TABLE

Travel restrictions to and from Ebola-affected areas implemented by authorities and companies as of 31 August 2014

Travel-related measure	Travel-related measure Authorities/ Companies	Starting date of intervention ^a	Target area	Additional details ^{b,c}
Flight suppression	Three European airlines	From 6 Aug 2014 to 28 Aug 2014	Liberia Sierra Leone	See SI
	Two Asian airlines	From 6 Aug 2014 to 14 Aug 2014	Guinea Kenya	See SI
	Six African airlines	From 6 Aug 2014 to 26 Aug 2014	Guinea Liberia Nigeria Sierra Leone	See SI
Travel ban and/or border closure	Ghana	1 Aug 2014	Liberia Nigeria Sierra Leone	Ban of all flights from the affected countries
	Zambia	8 Aug 2014	Liberia Nigeria Sierra Leone	Ban on entry for citizens of the target countries
	Mauritania	11 Aug 2014	Liberia Nigeria Sierra Leone	Ban on entry for citizens of the target countries
	Chad	11 Aug 2014	Liberia Sierra Leone	Ban of all flights
	Cote D'Ivoire	13 Aug 2014	Nigeria	Ban of all flights, closure of land borders
	Nigeria	13 Aug 2014	Guinea Liberia Sierra Leone	Ban of all flights from the affected countries
	Botswana	14 Aug 2014	Guinea Liberia Sierra Leone	Banned travellers from affected countries
	Equatorial Guinea	15 Aug 2014	Guinea Liberia Sierra Leone	Suspended the issuance of visas
	Gambia	15 Aug 2014	Guinea Liberia Sierra Leone	Ban of all flights
	Kenya	16 Aug 2014	Guinea Liberia Sierra Leone	Ban of all flights
	Cape Verde Islands	19 Aug 2014	Guinea Liberia Sierra Leone	Border closure
	South Africa	21 Aug 2014	Guinea Liberia Sierra Leone	Ban on entry for citizens of target countries
	Cameroon	21 Aug 2014	Guinea Liberia Sierra Leone	Border closure
	Senegal	21 Aug 2014	Guinea Liberia Sierra Leone	Closure of land borders
	Rwanda	24 Aug 2014	Guinea Liberia Sierra Leone	Border closure
	Gabon	26 Aug 2014	Guinea Liberia Sierra Leone	Border closure
	Namibia	26 Aug 2014	Guinea Liberia Sierra Leone	Border closure
	Guinea Bissau	Before 26 Aug 2014	Guinea Liberia Sierra Leone	Ban of all flights, closure of land borders
Togo	Before 26 Aug 2014	Guinea Liberia Sierra Leone	Ban of all flights	

SI: supplementary information.

^a Depending on the information available, this can be either the date of intervention or the date of the bulletin/news.

^b Closure of land borders is for all travellers irrespective of citizenship.

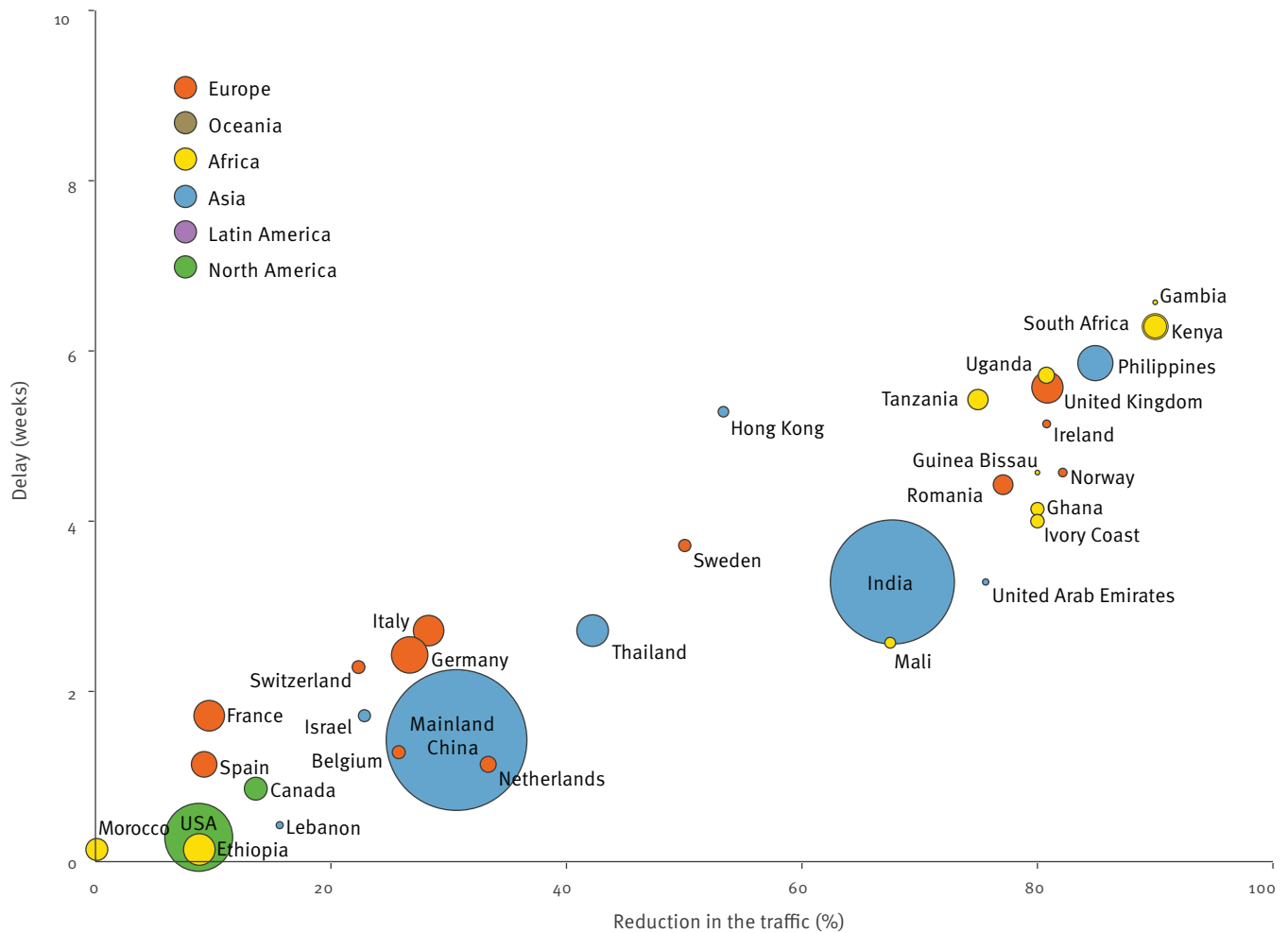
^c Border closure is generally for citizens of the target countries and travellers coming from the affected area, with the exception of nationals of the destination country.

The list is obtained from publicly available sources extracted from the search ["ebola" AND "travel"] on Twitter on 1 September 2014.

 Additional searches of news published on the Internet were performed to confirm and complement the initial list. More detailed information and references are provided in the supplementary information* available at <http://www.mobs-lab.org/ebola-eurosurvsup.html>

FIGURE 1

Modelled effect of travel restrictions on the risk of Ebola case importation for individual countries



The delay in the risk of case importation induced by the applied travel restrictions is shown for each country versus the overall reduction of the country's air traffic. The delay was calculated as the time after which the risk of case importation in the scenario with travel restrictions was equal to the value reached on 30 September 2014 in the baseline case. For clarity, only countries having a non-negligible risk of importation (> 0.5%) are shown in the plot. The size of the dots is proportional to the country's population. Colours indicate the continents.

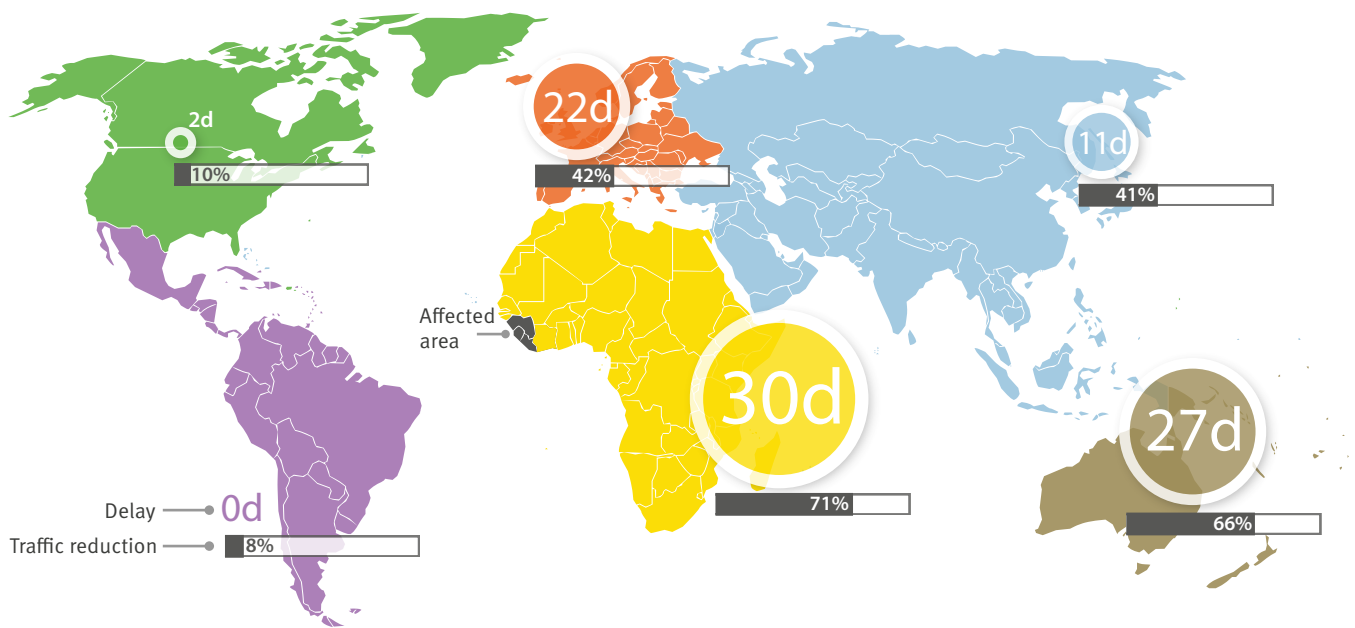
Methods

We used 2013 flight itinerary data providing travel volumes of passengers flying between any origin–destination pair of commercial airports in the world (International Air Transport Association (IATA), www.iata.org; Official Airline Guide (OAG), www.oag.com). Starting from the airport of origin, each itinerary reports all connecting airports to reach the final destination and the airline companies handling the connecting flights along the given route. We collected publicly available information on the travel restrictions related to Ebola-affected regions up to 31 August 2014. We considered both travel bans implemented by national authorities and flight discontinuations by individual airlines (Table). Restrictions are heterogeneous in terms of start date and target country in the affected area (e.g. some concern the entire Western Africa area and others just one of its countries). Flight suspensions by airline company *A* targeting the set of countries *C* were considered by removing from the flight database all

itineraries (and associated travel volumes) to *C* where *A* was the dominant airline. Then, travel bans and border closures implemented by country *B* targeting the set of countries *C* were considered by singling out all itineraries connecting *B* with *C* (in both directions) and reducing by a factor *r* the associated travel volumes, with $r_{neighbours} = 80\%$ for the affected area's neighbouring countries and $r_{others} = 90\%$ for all other countries, to model residual human mobility and non-compliance to policies. The resulting overall traffic reduction for each country was obtained by combining the effect of flight discontinuation and country level travel bans. We further required that the overall reduction could not be larger than *r*. This additional constraint is meant to model additional types of possible movements not captured by the air travel data (e.g. cross-border ground movement) and also adaptation to the restrictions (e.g. rearrangements of flight itineraries to other airline companies) for which detailed data are not currently available.

FIGURE 2

Modelled overall delays predicted for Ebola case importation by continent, following the application of the travel restrictions



Grey bars below the circles indicate the overall travel reduction per continent resulting from the currently applied travel restrictions. The size of the discs is related to the duration of the delay.

We used the Global Epidemic and Mobility model [10,11] applied to the EVD outbreak [9] to simulate case importation events in 220 countries around the world. The model [9] accounts for EVD transmission in the general community, in hospital settings, and during funeral rites [12]. Basic reproductive numbers for each of these settings were inferred through a Monte Carlo likelihood analysis considering more than 3,500,000 simulations that sampled the disease model parameter space and the case data on the EVD outbreak up to 27 August 2014. Other epidemiological parameters were taken from the literature [9,12,13]. The spatio-temporal epidemic evolution is modelled using individual-level dynamics where transitions are mathematically defined by chain binomial and multinomial processes to preserve the discrete and stochastic nature of the processes. Individuals in the latent state are allowed to follow the same mobility patterns and international travel behaviour as those who are not infected. Travel probabilities are calculated based on the integrated flight database and mechanistically simulated travel and commuting patterns. More details on the model and on the parameters' inference procedure are provided in [9] and in the supplementary information* (<http://www.mobs-lab.org/ebola-eurosurvsup.html>).

To assess the effect of current travel restrictions on the risk of case importation, we compared the international spread of the EVD epidemic obtained from numerical simulations of the model with and without the travel reductions. We focus on short-term

projections and calculate the probability of case importation per country (and per continent) predicted for 30 September 2014 in the baseline scenario without travel restrictions. The probability of importation at that date is still relatively small for most of the countries and detailed values for different dates can be found in [9]. We then compute the time delay needed to reach the same value of case importation probability per country (or continent) once the travel restrictions shown in the Table are implemented.

Results

The modelled travel restrictions impacted airline passenger volume to countries worldwide in a very heterogeneous manner (Figure 1, reporting results for countries with a case importation probability larger than 0.5% as of 30 September 2014). Notably, flight suppressions and border closures did not affect solely the countries implementing such measures but they also had considerable repercussions on others (e.g. India and the Philippines following the suppression of Emirates Airline flights). With few exceptions, African countries were predicted to experience traffic reductions greater than 70% due to generalised travel bans.

The total estimated reduction of 60% of airline passenger traffic connecting the West Africa region currently most affected by Ebola to the rest of the world was shown to be insufficient to prevent the exportation of Ebola cases. The observed traffic reductions were shown to delay the risk of case importation per country

from a few days to a few weeks (Figure 1). The majority of the countries (56%, mainly in Central Europe, Asia and the Americas) would not experience a delay longer than one month. At the continental level, the delay was predicted to be negligible for the Americas, and at most one month for the African continent (Figure 2). Results confirmed previous empirical evidence from past epidemics of other infectious diseases and were in agreement with mathematical modelling studies of the relationship between the exponential growth rate of an epidemic in a source region and the exportation to other regions [14-18]. Those can be summarised with the simple rule of thumb that a 50% travel reduction produces a delay equal to the doubling time of the number of cases.

Discussion

Although the current travel restrictions postpone the spread of EVD to other continents by at most a few weeks, they can impose heavy logistical constraints on the management of the epidemic in the countries severely hit by the disease and ill-equipped to cope with its alarming rapid spread [4-6]. If not offset by massive humanitarian operations, they can cause major shortages of food, energy and essential resources, with the potential to severely compromise local economies [19].

Similar to what happened during the severe acute respiratory syndrome (SARS) outbreak in 2003 [20], adverse effects on local economies of the same countries implementing the bans may also occur, as a reduced connectivity and the increased apprehension may induce a considerable reduction in the demand for service industries (business travel, tourism and associated services).

International agencies suggest that currently unaffected countries should invest in health system preparedness, strengthening their own capacity to detect and contain newly imported cases [21]. These measures are expected to substantially reduce the risk of importation. Indeed, while the relatively long latency period of EVD may allow exposed individuals to travel long distances, infectiousness occurs at symptom onset only, so that potentially infectious individuals can be clinically recognised. The mode of transmission is expected to minimise the risk of spread during a flight [21].

It is also worth mentioning that delays in the global spread of the outbreak may have to be evaluated with respect to the development timeline of pharmaceutical interventions. For instance, Ebola vaccines are being fast-tracked, and field trials are planned, probably in healthcare workers at high risk of exposure to the virus in the affected areas [22].

The results presented here need to be considered in light of the assumptions and limitations of the modelling approach used. We considered all travel restrictions obtained from publicly available sources that were implemented up to the end of August 2014, but

this list may not be complete and not all information could be verified with the original sources. In the presence of uncertainty (e.g. vague information or inconsistency between different news) we assumed the scenario with the strongest traffic reduction in order to provide the best-case scenario in terms of resulting delay. An additional world-wide fear-induced decrease of tourist and business travel to the region has been observed [23,24] in September and has probably further increased the delay in case importation, although only logarithmically with the magnitude of the traffic reduction [15,16].

The simulation presented was based on the study of the current West African outbreak described in Gomes et al. [9], which contains estimates of the incubation period and generation time based on past Ebola outbreaks. Recent estimates for the current outbreak have been published by Hollingsworth et al., and Althaus et al. [13,25]. Updated results on the risk of the epidemic spread are regularly posted on our website <http://www.mobs-lab.org/ebola.html> to account for the most recently published epidemiological information. We note that, although these parameters affect the absolute value of the probability of importation, they do not affect the relative delay depending on the epidemic growth rate [15,16].

Detailed data on unmeasured movements during the epidemic and on possible rearrangements of air travel volumes following decisions of airline companies to suspend flights are not available to be implemented directly into the model. For this reason, we took these aspects into account by considering a maximum of 90% overall traffic reduction (80% for countries bordering the currently affected area), representing the maximum ability of a country to implement the border closures. A sensitivity analysis exploring smaller values of these upper bounds (70% for neighbouring countries and 80% for the others) yielded delays in the risk of case importations reduced to five weeks for the African countries with the largest overall reductions (supplementary information*).

Conclusion

This study indicates that travel bans are only delaying the further international spread of the Ebola outbreak in West Africa for a limited time, at the risk of compromising connectivity to the region, mobilisation of resources to the affected area and sustained response operations, all actions of critical value for the immediate local control of EVD and for preventing its further geographical spread. Any decision making process on this issue must take into account complex cost-benefit analyses of travel bans.

*Note

Supplementary information made available by the authors on an independent website is not edited by *Eurosurveillance*, and *Eurosurveillance* is not responsible for the content. The

material can be accessed at: <http://www.mobs-lab.org/ebo-la-eurosurvsup.html>

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Conflict of interest

None declared.

Authors' contributions

CP, VC, MG, AP, AV provided the data. CP, LR performed the computational experiments. CP VC AV conceived and designed the study. All authors discussed the results, edited and commented the manuscript draft. All authors read and approved the final manuscript.

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EbolaTracks: an automated SMS system for monitoring persons potentially exposed to Ebola virus disease

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We report development and implementation of a short message service (SMS)-based system to facilitate active monitoring of persons potentially exposed to Ebola virus disease (EVD), whether returning from EVD-affected countries, or contacts of local cases, should they occur. The system solicits information on symptoms and temperature twice daily. We demonstrated proof-of-concept; however this system would likely be even more useful where there are many local contacts to confirmed EVD cases or travellers from EVD-affected countries.

Background

The 2014–2015 Ebola virus disease (EVD) outbreak in West Africa is the largest in history, with widespread and ongoing transmission occurring in Guinea, Liberia, and Sierra Leone [1]. In addition, four countries (Mali, Nigeria, Senegal, and the United States of America (US)) have had EVD cases imported from West Africa. Moreover aid and healthcare workers (HCW) who developed EVD in West Africa have been evacuated by air for treatment in the US and several European countries [2]. One or more secondary cases have occurred in Mali, Nigeria, Spain and the US [2]. Internationally, public health authorities recommend surveillance of contacts of people with Ebola virus infection for 21 days following their last potential exposure so they can be promptly isolated and treated if they develop illness, minimising opportunities for further spread [3–6]. Depending on an individual risk assessment, and with some variation between countries, passive or active monitoring is recommended for HCWs, household and community contacts of persons with EVD, and in some instances, for travellers from EVD-affected countries irrespective of a specific exposure history.

Limited experience outside West Africa to date demonstrates that monitoring contacts of persons with EVD requires ‘substantial time, resources, and coordination between local health jurisdictions’ and that the number of persons requiring follow-up can quickly escalate [7]. Short message services (SMS) technology has been effectively used in a variety of public health and medical monitoring programmes [8–13]. Given our prior

success in using SMS to conduct vaccine safety surveillance [14], we sought to develop an SMS-based system to streamline active monitoring of persons potentially exposed to EVD. Here we describe an automated SMS system implemented by the Department of Health in Western Australia (WA Health) to actively monitor travellers returning from EVD-affected countries, and contacts of any locally diagnosed EVD cases in WA (should the need arise).

Description of the system

The ‘EbolaTracks SMS system’ is designed to facilitate active monitoring of EVD contacts for 21 days following their last possible exposure to Ebola virus. As there have been no EVD cases diagnosed in WA, the system has thus far focused on monitoring persons who have travelled from the EVD-affected countries Guinea, Liberia, and Sierra Leone. These travellers, potentially exposed to EVD, are identified by federal authorities at Perth International Airport and their contact details and travel history are recorded. WA Health then provides these individuals with an EbolaTracks monitoring pack, which includes information about EVD, an explanation of the purpose of the system and its operation, a digital thermometer, instructions on how to take and report temperature by SMS to WA Health, and a mobile phone with one month’s credit if they do not have their own. Based on reported exposures, travellers (or potentially local contacts) are classified as casual, low, or high risk, according to Australian criteria [6]. Participants are also categorised according to exposure type as HCW, household contacts, or ‘other’, which includes travellers from EVD-affected countries and local contacts in settings such as public transport. Those enrolled into the system are either manually entered as individual records or batch imported via a spreadsheet (in the case of larger volumes). The enrolment details include everything captured on the enrolment form (i.e. demographics, date of last possible exposure, contact details and information about risk).

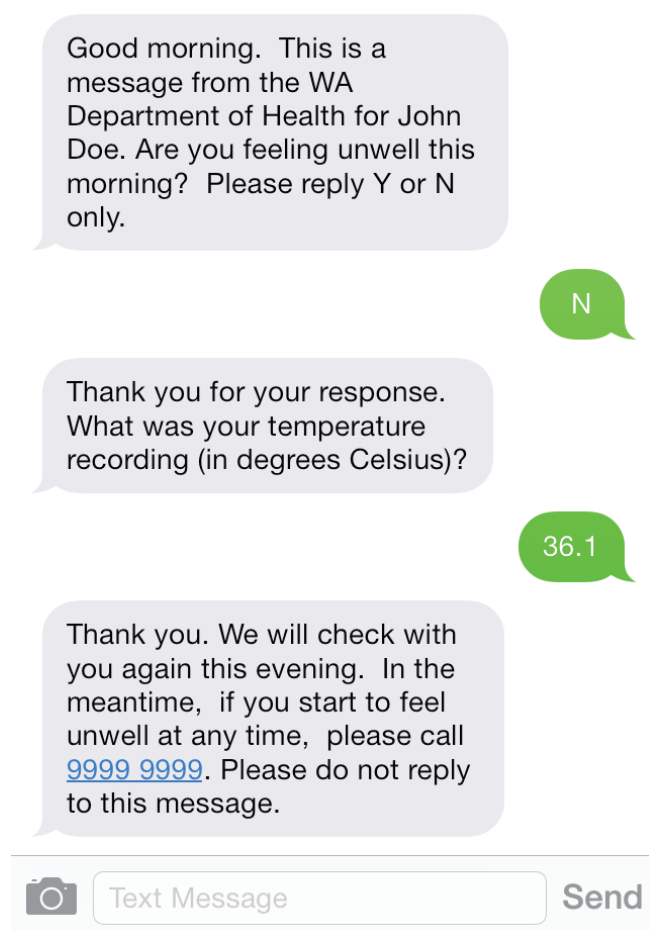
The EbolaTracks software was developed using the database programme FileMaker and runs on the Microsoft Windows 7 operating system. The SMS

functionality utilises an SMS gateway to send and receive messages via mobile telephone networks. Persons under surveillance are requested to take their temperature twice daily between the hours of 8 and 9AM and again between 5 and 6PM.

EbolaTracks participants are contacted twice daily by SMS, at 9AM and 6PM respectively. At each of those times, the system sends two consecutive SMSs. The first SMS asks if the participant is feeling unwell and requests a 'Y' (for yes) or 'N' (for no) response by SMS. Should the participant's response differ from the 'Y' or 'N' format requested, the software can convert ca 50 commonly used variations, such as 'Yes' or 'No', and can appropriately parse answers that include spaces and/or punctuation. Following the first SMS and response, a second SMS asks the participant to report their temperature, recorded in degree Celsius (Figure). In interpreting the participant's SMS response with their temperature, the software will filter out all characters except numbers, full stops and commas.

FIGURE

An example of the text messages sent from EbolaTracks each morning with responses from a fictitious participant



'John Doe' is a fictional name and '9999-9999' is not the actual telephone number provided.

TABLE

Individuals undergoing 21 day health monitoring using EbolaTracks, Western Australia, 21 November 2014–5 January 2015 (n=22)

Residence ^a	Date of last potential exposure to Ebola virus	Monitoring completion date ^b	Risk type[6]	Risk Level [6]
Urban	16/11/2014	06/12/2014	Other	Casual
Urban	19/11/2014	10/12/2014	Healthcare worker	Low
Rural	29/11/2014	19/12/2014	Other	Casual
Urban	29/11/2014	19/12/2014	Other	Casual
Urban	29/11/2014	19/12/2014	Other	Casual
Urban	30/11/2014	20/12/2014	Healthcare worker	Low
Urban	01/12/2014	21/12/2014	Other	Casual
Urban	03/12/2014	23/12/2014	Other	Casual
Urban	06/12/2014	27/12/2014	Other	Casual
Urban	10/12/2014	30/12/2014	Other	Casual
Rural	10/12/2014	17/12/2014	Other	Casual
Rural	10/12/2014	30/12/2014	Other	Casual
Urban	16/12/2014	04/01/2015	Other	Casual
Urban	17/12/2014	02/01/2015	Other	Casual
Urban	18/12/2014	06/01/2015	Other	Casual
Urban	18/12/2014	08/01/2015	Other	Casual
Urban	18/12/2014	08/01/2015	Other	Casual
Urban	18/12/2014	08/01/2015	Other	Casual
Urban	19/12/2014	09/01/2015	Other	Casual
Urban	21/12/2014	11/01/2015	Other	Casual
Rural	21/12/2014	11/01/2015	Other	Casual
Urban	25/12/2014	15/01/2015	Other	Casual

^a Urban means residing within a greater metropolitan area, with access to a tertiary hospital with capacity to test for and treat patients with Ebola virus disease; rural means residing outside a metropolitan area.

^b The monitoring completion date indicates either the end of the 21 day monitoring period or the day the individual left Western Australia.

For any participants who report feeling unwell or a temperature $\geq 37.5^{\circ}\text{C}$, EbolaTracks automatically sends both an SMS and an email alert to an on-call medical officer, who then telephones the individual to assess their condition and determine appropriate management. In addition, if an individual does not respond within an hour, EbolaTracks generates an SMS and email alert to the on-call officer, who then contacts the person to check their condition and to ensure that they are monitoring their temperature. Any SMS responses that cannot be interpreted by the programme are considered non-responses during automated processing and the on-call officer is notified. The on-call officer can review these responses, interpret and manipulate them manually, or may contact the participant if further clarification is needed.

Once enrolled, the automated system will send and receive SMS messages for all active records. Each

participant is included in the process until they reach 21 days after the date of last possible exposure to EVD or they depart WA.

Users of the software have the opportunity to monitor the automated process running in real-time and view the responses as they are received. All historical responses can be reviewed at any time. If no alerts are generated, it means all people currently under surveillance have answered both messages and all have reported being well and afebrile, and no further action is required.

The database used to send and receive SMS messages to/from persons who have been potentially exposed to EVD is maintained on a password protected/secure server within the WA Health Department. Any mobile telephone numbers used are verified with the contact before enrolment in EbolaTracks, and the ensuing SMS communications are subject to the same level of security as voice calls on commercial telephone networks.

Experience using EbolaTracks

EbolaTracks became operational on 21 November 2014. Twenty-two individuals who have arrived in WA from EVD-affected countries have been enrolled as of 5 January 2015 and 14 of these participants have successfully completed active monitoring (Table). The average age of participants was 46 years (range: 28–68 years; 18 men and 4 women), whereby three returned from Guinea, three from Liberia, and 16 from Sierra Leone.

To date, the system has sent a total of 1,108 messages soliciting symptom information, of which 1,008 (91%) received a return SMS; the remaining 100 outgoing EbolaTracks messages received no reply or were uninterpretable and required telephone follow-up by the Department of Health to confirm that the participants remained well and afebrile. Of the 1,008 responses received, 1,007 replies indicated the individuals were well and afebrile; one participant reported an elevated temperature. At the end of December, this non-HCW who had returned from one of the EVD-affected countries six days prior, replied by SMS with a temperature of 37.7°C. This response generated an alert to the on-call medical officer who subsequently interviewed the traveller. Repeated measurements confirmed a low-grade fever but the individual was otherwise asymptomatic at the time of the call. They were advised to stay at home until further notice, and a programme of regular follow-up was established which included more frequent temperature monitoring and regular contact with the medical officer. The low-grade fever resolved within a day and the individual remains well.

Discussion

Interrupting chains of human-to-human transmission is the highest priority for preventing the spread of EVD. Early identification, isolation and testing of suspected cases is essential, both for providing optimal care to patients and for preventing further transmission [4].

Our experience suggests that an SMS-based symptom monitoring system can assist in these goals by facilitating active monitoring of potentially exposed individuals while conserving staff resources. In addition, we found EbolaTracks was relatively straight-forward to develop and implement, built over a 19 day period using a contracted systems designer for a cost of approximately €17,000.

A strength of EbolaTracks is that this system can accommodate large numbers of both potentially exposed incoming travellers from EVD-affected countries and HCWs, household and community contacts exposed to a domestic EVD case. Furthermore, it is easily scalable; while we have demonstrated proof-of-concept in WA, this SMS-based monitoring would likely be even more useful where there are a large volume of contacts to follow-up, for example, in European countries or the US which receive many more travellers from EVD-affected areas than does Australia – or when actively monitoring numerous healthcare and community contacts of an imported or local secondary case. By reducing the resources required to perform active monitoring of contacts, SMS-based systems permit expansion of active monitoring to situations now reliant on passive self-monitoring, thus improving public confidence in EVD control strategies. In our setting at least, an additional positive attribute is that the SMS approach is highly acceptable to participants as it provides potential benefits to them, with minimum imposition or inconvenience.

The potential value of using SMS systems for active monitoring of Ebola contacts is not limited to industrialised countries; mobile phone use is widespread in many parts of Africa and any country with a moderate to high level of mobile phone coverage ought to be able to benefit from this approach [15]. SMS has already successfully been integrated into the public health response to EVD in Nigeria and Senegal. In Nigeria, HCW used a real-time reporting application to upload laboratory test results and receive SMS information on individuals being monitored for EVD symptoms [16], and the United Nations Children's Fund (UNICEF) developed a cascade SMS system to educate people about Ebola virus transmission and prevention [17]. In Senegal, the Ministry of Health sent 4 million SMS messages to the public, warning of the dangers of EVD and how to prevent it as part of a coordinated public awareness campaign [18]. These examples highlight that SMS has already been successfully integrated into the public health response to the EVD outbreak, and our application extends this to automated, active monitoring of persons potentially exposed to EVD.

There are limitations of the SMS-based approach to monitoring EVD contacts. First, SMS monitoring cannot supplant the potential advantages of direct visual inspection recommended for high risk contacts as the lack of fever and illness is not independently verified. Thus, subject to resources, it may be preferable to

monitor persons at very high risk in-person, or potentially using video calls. Second, the system must be adequately explained to participants so that the number of uninterpretable responses and delayed responses requiring follow-up can be minimised. Third, not everybody will have a mobile phone or be able to use one; in our setting, we will provide an inexpensive mobile phone with time-limited credit to contacts who do not already have one, but so far this has not been necessary. Finally, we must acknowledge that some contacts to Ebola cases may be disinclined to self-report illness if they subsequently become unwell. We believe, however, that disincentives to self-reporting can be overcome by ensuring timely access to appropriate diagnostics and prompt provision of high quality medical care, should it be necessary.

As long as the current epidemic continues in West Africa, active monitoring of individuals travelling from EVD-affected countries, particularly those with documented exposures (such as HCW), remains a cornerstone of public health strategies to facilitate early identification of imported cases and prevent local transmission, in both developing and developed countries [19]. In WA, EbolaTracks has proven useful and efficient for monitoring travellers arriving from West Africa. While the future course of the current epidemic is unknown, large numbers of potential exposures stemming from air travel, use of public transport, and healthcare provided to an imported case are not inconceivable, as has occurred in the US [7]. In our assessment, SMS-based fever and symptom monitoring systems could be valuable tools for implementing large-scale active monitoring of contacts exposed to EVD and other serious infectious diseases.

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Conflict of interest

None declared.

Authors' contributions

PE conceived the concept. LT and AR worked with the programmer on the system development and performed data collection and analysis. All authors contributed to development of system methods and protocols. All authors discussed the results, edited and commented on the manuscript draft. All authors read and approved the final manuscript.

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Ebola response missions: To go or not to go? Cross-sectional study on the motivation of European public health experts, December 2014

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We surveyed European infectious disease epidemiologists and microbiologists about their decisions to apply for Ebola response missions. Of 368 respondents, 49 (15%) had applied. Applicants did not differ from non-applicants in terms of age, sex or profession but had more training in field epidemiology and more international experience. Common concerns included lack of support from families and employers. Clearer terms of reference and support from employers could motivate application and support outbreak response in West Africa.

Background

In 2014–15, Guinea, Liberia and Sierra Leone suffered from the largest ever recorded Ebola virus disease (EVD) outbreak [1]. In any response to infectious disease outbreaks, epidemiologists and microbiologists are crucial: they trace contacts, analyse epidemiological data and support laboratory testing [2,3]. The World Health Organizations' (WHO) Global Outbreak Alert and Response Network (GOARN), Médecins Sans Frontières (MSF), the United Nations (UN) and other organisations have been involved in the outbreak response and recruited experts for field missions to West Africa, but the lack of or limited number of volunteers restricted scaling up efforts [4].

Within the last 20 years, the European Union (EU)/ European Economic Area (EEA) countries and – since its foundation in 2005 – the European Centre for Disease Prevention and Control (ECDC) have trained ca 400 epidemiologists and microbiologists in outbreak response through the European Programme for Intervention Epidemiology Training (EPIET), the European Programme for Public Health Microbiology Training (EUPHEM) and associated Field Epidemiology Training Programmes (FETP -e.g. in Germany, Norway, the United Kingdom). The EPIET Alumni Network (EAN) incorporates alumni from these FETPs [5,6].

Between 19 November and 7 December 2014, we surveyed European public health professionals in order to identify motivations and obstacles regarding their involvement in the local response to the Ebola outbreak. The knowledge gained from our study might help deploying organisations to adapt their recruitment strategies and thus strengthen the international response to large-scale outbreaks and other international public health emergencies.

Data collection and analysis

We collected information regarding applications for Ebola response missions, personal and professional background, and views on statements concerning qualification, motivation, fears and concerns related to those missions using a specifically developed online questionnaire.

The questionnaire included 85 questions. It was piloted among experts during the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE, 5–7 November 2014) and programmed in LimeSurvey software, hosted on a server located in the Netherlands [7].

We recruited participants via respondent-driven sampling. First, we sent the online questionnaire to current EAN-members and other members of European public health institutes using informal networks. Second, we invited respondents to further distribute the link to the questionnaire into their professional networks.

We only analysed filled-in questionnaires of participants who had given informed consent. The data protection officer at the Robert Koch Institute approved this anonymous study.

In the analysis, we compared respondents who applied with those who did not apply for Ebola field missions in terms of various characteristics. Additionally, for

each statement we compared agreeing and disagreeing respondents by frequency of applications to Ebola field missions, in order to measure the impact of the statement on the motivation to apply for missions. We calculated prevalence ratios (PR), 95% confidence intervals (95% CI) and p values (chi-square test and t-test) in STATA/SE 12.0 and considered a point estimate $p \leq 0.05$ as statistically significant.

Characteristics of respondents

A total of 368 respondents gave informed consent. Their median age was 38 years (range 21–66 years) and 69% were female. Fifty-one percent (173/342) had children; the median age of the youngest child was 5 years (range 0–37 years). Respondents resided in 32 different countries; 25 of these countries were part of the European Union (represented by 95%; 321/337 respondents); respondents from other countries such as Barbados, Mozambique, Norway, Switzerland, Turkey and the United States were also included.

Of all respondents, 249 (68%) were epidemiologists, 43 (12%) were microbiologists and 98 (27%) specified other professional backgrounds, including statistics, anthropology, biology, and veterinary medicine. Fifty-two percent (138/264) were medical doctors (multiple answers were possible). The median professional experience was six years (range 0–35 years). Most respondents worked in the public sector (97%; 316/327), had a permanent position (64%; 211/330), and had completed (or were currently enrolled in) an FETP (58%; 189/327). Forty-six percent (151/330) were involved in Ebola-related activities at the time of the survey. Twenty-eight percent (93/329) mentioned previous experience in international outbreak response, partly in sub-Saharan Africa ($n = 52$) or other developing countries ($n = 21$).

Fifteen percent (49/329) had applied for recent Ebola missions to West Africa. Deploying organisations included WHO ($n = 34$), MSF ($n = 14$) and others ($n = 16$). Eighteen of the 49 applicants had already completed a mission, including 13 deployed by WHO and two deployed by MSF (average duration of missions 28 days; range 4–60 days).

The vast majority of respondents was fluent in English (89%; 290/327), generally interested in missions (80%; 249/312) and felt physically and psychologically fit (81%; 248/308 and 74%; 229/310, respectively; Figure 1). Less than half considered themselves to be fluent in French (41%; 132/323).

Respondents' views and attitudes on Ebola missions

Seventy five percent of respondents thought they could be of help (245/328), 63% considered themselves qualified (205/328), 67% felt they were sufficiently trained about Ebola (217/325) and 71% had sufficient knowledge about self-protection from Ebola virus infection (229/322). Answers were more diverse concerning

having the required vaccinations (52%; 160/308) and support of their supervisors (46%; 146/314). A minority had previous socio-cultural experience in the affected region (31%; 100/323) or time to go (27%; 82/305). Only 82 of 300 respondents (27%) had been asked directly to join one of the missions.

Factors increasing the motivation to apply for missions

Many respondents pointed to elements that would increase their motivation to apply, including a clear job description (88%; 248/283), meaningful tasks (84%; 233/277), guaranteed medical evacuation (83%; 232/281), a better match with own skills (82%; 230/279) and better preparation (78%; 220/281). Additionally, encouragement by the employer (74%; 205/276), personal recommendation by colleagues (59%; 157/266), or confidence that someone else would take care of their routine work (61%; 163/267) could motivate many experts. The prospects to conduct research studies (35%; 96/271), write publications (32%; 86/272) and better payment (33%; 90/272) were less important in motivating applications (Figure 2).

Factors that may hinder applications

Most respondents stated that their families were concerned about their well-being (87%; 265/303), or that their families did not want them to go (62%; 187/302). Sixty-two percent (196/315) agreed that they were essential at their current job. Fewer considered other issues more important than Ebola (27%; 77/283) or regarded missions as too long (24%; 70/290), or not well enough paid (12%; 34/281). The need to use personal protective equipment (PPE) (16%; 47/297), possibility of quarantine (17%; 49/293) or stigmatisation after return (11% 33/309) did not seem to be a major concern.

Comparison between applicants and non-applicants to Ebola response missions

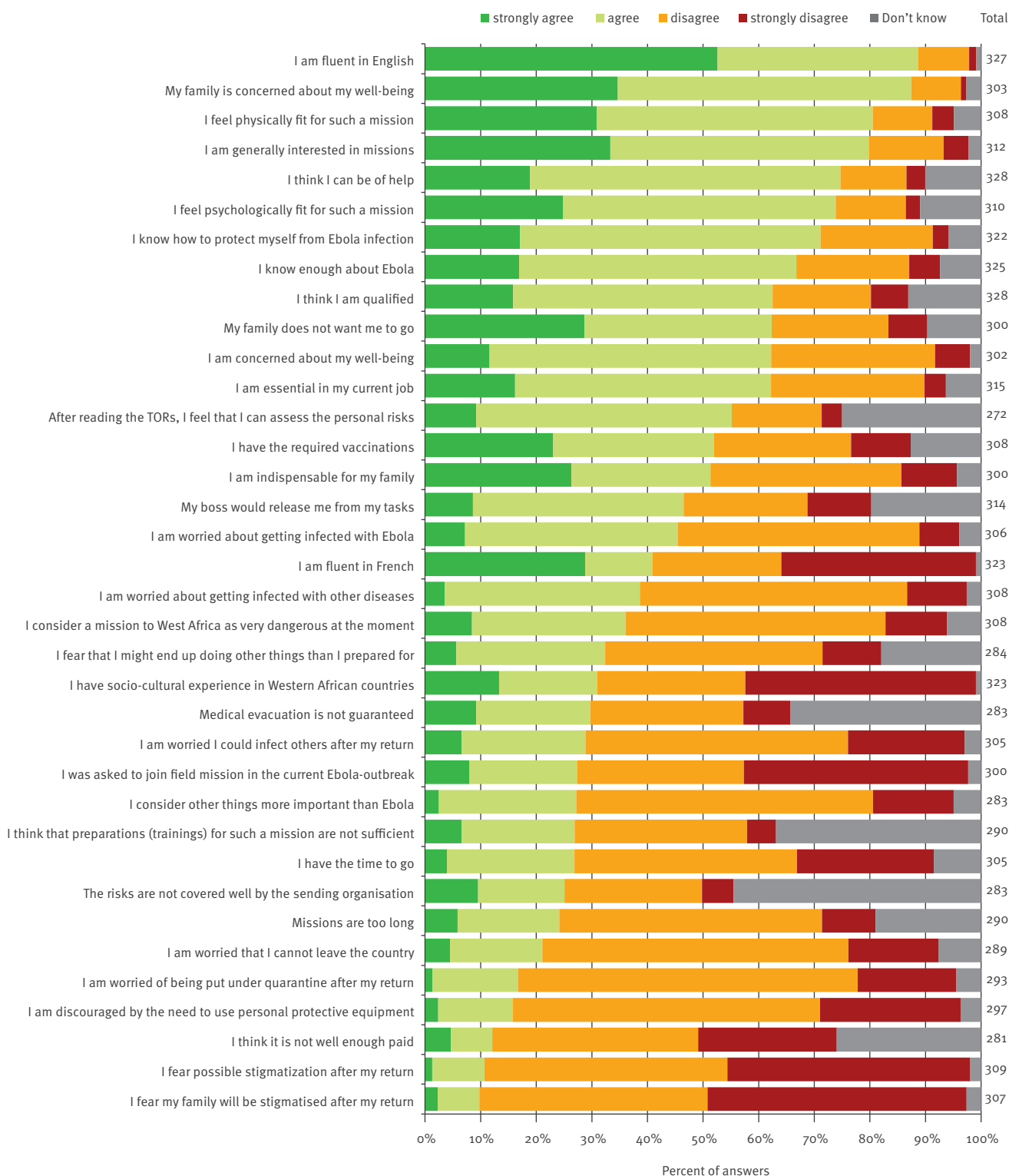
Applicants differed from non-applicants neither in terms of age, sex, professional background, years of experience, nor in the age of their youngest child. However, they less often considered a mission to West Africa as very dangerous (11%; 5/44 vs 43%; 103/239; $p < 0.001$) and less often worried about an Ebola infection (23%; 10/44 vs 52%; 126/244; $p < 0.001$).

Applicants were more often trained in an FETP (76%; 37/49 vs 54%; 145/268, $p = 0.005$) and experienced in international outbreak response missions (59%; 29/49 vs 23%; 62/273; $p < 0.001$), especially in sub-Saharan Africa (46%; 22/48 vs 10% 28/270; $p < 0.001$).

Applicants were significantly more often directly asked to join an outbreak response mission (58%; 22/38 vs 23%; 58/250; $p < 0.001$), had the time to go (59%; 22/37 vs 24%; 58/238; $p < 0.001$), had previous socio-cultural experience in West Africa (59%; 27/46 vs 26%; 69/268; $p < 0.001$), and had the required vaccinations

FIGURE 1

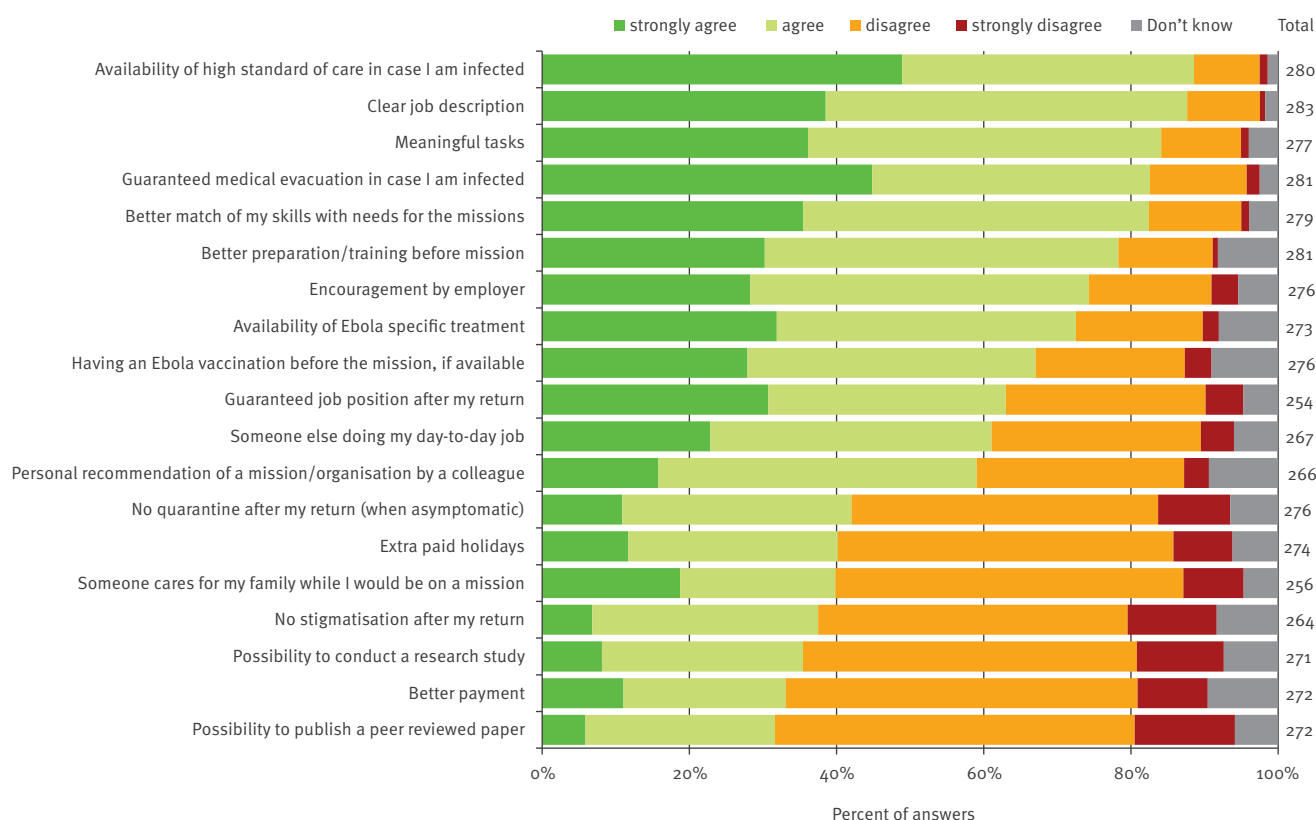
Statements concerning Ebola response mission by level of agreement of European public health professionals, December 2014



TOR: Terms of reference.

FIGURE 2

Motivations for European public health professionals to apply for an Ebola response mission, December 2014



(90%; 37/41 vs 54%; 122/225; $p < 0.001$). Applicants also had more confidence in their knowledge on Ebola (91%; 42/46 vs 69%; 170/248, $p = 0.002$), considered themselves as sufficiently qualified (90%; 43/48 vs 68%; 158/232, $p = 0.003$) and knew how to protect themselves from Ebola (94%; 45/48 vs 72%; 182/252, $p = 0.001$).

Comparison between experts who agree and those who disagree with statements

The table displays the frequency of applications depending on the views and attitudes of respondents (Table).

Nobody applied to an Ebola response mission if not generally interested in such missions, physically fit or convinced to be of help. The proportion of applicants was highest among those who were directly asked to join a mission, had the time to go and had previous socio-cultural experience in West Africa (28%; 22/80 each). Few applicants were found among respondents who were worried about an Ebola infection (8%; 10/136) or considered a mission to West Africa as very dangerous (5%; 5/108).

Experts who had returned from missions

Among the 18 respondents, who had already completed their deployment by the time of the survey, no

one regarded a mission to West Africa currently as very dangerous. However, compared with the applicants who were still ahead of their deployment ($n = 26$), they were less often convinced that reading the terms of references of a mission revealed the associated risks (8/12 vs 17/18). They agreed more often that medical evacuation was not guaranteed (7/12 vs 6/15), that risks were not covered well enough by sending organisations (5/12 vs 4/12), and that the preparation and trainings for such a mission were insufficient (5/12 vs 3/17). In general, they were more concerned about infections with other diseases than Ebola virus disease (7/15 vs 8/25). None of these differences were significant.

Discussion

International efforts to support the local response to the Ebola outbreak in West Africa encounter various difficulties and there may be questions regarding the mandate of deploying organisations, international treaties, and bilateral agreements. However, even if these were resolved, a considerable number of volunteering experts would be needed for a concerted and sustained response. Moreover, the individual decision to go or not to go on an Ebola response mission to West Africa will of course depend on careful personal considerations.

TABLE

Frequency of applications to Ebola response mission among respondents agreeing or not with various statements, European experts, December 2014

Statement ^a	Frequency of applications				Prevalence Ratio ^b	[95%CI]	P value
	Among agreeing respondents		Among disagreeing respondents				
	% (n/N)	% (n/N)	% (n/N)	% (n/N)			
I am generally interested in missions	18	(45/244)	0	(0/55)	NA	NA	0.001
I think I can be of help	20	(48/240)	0	(0/49)	NA	NA	0.001
I feel physically fit for such a mission	18	(45/244)	0	(0/44)	NA	NA	0.002
I feel psychologically fit for such a mission	19	(42/226)	2	(1/46)	8.55	1.21–60.55	0.005
I have the required vaccinations	23	(37/159)	4	(4/107)	6.22	2.29–16.96	<0.001
I know how to protect myself from Ebola infection	20	(45/227)	4	(3/73)	4.82	1.54–15.06	0.001
I know enough about Ebola	20	(42/212)	4	(4/82)	4.06	1.50–10.97	0.002
I was asked to join field mission in the current Ebola outbreak	28	(22/80)	8	(16/208)	3.58	1.98–6.45	<0.001
I have the time to go	28	(22/80)	8	(15/195)	3.58	1.96–6.53	<0.001
I think I am qualified	21	(43/201)	6	(5/79)	3.38	1.39–8.22	0.003
I have socio-cultural experience in Western African countries	28	(27/96)	9	(19/218)	3.23	1.89–5.51	<0.001
My boss would release me from my tasks	21	(30/145)	11	(11/104)	1.96	1.03–3.72	0.034
I am concerned about my well-being	11	(20/185)	23	(24/106)	0.48	0.28–0.82	0.007
I am worried I could infect others after my return	8	(7/84)	18	(37/207)	0.47	0.22–1.00	0.040
I am indispensable for my family	8	(12/152)	21	(28/132)	0.37	0.20–0.70	0.001
I am worried about getting infected with Ebola	7	(10/136)	22	(34/152)	0.33	0.17–0.64	<0.001
I consider a mission to West Africa as very dangerous at the moment	5	(5/108)	22	(39/175)	0.21	0.08–0.51	<0.001

CI: confidence interval; NA: not applicable.

^a Only statements with significant differences are shown.

^b Prevalence ratios are the proportions of applicants in agreeing over proportions of applicants in disagreeing respondents.

Our study may be limited by the convenience sampling, the possibility of information bias - i.e. respondents may have changed their decision and applied afterwards or withdrawn their application, which would result in misclassification - and the influence of social desirability bias. Nevertheless, it clearly showed that many European public health professionals felt sufficiently qualified and were willing to support the Ebola outbreak response in West Africa. Criteria that pertained to most respondents, including all those who applied for a response mission, were general interest in participating in such missions, thinking to be of help and physical fitness. Some respondents had applied for Ebola outbreak response missions despite concerns about their well-being, lack of support by their families, having small children and not having previous experience in international outbreak response missions. FETP training, international experience and confidence in own qualifications encouraged application, indicating the importance of investing into applied epidemiology and public health microbiology trainings.

A variety of obstacles hindered individual engagement though, including family constraints, uncertainty about the involved risks and work-related obstacles. Recently published articles on obstacles for volunteering health

care workers in the United States and the United Kingdom also reported a lack of employers' support [8-10].

The engagement of more than 150 respondents in Ebola-related activities at the time of the survey indicated intensive resource investments of non-affected countries in their own Ebola preparedness efforts. The focus on improving own preparedness in non-affected countries is understandable. However, it might be worth reviewing how this impacts the availability of international experts for the support of affected countries.

Although stigmatisation after return, uncertainties regarding insurance coverage and medical evacuation were not considered to be a major concern, the number of applications for Ebola response missions might increase if deploying organisations took these issues into account in the planning of missions. Our survey showed that clear job descriptions, meaningful tasks, and improved preparation and training efforts would enhance the willingness of experts to apply for Ebola response missions. These understandable and realistic expectations towards the deploying organisations were also supported by the views of returning experts.

Finally, European public health organisations, deploying organisations and policy makers should further improve the required general conditions to enable the deployment of experts to international missions. This includes sustained investment in developing competencies and broadening international experience of experts e.g. through FETPs, and encouraging employers to support their employees if they volunteer for missions. These efforts should strengthen the response to the present Ebola outbreak, as well as improve and secure international response to future crises.

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Conflict of interest

None declared.

Authors' contributions

UR and MD drafted the questionnaire, conducted the analysis, wrote the manuscript; EP, CW, MadH and AG contributed to the questionnaire and revised the draft manuscript.

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Australian Hajj pilgrims' knowledge, attitude and perception about Ebola, November 2014 to February 2015

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Upon return from Hajj 2014, 150 Australian pilgrims were interviewed about their understanding of the Ebola epidemic. Most (89%, 134/150) knew of the epidemic before travelling and 60% (80/134) of those knew Ebola transmits through body fluids. Pilgrims who received pre-travel health advice were more conscious of Ebola (69% vs 31%, $p=0.01$) and adhered better to hand hygiene after touching an ill person (68% vs 31%, $p<0.01$). Mass media was the main information source (78%).

As the largest known, the 2014 Ebola outbreak has affected more than 24,700 people in the three most affected West African countries, claiming ca 10,200 (41%) lives [1,2]. With ca 100,000 pilgrims from those affected countries attending Hajj each year, the possible introduction of Ebola to a Hajj event could be catastrophic. To minimise the risk, the Saudi Arabian authorities suspended Hajj visas for pilgrims from the affected countries and at the time of publication of this report, no Hajj-associated Ebola case has been reported [3]. Without an effective vaccine, public awareness of the need to avoid exposure through minimising contact with patients and body fluids, using personal protective measures, and cancelling non-emergency travel to affected countries remain the mainstays of prevention [4]. However, travellers' awareness about Ebola has not been assessed. We conducted a short survey among Australian pilgrims returning from Hajj 2014 to assess their knowledge about Ebola, its mode of transmission, and their compliance to preventive measures during Hajj.

Survey

Between November 2014 and February 2015, an anonymous cross-sectional survey was conducted among Australian pilgrims returning home from Hajj in October 2014. Participants were recruited by two methods:

pilgrims attending post-Hajj seminars or social gatherings in New South Wales were invited to participate in person; other Australian pilgrims were invited to participate by telephone. The latter group were randomly chosen from a list of participants who took part in an ongoing cluster randomised trial during the Hajj 2014 which has been described elsewhere [5].

The questionnaire collected data on socio-demographic characteristics, travel itinerary, pre-travel health advice, pilgrims' knowledge on Ebola, and compliance to protective measures such as hand hygiene and use of face masks. Pilgrims' knowledge and attitude about Ebola were assessed through five questions: (i) whether the pilgrims had heard about Ebola before their travel; (ii) their knowledge on Ebola transmission; (iii) how serious they thought Ebola was; (iv) how concerned they were about contracting Ebola during Hajj; and (v) their perceived risk of Ebola at Hajj.

Participants' voluntary completion of the questionnaire was implicitly considered as consent and the survey was anonymous. This study was approved by the Human Research Ethics Committee (HREC) at the University of Sydney (Project no: 2014/599).

Knowledge, attitude and perception regarding Ebola among Hajj pilgrims

A total of 150 pilgrims participated. They were between 18 and 72 years old (median: 41 years), and 46% (69/150) were male. Half (75/150) had a university degree and about two thirds (96/150) were employed. One third (49/150) of the participants had pre-existing chronic medical conditions (Table 1). Seventy-nine per cent (119/150) of respondents performed Hajj for the first time, 7% (10/150) for the second time and 16% (24/150) had attended Hajj more than twice.

TABLE 1

Demographic characteristic and knowledge about Ebola of survey participants, Hajj pilgrims, New South Wales, Australia, November 2014–February 2015 (n = 150)

	n (%)	Had knowledge about Ebola
Age (years)		
18–30	28 (19)	25 (89)
31–45	75 (50)	72 (96)
46–65	39 (26)	33 (85)
>65	8 (5)	3 (38)
Sex		
Male	69 (46)	66 (96)
Female	76 (51)	66 (87)
Co-morbidities		
Diabetes	5 (3)	3 (60)
Asthma	9 (6)	8 (89)
Lung diseases	3 (2)	3 (100)
Heart diseases	1 (1)	1 (100)
Cancer	3 (2)	3 (100)
Education level		
None	5 (3)	3 (60)
School certificate (year 10 equivalent)	11 (7)	11 (100)
High school (year 12 equivalent)	22 (15)	19 (86)
Certificate/diploma	32 (21)	28 (88)
University degree	47 (31)	43 (91)
University postgraduate degree	28 (19)	28 (100)
Occupational status		
No	49 (33)	41 (84)
Yes	96 (64)	91 (95)
Occupational type		
Self-employed	17 (11)	17 (100)
Full time	61 (41)	57 (93)
Casual	4 (3)	4 (100)
Part time	14 (9)	13 (93)

Sixty-six per cent (99/150) reported receiving general health advice before Hajj; 20% (n=30) from travel agents, 16% (n=24) from general practitioners, 6% (n=9) from the Internet, 6% (n=9) from friends and family members, 4% (n=6) from the *smartraveller* website (<http://www.smartraveller.gov.au>), 3% (n=4) from professional travel health services and the remaining 11% (n=17) from other sources.

Eighty-nine per cent (134/150) of participants had been aware of the current Ebola outbreak before travelling. Of these, 78% (105/134) reported the mass media as their main source of information, followed by the Internet (9%; n=12), general practitioners (GPs) (6%; n=8), friends and family members (5%; n=6) and travel agents (1%; n=2).

Respondents aged 45 years and younger were more aware of the epidemic than older respondents (94% vs 76%; $p < 0.01$), and those with a university education

were more aware of Ebola than those with less education (54% vs 46%; $p = 0.05$). Pilgrims who sought health advice before travelling were more conscious of Ebola than those who did not seek such advice (69% vs 31%; $p = 0.01$).

Of those who had heard of Ebola, 60% (80/134) stated that the virus transmits through contact with infected body fluids, 17% (n=23) said it spreads through air, 1% (n=1) believed it transmits through contaminated food, whereas 22% (n=30) did not know how it transmits.

Eighty-six per cent (115/134) of participants thought that Ebola is a serious and life-threatening disease, 4% (n=6) thought it is serious but not life-threatening, 1% (n=1) said it is minor infection and 7% (n=10) did not know if it is serious.

Twenty-two per cent (29/134) of those who were aware of Ebola believed there was no risk of contracting it during Hajj, 38% (n=51) thought the risk was low, 19% (n=26) considered it a moderate risk and 21% (n=28) believed the risk was high. Nevertheless, 45% (60/134) were not concerned of contracting Ebola during Hajj, while 29% (n=39) were slightly concerned, 8% (n=11) were moderately concerned and 18% (n=24) were very concerned.

Regarding preventive measures during their tent stay in Mina, Saudi Arabia, about half of the participants reported using face masks, most reported washing hands with plain water and two thirds reported using soap (Table 2). More than half (55%) reported washing their hands after touching an ill person. Those who sought health advice before travelling were more likely to practice hand washing (97% vs 88%, $p = 0.03$), especially after touching an ill person (68% vs 31%, $p < 0.01$).

Of those who observed hand hygiene, 66% (98/148) believed it to be an effective method of preventing infections and 36% (53/148) considered it easy to implement. Of those who used face masks 61% (50/82) did so to protect themselves from disease, and 33% (27/82) to protect themselves from air pollution.

Discussion

This survey indicates that most Hajj pilgrims were aware of the Ebola outbreak. Pilgrims who received travel advice were more informed than those who did not; however, 40% of pilgrims had no accurate knowledge of Ebola transmission. Almost all respondents adhered to hand washing several times a day, but less than half complied with hand hygiene after touching an ill person.

This study shows that 40% of the respondents saw a risk of Ebola at Hajj, but 45% pilgrims had no fear of contracting Ebola during Hajj. Those who were younger and/or had higher levels of education were more aware of Ebola. A survey from the United States showed that

TABLE 2

Respondents' compliance with preventative health measures during Hajj 2014, New South Wales, Australia, November 2014–February 2015 (n = 134)

Preventative measures	Uptake n (%)	Pilgrims' perception about the effectiveness of these measures n (%)			
		Very effective	Moderately effective	A little effective	Not effective
Face mask use	83 (55)	52 (35)	58 (39)	19 (13)	21 (14)
Hand hygiene	148 (99)	107 (71)	29 (20)	10 (7)	4 (3)
Use of soap-based hand disinfectant	111 (74)	56 (37)	45 (30)	16 (11)	33 (22)
Alcoholic hand disinfectant	75 (50)	74 (49)	43 (29)	23 (15)	10 (7)
Avoiding contact with ill people	65 (43)	67 (45)	56 (37)	18 (12)	9 (6)

less educated respondents were more concerned about Ebola than those with better education [6].

Pilgrims who sought pre-travel health advice were more likely to be aware of Ebola and to practise hygienic measures than those who did not seek advice. A large Geo Sentinel study has confirmed that travellers who received pre-travel health advice were less likely to contract infectious diseases [7]. This survey shows that two thirds of pilgrims received some form of pre-travel advice and only one sixth received formal pre-travel advice despite the fact that all pilgrims routinely need to contact healthcare for mandatory vaccinations. This may indicate that although pilgrims visit GPs for vaccinations, formal pre-travel advice or sufficiently long interaction between the healthcare providers and travellers is rare. A previous survey by our team demonstrated that tour operators play an important role in providing Hajj pilgrims with advice on vaccination [8]. A study in the United Kingdom showed that community leaders (e.g. Imams) are important motivators of health promotion measures [9]. Direct engagement with the tour operators and community leaders could help reach the pilgrims with better pre-travel advice.

Adherence of hand hygiene among participants with just water was high (99%), however fewer participants (74%) reported using soap, and compliance with hand washing after touching an ill person was low (55%). The difference between soap use and plain water could reflect Muslims' daily practice of washing their hands, faces and nostrils five times a day before ritual prayer [10]. According to the European Centre for Disease Prevention and Control (ECDC), hand hygiene is strongly recommended for travellers who travel to or in countries affected by Ebola outbreak [11]. Compliance with the use of face mask was also low (55%). These findings are in agreement with a review by Benkouiten et al. who found that compliance of Hajj pilgrims was high for hand hygiene but not for use of face masks [12].

A large proportion of pilgrims reported that mass media was their main source of Ebola knowledge. It has been

demonstrated that social media activity increases during an outbreak and the main influencers of the activity were news media outlets (e.g. CNN, Yahoo, Reuters) [13]. However, social media (e.g. twitter) were also found to be the dominant source of misinformation on Ebola [14]. Therefore, public health authorities should be encouraged to influence social media feeds through integration of correct health education with mass media. Studies involving pilgrims from other countries have shown that pilgrims' exposure to health messages can improve their engagement in protective measures [15] and direct health education for pilgrims is another effective way of improving their knowledge on preventive measures [16].

Although the findings from this survey cannot be generalised for all travellers, they provide important information about the knowledge about Ebola and hygiene practices of participants of one of the world's largest annual mass gatherings. Also, it should be noted that, at the moment, the risk of Ebola at Hajj is only theoretical and there are many other common infections that are preventable (e.g. by vaccination) but often take a heavy toll [17]. More importantly, the risk of Middle East Respiratory Syndrome coronavirus (MERS-CoV) remains a concern, while, according to a survey conducted early last year, only 35% of the Australian Hajj pilgrims were aware of the MERS-CoV epidemic in Saudi Arabia [18]. Public health authorities, media and GPs should encourage the travellers to seek formal travel health advice to prevent those infections. Further studies are needed to analyse this and formulate strategies to keep the travellers informed about infectious diseases.

Conflict of interest

Professor Robert Booy has received funding from vaccine manufacturers; the other authors have declared no conflict of interest in relation to this work.

Authors' contributions

Amani S Alqahtani: designing the study, data collection, analysing data and drafting the manuscript. Harunor Rashid: designing the study, supervising data analysis and revising all versions of the manuscript. Kerrie E. Wiley, Harold W. Willaby, Nasser F. BinDhim, Mohamed Tashani, Anita E. Heywood and Robert Booy: substantial contribution to study design, and drafting and editing the manuscript.

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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

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Current Ebola virus disease (EVD) diagnosis relies on reverse transcription-PCR (RT-PCR) technology, requiring skilled laboratory personnel and technical infrastructure. Lack of laboratory diagnostic capacity has led to diagnostic delays in the current West African EVD outbreak of 2014 and 2015, compromising outbreak control. We evaluated the diagnostic accuracy of the EVD bedside rapid diagnostic antigen test (RDT) developed by the United Kingdom's Defence Science and Technology Laboratory, compared with Ebola virus RT-PCR, in an operational setting for EVD diagnosis of suspected cases admitted to Ebola holding units in the Western Area of Sierra Leone. From 22 January to 16 February 2015, 138 participants were enrolled. EVD prevalence was 11.5%. All EVD cases were identified by a positive RDT with a test line score of 6 or more, giving a sensitivity of 100% (95% confidence interval (CI): 78.2–100). The corresponding specificity was high (96.6%, 95% CI: 91.3–99.1). The positive and negative predictive values for the population prevalence were 79.0% (95% CI: 54.4–93.8) and 100% (95% CI: 96.7–100), respectively. These results, if confirmed in a larger study, suggest that this RDT could be used as a 'rule-out' screening test for EVD to improve rapid case identification and resource allocation.

Introduction

More than one year after the first human-to-human transmission, the largest Ebola virus disease (EVD) outbreak continues in West Africa, with an estimated 24,701 cases reported and 10,194 deaths by 15 March 2015 [1]. To date, Sierra Leone is the most severely affected country.

Case identification is essential for effective EVD control and rapid case detection is critical for rationalisation of resources and implementation of early treatment interventions [2]. A locally adapted EVD clinical case definition allows suspected cases to be identified and isolated in Ebola holding units (EHU), but this alone is inadequate to reliably differentiate EVD cases from patients with other conditions that mimic EVD presentation [3]. A confirmed EVD diagnosis is a prerequisite for transfer of a patient to an EVD treatment centre (ETC) to access EVD-specific care. All patients meeting the suspected case definition require isolation, laboratory sampling and diagnostic testing. For such patients, a negative EVD result is required before admission into general healthcare.

Current EVD diagnosis relies on reverse transcription-PCR (RT-PCR) technology [4]. This test is highly sensitive and specific but requires skilled laboratory personnel and technical infrastructure [5]. In the early months of the current West African outbreak, these personnel and infrastructure were largely absent locally. As the EVD response has grown, laboratory infrastructure in the region has improved, but this may not be sustainable in the long term or available at the onset of future outbreaks. In addition, the current EVD diagnostic pathway has cost, resource and safety implications relating to venous blood sampling inside the EHU, timely transport of samples to the EVD diagnostic laboratory, potential for labelling error, and rapid relay of results [6].

One immunofiltration antigen-based assay developed in the mid-2000s has been tested on field specimens from 2003, but is not yet available in routine clinical practice and requires a photometer for analysis [7].

A rapid diagnostic test for EVD, performed at the bedside in EHUs or other isolation facilities would be of great benefit [8]. The Defence Science and Technology Laboratory (DSTL) in the United Kingdom (UK) has developed a rapid antigen diagnostic test (RDT) for EVD diagnosis. The DSTL EVD RDT is a bedside lateral flow assay using capillary blood rather than venous blood to detect presence of an undisclosed Ebola virus antigen. The test can be conducted and interpreted with minimal training and the result is obtained within 20 min. A semi-quantitative result is obtained by scoring a test line on colour intensity.

In this study, we evaluate the diagnostic accuracy of the DSTL EVD RDT compared with the gold standard Ebola virus (EBOV) RT-PCR in an operational setting for EVD diagnosis of suspected EVD cases admitted to EHUs in the Western Area of Sierra Leone.

Methods

The study was conducted at four EHUs in the Western Area of Sierra Leone that routinely isolated suspected EVD cases and collected diagnostic blood samples for EVD testing: Connaught Government Hospital (the national adult referral hospital), Macauley Street Government Hospital, Rokupa Government Hospital, and Newton Health Centre. These sites belong to a network of holding units supported by King's Sierra Leone Partnership (KSLP) and managed by the Ministry of Health and Sanitation (MOHS) and use a screening tool based on the national case definition for suspected EVD cases, combining exposure risk evaluation and a symptom checklist for identification of suspected EVD cases. Each centre had trained phlebotomists and local healthcare workers who routinely provided patient care. Clinical staff were invited to training in the use of the RDT and study protocol which was undertaken in three one-hour sessions.

Staff who completed the training were approved to enrol patients and perform the RDT. Trained clinical staff obtained verbal informed consent from consecutive patients newly admitted to the EHU during the study period, wearing appropriate personal protective equipment [9]. Patients who could not give informed consent (e.g. due to young age, cognitive impairment or confusion) and patients who withheld consent were not enrolled.

Enrolment occurred on the day of admission or on the following day when patients were admitted during the night. In all cases, enrolment occurred before the results of routine EVD diagnostic testing were available, i.e. only suspected cases were enrolled. The RDT was performed at the bedside. All equipment for the RDT was provided in individually packaged test kits.

Capillary blood for the RDT was obtained using a sterile lancet to prick a finger. Blood was applied to the well of the lateral flow device with a small pipette, followed by three drops of buffer. After 20 min, the RDTs were read in designated areas with good lighting and scores were obtained with the aid of a scorecard. RDTs were scored C when a single control (C) line was visible and CT when the C line and the test (T) line were visible. If visible, the T line was scored [2-10] on colour intensity by matching the T line to samples on the scorecard. Clinical staff performing RDTs were blind to RDT score interpretation.

Venepuncture for routine EVD diagnostic testing was performed as per routine clinical care, usually on the same day as the RDT. Venous blood samples were transported to the Public Health England (PHE) laboratory at Port Loko for EVD RT-PCR testing with the Altona RealStar Filovirus screen kit for real-time PCR (Altona Diagnostics GmbH, Germany). Extraction was performed using a manual method with the Qiagen QIAamp Viral RNA kit (Qiagen). Altona quote a detection limit of 1.39 copies/ μ L of eluate (range: 0.69 to 5.32) for Zaire EBOV and 100% specificity against a range of viruses. In a small number of cases, routine EVD diagnostic testing by RT-PCR on venous blood was performed at other local diagnostic laboratories. Laboratory personnel were blind to the RDT result. The Altona assay has been selected by the World Health Organization (WHO) as the reference standard for this outbreak.

Study enrolment and results were recorded in a password protected spreadsheet and matched to EVD RT-PCR results for analysis by the study coordinator (NFW). Analysis was performed in Excel (Microsoft Corporation), Prism 6 (GraphPad Software, Inc), and Medcalc version 15.2.2 (Medcalc Software, Ostend Belgium). As the DSTL EVD RDT provides a quantitative result, analysis was performed to establish the diagnostic accuracy of the test for the range of CT scores, in comparison with the gold standard result. Results were anonymised before dissemination. Reporting of results follows the STARD (Standards for Reporting Diagnostic Accuracy Studies) statement [10].

The study was approved by the Sierra Leone Ethics and Scientific Review Committee (SLESRC, 16/01/2015).

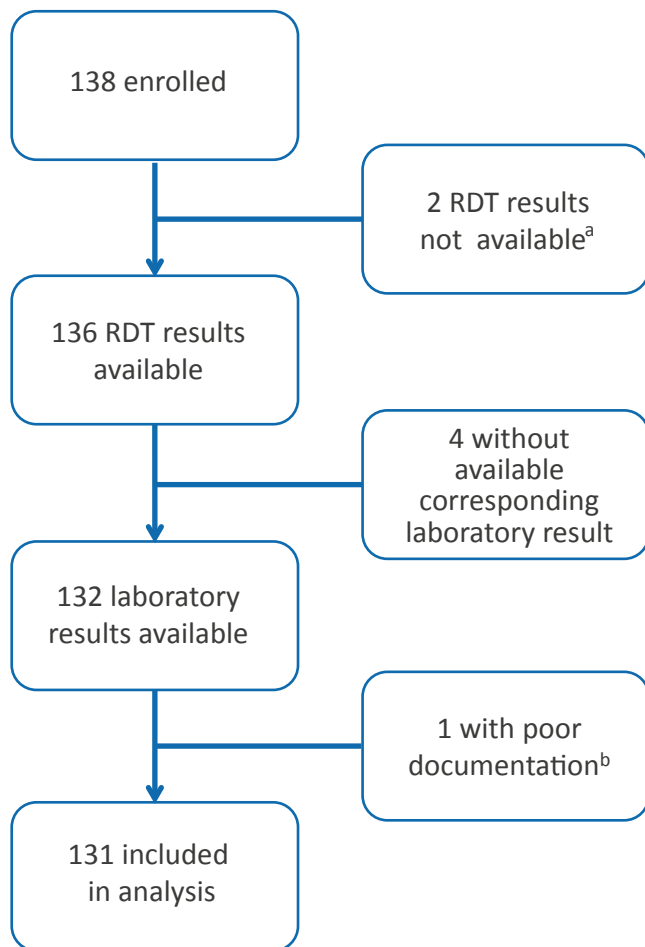
Results

Participants and enrolment

Participants were recruited consecutively at study sites, from 22 January to 16 February 2015. A total of 138 participants were enrolled. At Connaught Hospital, 112 patients were enrolled. This constituted 83% of 135 total admissions at Connaught Hospital EHU during the study period. Seven enrolled participants were excluded at the analysis stage because insufficient information was available (Figure 1). Of these patients, four had RDT tests performed but did not have corresponding EVD RT-PCR results available. The RDT result

FIGURE 1

DSTL rapid diagnostic antigen test for Ebola virus disease, study enrolment and inclusion, Sierra Leone, January–February 2015 (n = 138)



DSTL: Defence Science and Technology Laboratory; RDT: rapid diagnostic antigen test.

^a In one case the RDT attempt failed as an extremely small volume of blood was collected after the pinprick, in a second case no RDT result was documented.

^b Possible double entry of a patient with discordant RDT results

was negative in each of these cases. One patient had a negative EVD RT-PCR result but did not have an RDT result recorded. One patient had neither RDT nor EVD RT-PCR result available. One patient with a negative RDT had no corresponding EVD RT-PCR result available but similar clinical details to a subsequent participant, suggesting that this was an error in documentation and possibly a double entry. Finally, 131 participants were included in the analysis. Of those, 90 (68.7%) were male, and the median age was 32 years (interquartile range (IQR): 24–47 years).

Ebola virus disease diagnosis

Fifteen of 131 patients tested positive for EVD by EVD RT-PCR, giving a study EVD prevalence of 11.5% (Figure 2). Data on duration of symptoms before presentation for EVD-positive patients was available for seven of 15

(47%) cases. In these patients, median symptom duration before date of EVD diagnostic testing was four days (IQR: 3–5 days). The PHE Port Loko laboratory processed 125 of the laboratory samples (95%). Three samples were processed at the PHE Kerry Town laboratory using the same diagnostic assay and standard operating procedure as PHE Port Loko, and three samples were processed at other laboratories.

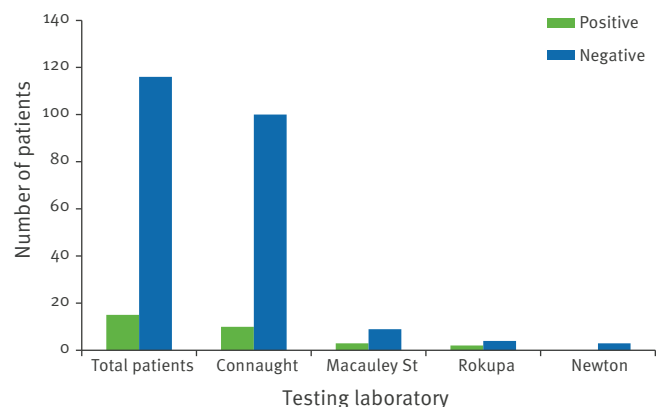
Performance of the rapid diagnostic antigen test

Twenty-four patients had RDT results with both C and T line visible (CT). In 15 of these patients, an EVD diagnosis was made by positive EVD RT-PCR and in nine cases, EVD RT-PCR results were negative (Table 1). In all confirmed cases of EVD, a T line was present on the RDT (Table 1 and Figure 3). Higher CT scores were found in patients with EVD than those without EVD (Table 1 and Figure 3).

Table 2 details the sensitivity and specificity of the RDT with increasing CT score. If any test with a visible T line (corresponding to CT score of CT₂ and above) was classified as positive, the RDT had a sensitivity of 100% (95% confidence interval (CI): 78.2–100) and a specificity of 92% (95% CI: 85.8–96.4) compared with the gold standard RT-PCR. If any test with a T line score above 4 (corresponding to a CT score of CT₆ and above) was classified as positive, the RDT remained 100% sensitive (95% CI: 78.2–100), but had a higher specificity of 97% (95% CI: 91.4–99.1). The specificity of the test increased with higher CT score threshold for a positive result, but the corresponding sensitivity was reduced for a CT score of 8 or above. A specificity of 99% (95% CI: 95.3–100.0) was achievable if an RDT score above

FIGURE 2

Diagnosis by gold standard (Ebola virus PCR) in study participants for the DSTL rapid diagnostic antigen test for Ebola virus disease, Sierra Leone, January–February 2015 (n = 131)



DSTL: Defence Science and Technology Laboratory.

TABLE 1

Results of DSTL rapid diagnostic antigen test for Ebola virus disease, Sierra Leone, January–February 2015 (n = 131)

	RDT result		RDT test (T) line score				
	C	CT	CT ₂	CT ₄	CT ₆	CT ₈	CT ₁₀
EVD PCR-positive (n)	0	15	0	0	4	5	6
EVD PCR-negative (n)	107	9	1	4	2	1	1

DSTL: Defence Science and Technology Laboratory; EVD: Ebola virus disease; RDT: rapid diagnostic antigen test.

CT₈ was classified as positive, but the corresponding sensitivity was low at 40% (95% CI: 16.3–67.7).

The positive predictive value (PPV) of the DSTL EVD RDT, for the study population EVD prevalence of 11.5%, was 79.0% (95% CI: 54.4–93.8) for a CT score of 6 and above and increased at higher CT score thresholds for a positive result (Table 3). A negative predictive value of 100% was achievable if a CT score 2 and above, a CT score 4 and above, or a CT score 6 and above, were classified as a positive result.

Discussion

Our data suggest that the DSTL EVD RDT is highly sensitive, specific and performs well in an operational setting. A high sensitivity is critical to EVD diagnostic test acceptability. A highly sensitive screening test such as this would allow high-risk suspected EVD cases to be prioritised for isolation and confirmatory diagnostic testing with RT-PCR, reducing non-EVD admissions in EHUs. If the sensitivity was lower, EVD-positive cases could be inappropriately discharged to inpatient wards, with risks of onward nosocomial transmission.

Although the specificity was high, a small number of non-EVD patients tested positive with the RDT at all T Line scores. Using the DSTL EVD RDT as a ‘rule-in’ test for EVD would result in some EVD-negative patients being inappropriately referred to ETCs and exposed to nosocomial risk, unless confirmatory testing by RT-PCR was undertaken.

Therefore the RDT may be best used as a ‘rule-out’ screening test. If the high sensitivity of the RDT is confirmed by further evaluation, this would allow RDT-negative patients to be discharged, reducing pressure on isolation unit beds and diagnostic laboratories. It would allow safe and rapid referral of sick, RDT-negative patients to general wards to receive appropriate healthcare, or for patients with milder illness to be discharged. In addition, emergency surgical procedures and obstetric deliveries could be performed without EVD transmission risk, following a negative RDT. This would allow healthcare workers to confidently and safely treat non-EVD conditions without being exposed to potentially infectious patients and may allow normal healthcare services to be maintained in future epidemics. This has been a significant challenge during the current epidemic [11]. Those with a positive RDT should be considered high-probability suspected EVD cases, prioritised for isolation in the appropriate risk-stratified area of the EHU, with confirmatory diagnostic testing performed by RT-PCR.

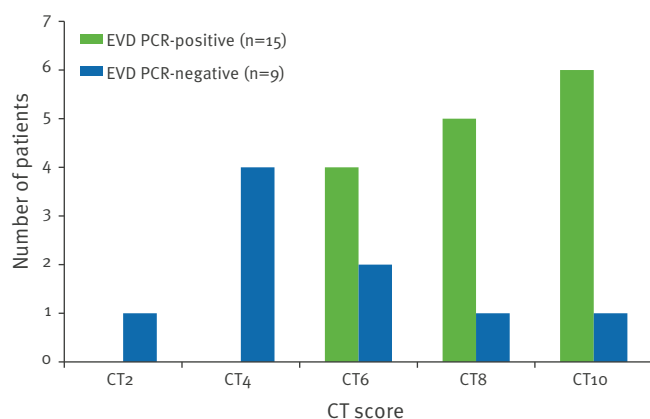
Our results, particularly if confirmed by larger studies on stored samples, support the use of this test for screening purposes.

Limitations

The number of admissions in the study period was lower than expected and the EVD prevalence lower than that observed in late 2014, reducing the power of the study. In addition, it was intended that all consecutive EHU admissions should be recruited at study sites. This was not always possible as a limited number of trained staff were available to enter the EHUs to enrol patients and some patients were unable to give informed consent. However, at Connaught Hospital EHU, the main site of enrolment, the majority (83%) of admissions were enrolled. The wide confidence intervals around sensitivity will need further confirmatory work before routine clinical use.

FIGURE 3

CT scores for the DSTL rapid diagnostic antigen test for Ebola virus disease, Sierra Leone, January–February 2015 (n = 24)



DSTL: Defence Science and Technology Laboratory; EVD: Ebola virus disease.

TABLE 2

Diagnostic accuracy of DSTL rapid diagnostic antigen test for Ebola virus disease compared with gold standard PCR, by CT score, Sierra Leone, January–February 2015 (n = 131)

CT score	Sensitivity %	95% CI	Specificity %	95% CI
≥2	100.0	78.2–100.0	92.2	85.8–96.4
≥4	100.0	78.2–100.0	93.1	86.9–97.0
≥6	100.0	78.2–100.0	96.6	91.4–99.1
≥8	73.3	44.9–92.2	98.3	93.9–99.8
10	40.0	16.3–67.7	99.1	95.3–100.0

CI: confidence interval; DSTL: Defence Science and Technology Laboratory.

The prevalence of EVD was low in our study compared with earlier in the outbreak, when up to 75% of admissions to the Connaught Hospital EHU were EVD-positive. This has resulted in a relatively low PPV for the RDT. As the PPV only applies for a particular population prevalence, the performance of the test should be confirmed at a higher population prevalence. It is likely that the PPV would be higher at a higher EVD prevalence.

We compared the RDT result to gold-standard EVD diagnosis with RT-PCR. The WHO recommends repeat testing of symptomatic patients who test negative for EVD by RT-PCR less than three days after the onset of their illness, as the sensitivity of EVD RT-PCR may be lower early in the clinical course of EVD [4]. Our routine practice complied with this policy. However, it remains possible that we have classified some patients as false-positive RDTs who were infected with Ebola virus but had RT-PCR results below the assay detection limits. If this was the case, our study underestimates the diagnostic accuracy of the DSTL EVD RDT. PHE has now moved to an alternative in-house assay which is more sensitive than the Altona RT-PCR and may verify the DSTL test results in any future work. Further study is required to assess the performance of the RDT early

TABLE 3

Positive and negative predictive values of DSTL rapid diagnostic antigen test for an Ebola virus disease prevalence of 11.5%, by CT score, Sierra Leone, January–February 2015 (n = 131)

CT score	PPV %	95% CI	NPV %	95% CI
≥2	62.5	40.6–81.2	100.0	96.6–100.0
≥4	65.2	42.7–85.6	100.0	96.6–100.0
≥6	79.0	54.4–93.8	100.0	96.7–100.0
≥8	84.6	54.5–97.6	96.6	91.5–99.1
10	85.7	42.2–97.6	92.7	86.7–96.6

CI: confidence interval; DSTL: Defence Science and Technology Laboratory; NPV: negative predictive value; PPV: positive predictive value.

in the clinical course of EVD and in the EVD incubation period.

Relationship to other studies

The WHO approved the first RDT for use as a screening test for EVD (ReBOV Antigen Rapid Test) on the basis of a reported sensitivity of 91.8% (95% CI: 84.5–96.8) and a specificity of 84.6% (95% CI: 78.8–89.4). This RDT was evaluated on 147 fresh venous blood and 146 frozen plasma samples in a laboratory setting in Sierra Leone [12]. Performance of this test in an operational setting has not been reported. Our findings suggest that the DSTL EVD RDT performs well against this benchmark, exceeding these reported findings in an operational setting.

Conclusion

The performance of the DSTL EVD RDT in this study strongly supports its use as a ‘rule-out’ screening test for EVD. Further laboratory and operational data are required to improve confidence and inform further on sensitivity and specificity in a broader setting.

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Conflict of interest

None declared.

Authors’ contributions

NF Walker, CS Brown, D Youkee, K Russell, N Bentley, T Boyles, A Simpson, T Brooks, A Kamara, TB Kamara, M Lado, O Johnson designed the research; NF Walker, P Baker, D Youkee, N Williams, A Kalawa, B Healey and the RDT study team performed the research; AF Samba, F Koroma, MB King, BE Parker, M Thompson, B Kargbo, D Bash-Taqi, TB Kamara, A Kamara contributed vital technical support; NF Walker, CS Brown, P Baker analysed the data; NF Walker, CS Brown, P Baker, T Boyles wrote the draft manuscript; all authors have seen and approved the final manuscript.

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Preparedness for admission of patients with suspected Ebola virus disease in European hospitals: a survey, August-September 2014

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In response to the Ebola virus disease (EVD) outbreak in West Africa, the World Health Organization has advised all nations to prepare for the detection, investigation and management of confirmed and suspected EVD cases in order to prevent further spread through international travel. To gain insights into the state of preparedness of European hospitals, an electronic survey was circulated in August–September 2014 to 984 medical professionals representing 736 hospitals in 40 countries. The survey addressed the willingness and capacity to admit patients with suspected EVD as well as specific preparedness activities in response to the current Ebola crisis. Evaluable responses were received from representatives of 254 (32%) hospitals in 38 countries, mostly tertiary care centres, of which 46% indicated that they would admit patients with suspected EVD. Patient transfer agreements were in place for the majority of hospitals that would not admit patients. Compared with non-admitting hospitals, admitting hospitals were more frequently engaged in various preparedness activities and more often contained basic infrastructural characteristics such as admission rooms and laboratories considered important for infection control, but some gaps and concerns were also identified. The results of this survey help to provide direction towards further preparedness activities and prioritisation thereof.

Introduction

The unprecedented and devastating epidemic of Ebola virus disease (EVD) in West Africa, with over 15,000 reported cases and nearly 5,500 deaths as of 21 November 2014 [1], has ignited increasing global concerns about the potential introduction and

further spread of the disease by international travel and repatriation [2–4]. For this reason, the World Health Organization (WHO) has advised all nations, including those not directly neighbouring currently-affected countries, to prepare for the detection, investigation and management of confirmed and suspected EVD cases [4]. In view of the non-specific nature of initial symptoms, suspected patients essentially include all travellers with unexplained febrile illness recently arrived from areas with ongoing EVD transmission, particularly when accompanied by gastrointestinal symptoms. The current assessment is that travel-associated cases will remain rare across Europe, but that the occurrence of EVD in returning healthcare workers is a realistic scenario [5,6]. The recent experiences with both types of EVD cases in the United States and Europe, with local transmission to healthcare workers, illustrate the importance of being prepared [7,8].

To gain insights into the preparedness of European hospitals and identify potential gaps in preparedness at hospital level, we conducted a survey of hospitals in 40 European and western Asian countries, focusing on the willingness and capacity to admit patients with suspected EVD and on specific preparedness activities of hospitals in response to the current Ebola crisis. It should be emphasised that the survey did not address preparedness for EVD at national levels but was solely intended to explore the preparedness at the hospital level.

This survey is an initiative of the PREPARE project. PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics) is an European Union

TABLE 1

Admission, guidelines and preparedness for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014

	Total (%)	Would admit patient with suspected EVD (%)	Would not admit patient with suspected EVD (%)	Do not know (%)	p-value
Hospital type	236	111 (47.0)	99 (42.0)	26 (11.0)	-
Primary	5 (2.1)	2 (1.8)	2 (2.0)	1 (3.8)	-
Secondary	46 (19.5)	13 (11.7)	23 (23.2)	10 (38.5)	-
Tertiary	185 (78.4)	96 (86.5)	74 (74.7)	15 (57.7)	-
National guidelines					
Yes	181 (76.7)	90 (81.1)	75 (75.8)	16 (61.5)	0.047
No	30 (12.7)	14 (12.6)	13 (13.1)	3 (11.5)	-
Do not know	25 (10.6)	7 (6.3)	11 (11.1)	7 (26.9)	-
Topics covered					
Triage criteria	165 (91.2)	83 (92.2)	70 (93.3)	12 (75.0)	0.78
EBOV diagnostics	160 (88.4)	84 (93.3)	64 (85.3)	12 (75.0)	0.09
Other diagnostics	143 (79.0)	79 (87.7)	54 (72.0)	10 (62.5)	0.01
Infection control	174 (96.1)	89 (98.9)	72 (96.0)	13 (81.2)	0.23
Clinical management	137 (75.7)	76 (84.4)	52 (69.3)	9 (56.2)	0.02
Hospital guidelines					
Yes	153 (64.8)	93 (83.8)	52 (52.5)	8 (30.8)	<0.01
No	60 (25.4)	13 (11.7)	36 (36.4)	11 (42.3)	-
Do not know	23 (9.7)	5 (4.5)	11 (11.1)	7 (26.9)	-
Topics covered					
Triage criteria	146 (95.4)	90 (96.8)	49 (94.2)	7 (87.5)	0.46
EBOV diagnostics	123 (80.4)	82 (88.2)	38 (73.1)	3 (37.5)	0.02
Other diagnostics	133 (86.9)	90 (96.8)	38 (73.1)	5 (62.5)	<0.01
Infection control	151 (98.7)	93 (100)	51 (98.1)	7 (87.5)	0.18
Clinical management	118 (77.1)	79 (84.9)	34 (65.4)	5 (62.5)	<0.01
Preparedness efforts					
Revision protocols	168 (71.2)	95 (85.6)	64 (64.6)	9 (34.6)	<0.01
Training HCW	131 (55.5)	81 (73.0)	46 (46.5)	4 (15.4)	<0.01
Hospital OMT	121 (51.3)	79 (71.2)	41 (41.4)	1 (3.8)	<0.01
National OMT	89 (37.7)	57 (51.4)	31 (31.3)	1 (3.8)	<0.01
Exercise	67 (28.4)	51 (45.9)	16 (16.2)	0 (0)	<0.01

EVD: Ebola virus disease; EBOV: Ebola virus; HCW: healthcare worker; OMT: outbreak management team.

Primary care: general practice and basic district hospital services; secondary care: district hospitals with basic specialty functions; tertiary care: specialised care, usually on referral from primary or secondary care, with facilities for special investigations and treatment.

(EU)-funded project that aims to establish preparedness for harmonised clinical research studies on epidemic infectious diseases, hence providing real-time evidence for clinical management of patients and to inform public health responses (www.prepare-europe.eu). PREPARE is a partnership of established and developing European clinical research networks, covering primary care (GRACE and TRACE) and hospital care (CAPNETZ, COMBACTE, ESICM and PENTA) in more than 40 European countries, including all EU Member States. The survey was performed in above-mentioned hospital care networks.

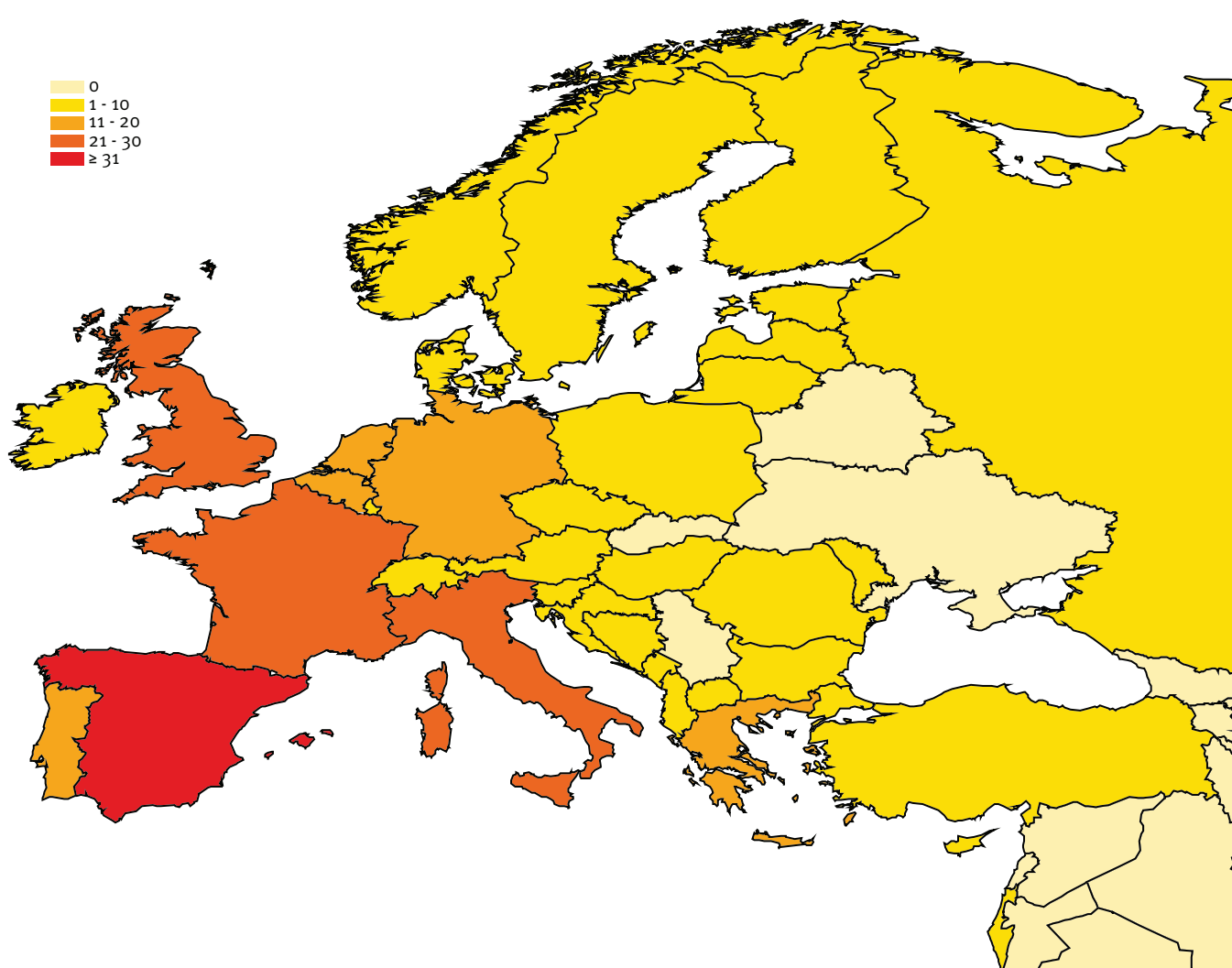
Methods

Survey

A questionnaire was developed in English, addressing: characteristics of the hospital such as the geographic location, type (primary, secondary or tertiary care) and size of the hospital; the availability and content of national and hospital guidelines or protocols for the management of patients with suspected or confirmed haemorrhagic fever; the performance of preparedness activities in response to the Ebola crisis (e.g. revision of protocols, exercises to test the protocols, formation of a hospital outbreak management team, training of healthcare workers, or immediate plans to do so); and arrangements for Ebola virus (EBOV) diagnostics.

FIGURE 1

Geographic distribution and numbers of responding hospitals, survey on willingness and capacity to admit patients with suspected Ebola virus disease, August–September 2014 (n=236)



In addition, the questionnaire asked whether hospitals would, in principle, admit patients with suspected EVD, and if not, whether local or national agreements were in place for transfer to another hospital. For hospitals that would admit patients with suspected EVD, additional questions were asked about the characteristics of admission rooms (e.g. presence of an ante-room, negative pressure, high-efficiency particulate air (HEPA) filtration). An open question was added to capture specific suggestions or needs in relation to EVD preparedness that could be addressed by the PREPARE project. Respondents could indicate whether or not permission was granted to use the anonymised results in reports or publications. The complete questionnaire is available upon request from the authors.

After pilot testing in three hospitals, an online link to the electronic questionnaire was circulated by email to 984 medical professionals representing 736 hospitals in 38 European and 2 western Asian countries (Turkey and Israel). All hospitals were affiliated with the

PREPARE project through membership of one or more of the following clinical research networks: CAPNETZ (www.capnetz.de), COMBACTE (www.combacte.com), ESICM (www.esicm.org), and PENTA (www.penta-id.org).

The survey was started on 27 August 2014 and closed on 19 September 2014. Reminders to complete the survey were sent weekly during this three-week survey period.

Analysis

Descriptive statistics were used to analyse the survey data at the hospital level. In case of discrepant responses from multiple representatives of the same hospital, affirmative or negative answers took precedence over 'do not know' replies. Comparisons were made between hospitals that would admit patients with suspected EVD and those that would not or did not know. In addition, comparisons were made between hospitals in the four regions of Europe

(eastern, northern, southern, western) and western Asia, as defined by the United Nations Statistics Division's Geoscheme [9]. Differences between groups were analysed using chi-squared statistics. A p-value of less than 0.05 was considered significant. Analyses were performed using Microsoft Excel version 14.4.3 (Microsoft Corporation).

Results

Survey characteristics

Responses were received from 266 out of 984 (27%) medical professionals of whom 12 did not provide permission to use the data for reporting. The remaining 254 respondents represented 236 of 736 hospitals (32%) in 38 European and western Asian countries. The majority of respondents were intensivists (122, 48%), followed by internists/infectious disease specialists (49, 19%) and clinical microbiologists (42, 17%). Among the remaining respondents were infection control specialist (19, 8%) and paediatricians (9, 4%). Hospitals represented in the survey were mostly tertiary care centres (78%) and were widely distributed across Europe and western Asia (Table 1, Figure 1).

Admission of patients with suspected EVD and characteristics of admission rooms

Of 236 hospitals, 111 (47%) stated that they would admit suspected EVD patients, 99 (42%) indicated that they would not admit such patients, and 26 (11%) did not know whether such patients would be admitted (Table 1). In the 99 hospitals indicating they would not admit patients, local or national agreements for transfer of patients were in place in the majority (local 25 (25%), national 67 (68%). Admission rooms of most of the 111 admitting hospitals, the majority of which were tertiary care centres (87%), had an anteroom (87%), availability of negative pressure (69%), and/or the presence of dedicated ventilation systems (59%) (Figure 2A). Less than half used HEPA filtration of exhausted air (42%). In five hospitals (5%), none of these assets were available.

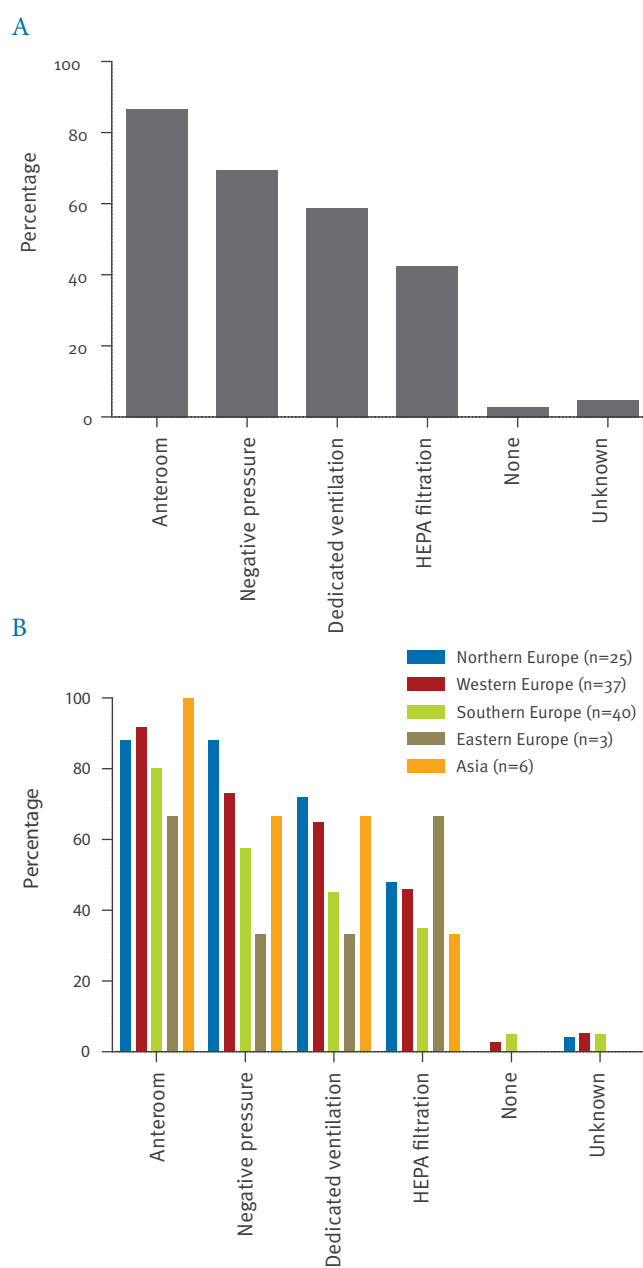
National and hospital guidelines for management of EVD patients

Respondents from 181 hospitals (77%) were aware of the existence of national guidelines for management of patients with haemorrhagic fever (including EVD) while 30 hospitals (13%) indicated these were not available. The remaining respondents did not know (Table 1). Available guidelines were based on those from WHO (63%), the European Centre for Disease Prevention and Control (ECDC) (43%) and/or the US Centers for Disease Control and Prevention (CDC) (34%), and covered triage criteria and infection control practices in more than 90% of guidelines, while diagnostics and clinical management were covered less frequently (Table 1).

Local hospital guidelines were available in 153 of 236 hospitals (65%), not available in 60 hospitals (25%) and the remaining respondents did not know (Table 1).

FIGURE 2

Characteristics of admission facilities in hospitals admitting Ebola virus disease-suspected patients, survey on willingness and capacity to admit patients with suspected Ebola virus disease, August–September 2014 (n=111)



HEPA: high-efficiency particulate air.

Percentages are represented overall (A) and per region (B).

Guidelines were based on national guidelines in 81% and on international guidelines in the remaining cases (19%). Similar to national guidelines, triage criteria and infection control practices were covered in more than 95% of local guidelines with less frequent coverage of other topics.

The availability of national, and even more so of hospital guidelines was highest in hospitals that would

TABLE 2

Laboratory infrastructure and diagnostics for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian hospitals, August–September 2014

	Total (n=236) (%)	Would admit patient with suspected EVD (n=111) (%)	Would not admit patient with suspected EVD (n=99) (%)	Do not know (n=26) (%)
Microbiology laboratory present	231 (97.9)	109 (98.2)	97 (98.0)	25 (96.2)
BSL2				
Yes	132 (57.1)	76 (69.7)	49 (50.5)	7 (28.0)
No	26 (11.3)	9 (8.3)	16 (16.5)	1 (4.0)
Do not know	73 (31.6)	24 (22.0)	32 (33.0)	17 (68.0)
BSL3				
Yes	56 (24.2)	39 (35.8)	14 (14.4)	3 (12.0)
No	93 (40.3)	43 (39.4)	46 (47.4)	4 (16.0)
Do not know	82 (35.5)	27 (24.8)	37 (38.1)	18 (72.0)
Ebola virus diagnostics				
On site	17 (7.2)	14 (12.6)	1 (1.0)	2 (7.7)
National reference laboratory	140 (59.3)	64 (57.7)	65 (65.7)	11 (42.3)
International reference laboratory	30 (12.7)	22 (19.8)	8 (8.1)	0 (0)
Not performed	4 (1.7)	3 (2.7)	1 (1.0)	0 (0)
Do not know	45 (19.1)	8 (7.2)	24 (24.2)	13 (50.0)

EVD: Ebola virus disease; BSL: biosafety level.

admit patients with suspected EVD compared with those that would not admit patients or did not know (Table 1).

Laboratory infrastructure and Ebola virus diagnostics
Microbiology laboratories were present in nearly all hospitals (98%) (Table 2). In these laboratories, biosafety level (BSL) 2 and 3 facilities were available in 57% and 24%, respectively and not available in 11% and 40%, respectively. In the remaining cases respondents were not aware of the biosafety levels of the laboratory (32% and 36%, respectively). Availability of BSL 2 and 3 facilities was higher in hospitals that would admit patients (70% and 36%, respectively) compared with those that did not (51% and 14%, respectively).

EBOV diagnostics were performed on site in 17 hospitals, which included 14 hospitals that would admit patients, 1 that would not admit patients and 2 that did not know. For the majority of remaining hospitals, agreements and procedures were in place for performance of Ebola diagnostics in national (59%) or international (13%) reference laboratories.

Preparedness activities

Preparedness activities in response to the EVD outbreak included revision of hospital protocols or guidelines in 168 hospitals (71%), education and training of healthcare workers (HCWs) in 131 (56%), formation of an outbreak management team (OMT) in 121 (51%) and participation in regional or national preparedness committees in 89 (38%) (Table 1). In 67 hospitals (28%), exercises to test procedures and protocols were

completed or planned in the immediate future. All preparedness activities were performed more frequently in hospitals that would admit patients (Table 1, Figure 3).

Regional differences in Europe

Northern and western Europe had the highest proportions of hospitals that would admit patients with suspected EVD (57% and 56% respectively) and this proportion was lowest in eastern European states (12%) (Table 3). Differences were noted between regions with respect to availability of national and local guidelines, laboratory infrastructure and preparedness activities, with highest frequencies mostly observed in western European countries, followed by southern, northern and eastern European states (Table 3, Figure 2B).

Inventory of needs and suggestions

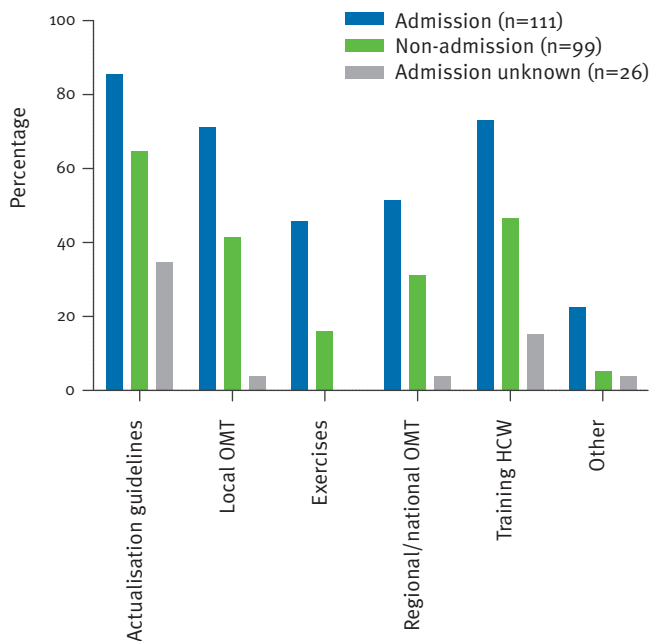
Suggestions were received from 60 of 266 respondents, of whom 42 (70%) emphasised the need for education, information and harmonised guidelines for infection control, diagnostic procedures and clinical management. Most remaining suggestions pertained to the need for support and clinical research in affected West African countries.

Discussion

Our exploratory survey was initiated less than three weeks after WHO's Public Health Emergency of International Concern (PHEIC) declaration on 8 August 2014 [4], to provide initial insights into the state of EVD preparedness in European hospitals at that time. It should be emphasised that this survey explored the

FIGURE 3

Preparedness activities for patients with suspected Ebola virus disease in European hospitals, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014



HCW: healthcare workers; OMT: outbreak management team.

Percentages are shown separately for admitting and non-admitting hospitals and for those not aware whether Ebola virus disease-suspected patients would be admitted.

preparedness to admit patients with suspected EVD at the level of hospitals and no inferences can be made from the results of this survey with regards to preparedness at national levels.

At the time of the survey (August–September 2014), the vast majority of admitting hospitals were engaged in various preparedness activities such as revision of protocols, training of HCWs and implementation of a local OMT. Recent healthcare-associated cases in the US and Spain have demonstrated the importance of training of HCWs in personal protective equipment regimens [7,8], and the finding that 27% of hospitals indicated they had not performed or planned training of HCWs shows room for improvement. At the time of the survey, 46% of admitting hospitals had planned or carried out exercises to test protocols. Given the complexity of issues surrounding admission of patients with suspected EVD, such exercises are essential. Preparedness activities were significantly less frequent in hospitals that would not admit patients or were not sure whether they would. Although unlikely, suspected EVD patients may present at any healthcare setting, and so awareness of initial management of suspected cases is important for all settings, including non-admitting centres. Almost all respondents indicated the availability of initial triage protocols, suggesting that undetected hospitalisations are unlikely. However, some training of HCWs

for this scenario also in non-admitting hospitals seems prudent.

Technical characteristics of admission rooms varied across admitting hospitals, with differences observed between European regions. Admission rooms in a substantial proportion of hospitals lacked one or more characteristics considered to be important for control of highly infectious pathogens and 5% of hospitals appeared to have none of these characteristics. The required conditions for treatment of EVD patients is an issue of some debate: EBOV is not considered to be transmitted by aerosol, which is the underlying assumption in the design of high-containment patient rooms, but the intensive-care setting may include exceptional circumstances where infectious droplets or aerosols may be generated, e.g. during intubation and ventilation [10,11]. Therefore, while standard contact precautions would generally suffice for management of EVD patients, this may differ for such high-care settings. Our analysis did not provide this level of detail. Of note, the proportions of hospital admission rooms with characteristics such as the presence of an ante-room and availability of negative pressure were higher than observed in a previous survey of emergency departments in 14 European countries (87% and 69% vs 46% and 42%, respectively) but, not unexpectedly, lower than those observed in a survey of 48 isolation facilities for highly infectious diseases in 16 European countries (100% and 90% respectively) [12,13].

With regards to laboratory infrastructure, our survey data lacked the resolution to assess in detail whether and to what extent laboratories are compliant with recommendations from WHO, ECDC and/or CDC. However, it should be noted that 8% of admitting hospitals did not appear to have the absolute minimal level laboratory containment (BSL2) needed for handling specimens from EVD patients, which indicates less than optimal capacity for biocontainment during processing blood specimens for EBOV diagnostics and/or routine supportive diagnostics. During the course of illness, clinical specimens can contain very high viral loads for extended periods of time [14,15], and a careful assessment of the risks for processing such specimens in the local laboratories is crucial. Laboratories without BSL2 containment should therefore be encouraged to upgrade their facilities and refer samples to laboratories with BSL2 or preferably BSL3 facilities in the meantime.

Availability of national and local hospital guidelines for management of patients with (suspected) haemorrhagic fever was indicated by a majority of respondents with highest availabilities observed in admitting hospitals and in western European countries. Of note, discordant responses from the same country in relation to availability of national guidelines were observed on several occasions (data not shown), indicating that differences in awareness of guidelines exist within countries. This might illustrate the importance and

TABLE 3

Geographical comparisons of hospitals and willingness and capacity to admit patients with suspected Ebola virus disease, results from survey of representatives from 236 hospitals in 38 European and western Asian countries, August–September 2014

	Geographical region ^a				
	Northern Europe	Southern Europe	Eastern Europe	Western Europe	Western Asia
Number of hospitals (%)					
Received questionnaire	138	257	106	219	16
Responded	44 (31.8)	93 (36.2)	26 (24.5)	66 (30.1)	7 (43.8)
Would admit suspected EVD patient	25 (56.8)	40 (43.0)	3 (11.5)	37 (56.1)	6 (85.7)
Would not admit suspected EVD patient	14 (31.8)	41 (44.1)	18 (69.2)	25 (37.9)	1 (14.3)
Do not know	5 (11.4)	12 (12.9)	5 (19.2)	4 (6.1)	0 (0)
National guidelines					
Yes	34 (77.3)	71 (76.3)	12 (46.2)	57 (86.4)	7 (100)
No	3 (6.8)	15 (16.1)	6 (23.1)	6 (9.1)	0 (0)
Do not know	7 (15.9)	7 (7.5)	8 (30.8)	3 (4.5)	0 (0)
Hospital guidelines					
Yes	26 (59.1)	57 (61.3)	12 (46.2)	53 (80.3)	5 (71.4)
No	11 (25.0)	28 (30.1)	10 (38.5)	10 (15.2)	1 (14.3)
Do not know	7 (15.9)	8 (8.6)	4 (15.4)	3 (4.5)	1 (14.3)
Preparedness efforts					
Revision of protocols	26 (59.1)	65 (69.9)	14 (53.8)	56 (84.8)	6 (85.7)
Training HCWs	17 (38.6)	50 (53.8)	15 (57.7)	44 (66.7)	5 (71.4)
Hospital OMT	18 (40.1)	46 (49.5)	9 (34.6)	43 (65.2)	5 (71.4)
National OMT	10 (22.7)	33 (35.5)	6 (23.1)	37 (56.1)	3 (42.9)
Exercise	8 (18.2)	24 (25.8)	3 (11.5)	31 (47.0)	1 (14.3)
Admission rooms					
Anteroom	22 (88.0)	32 (80.0)	2 (66.7)	34 (91.9)	6 (100)
Negative pressure	22 (88.0)	23 (57.5)	1 (33.3)	27 (73.0)	4 (66.7)
Dedicated ventilation	18 (72.0)	18 (45.0)	1 (33.3)	24 (64.9)	4 (66.7)
HEPA filtration	12 (48.0)	14 (35.0)	2 (66.7)	17 (45.9)	2 (33.3)
None	0 (0)	2 (5.0)	0 (0)	1 (2.7)	0 (0.0)
Unknown	1 (4.0)	2 (5.0)	0 (0)	2 (5.4)	0 (0.0)
Laboratories					
Microbiology laboratory	44 (100)	92 (98.9)	24 (92.3)	65 (98.5)	7 (100)
BSL2					
Yes	18 (40.9)	51 (55.4)	11 (45.8)	46 (70.8)	6 (85.7)
No	4 (9.1)	16 (17.4)	2 (8.3)	3 (4.6)	1 (14.3)
Unknown	22 (50.0)	25 (27.2)	11 (45.8)	16 (24.6)	0 (0)
BSL3					
Yes	10 (22.7)	19 (20.7)	2 (8.3)	24 (36.9)	1 (14.3)
No	11 (25.0)	44 (47.8)	11 (45.8)	21 (32.3)	6 (85.7)
Unknown	23 (52.3)	29 (31.5)	11 (45.8)	20 (30.8)	0 (0)

BSL: biosafety level; EVD: Ebola virus disease; HCW: healthcare worker; HEPA: high-efficiency particulate air; OMT: outbreak management team.

^a European regions according to United Nations Geoscheme (United Nations Statistics Division, <http://unstats.un.org/unsd/methods/m49/m49regin.htm>) [7]. Included Asian countries are Israel and Turkey.

challenges of dissemination of guidelines, also at national levels. At the same time, the need and desire for guidance was illustrated by responses to our open request for suggestions, the vast majority of which emphasised a need for education, information and harmonised guidelines, especially for diagnostic issues and clinical management of patients.

Our survey has several limitations. First of all, although the geographical distribution of participating hospitals across Europe was excellent, the survey results may not be fully representative of European medical professionals and hospitals for several reasons. The survey was circulated only to hospitals actively participating in established clinical networks and these may not be representative of European hospitals overall. Furthermore, the response rate was fairly low: responses were received from 27% of colleagues representing 32% of hospitals, which means that the survey results may also not be fully representative of hospitals to which the survey was circulated. The majority of responses (78%) were from tertiary care hospitals, which might suggest overrepresentation of tertiary care settings. However, the extent of this possible overrepresentation could not be determined since no information was available about the settings (i.e. primary, secondary or tertiary care) of hospitals that did not participate in the survey. Nevertheless, as tertiary care centres generally have a central and leading role in preparedness efforts for emerging health crises, our survey results do serve as important indicators of the state of preparedness in Europe. Secondly, several of the questions in our survey remained unanswered ('do not know') a substantial proportion of respondents, likely due in large part to differences in medical background of respondents (ranging from intensive care specialists to clinical microbiologists) and the variety of topics addressed. However, close collaboration between these specialists is clearly needed to provide optimal and safe care for EVD patients. Thirdly, as the number of participating hospitals differed substantially between regions, with relatively low numbers from eastern Europe and western Asia, geographical differences in the results of this survey should be interpreted with caution. Finally, this survey represents a snapshot of the state of affairs six months after the EVD outbreak in West Africa became apparent to the world and three weeks after it had been declared a PHEIC. Since then, preparedness activities of hospitals, including training and exercises, will undoubtedly have intensified globally given the continuing and expanding crisis in West Africa and emergence of travel-associated cases elsewhere. It will be interesting to assess whether this is indeed the case in a future follow-up survey.

In summary, this survey has provided important initial insights into the preparedness and capacity to admit patients suspected for EVD in European hospitals. These results, including identified gaps or concerns, help to provide direction towards further preparedness activities and prioritisation thereof.

Platform for European Preparedness against (re-) emerging epidemics (PREPARE), and affiliated clinical networks Community-Acquired Competence Network (CAPNETZ www.capnetz.de), European Society of Intensive Care Medicine (ESICM www.esicm.org), COMbating BACTERial resistance in Europe (COMBACTE www.combacte.com) and Pediatric European Network for the Treatment of AIDS (PENTA <http://www.penta-id.org>).

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Conflict of interest

None declared.

Authors' contribution

Designed the study: MDdJ, PH, MK, HG. Executed the survey: MB, J-DC, CQ, TW, FL, JS. Prepared and analysed data: MDdJ, CR, FL, JS. Interpreted the results: MDdJ, CR, PH, MK, HG. Wrote the first draft: MDdJ. All authors reviewed, provided comments and approved the final manuscript.

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Association between temperature, humidity and ebolavirus disease outbreaks in Africa, 1976 to 2014

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Ebolavirus disease (EVD) outbreaks have been occurring sporadically in Central Africa since 1976. In 2014, the first outbreak in West Africa was reported in Guinea. Subsequent outbreaks then appeared in Liberia, Sierra Leone and Nigeria. The study of environmental factors underlying EVD epidemiology may provide useful insights into when and where EVD outbreaks are more likely to occur. In this paper, we aimed to investigate the association between climatic factors and onset of EVD outbreaks in humans. Our results suggest lower temperature and higher absolute humidity are associated with EVD outbreak onset in the previous EVD outbreaks in Africa during 1976 to 2014. Potential mechanisms through which climate may have an influence on ebolavirus infection in the natural host, intermediate hosts and humans are discussed. Current and future surveillance efforts should be supported to further understand ebolavirus transmission events between and within species.

Introduction

Ebolaviruses were first recognised as causing ebolavirus disease (EVD) in humans in outbreaks in South Sudan and the Democratic Republic of the Congo in Central Africa in 1976 [1,2]. The recent EVD outbreak in Guinea in 2014 is the first reported in West Africa [3]. Initial confirmed and probable cases in Liberia and Sierra Leone are reported to have travelled to Guinea [4]. These cases were followed by more extensive outbreaks in the two countries and later on a small number of ebolavirus disease cases were also detected in Nigeria. Genome sequencing analyses revealed that the Zaire ebolavirus causing the outbreak in Guinea was 97% identical to the Zaire ebolaviruses that had previously caused an outbreak in the Democratic Republic of the Congo and Gabon [5]. Phylogenetic analyses showed the virus isolated in Guinea belongs to a separate clade from previous Zaire ebolaviruses identified in the Democratic Republic of the Congo and Gabon [5]. Other ebolaviruses identified in previous EVD outbreaks in humans in Africa included the Sudan, Côte d'Ivoire and Bundibugyo species [1,6]. Despite the capacity of ebolaviruses to be transmitted between

species, including humans, only sporadic outbreaks have been reported and most of them were limited to Central Africa. The spread of the current EVD outbreak outside central African countries to those in western Africa with a high volume of cross-border and international travel have raised concern regarding further spread to other countries within and outside Africa. Despite recent progress in human trials of treatment and vaccines, ebolavirus infections continue to pose a serious public health threat due to the high case fatality risk.

In some previous outbreaks, investigations revealed a clear connection between EVD and contact with the natural reservoir or infected intermediate hosts including bats, chimpanzees and other primates [1,7]. The European Centre for Disease Prevention and Control rapid risk assessment concluded direct contact with contaminated secretions, blood, organs and other bodily fluids of living or dead infected persons or animals or with objects heavily contaminated with such fluids have a high potential to lead to transmission [8]. EVD has also arisen as a result of importation of infected animals and laboratory contamination [1] but was not followed by sustained human-to-human transmission.

Seasonal and cyclical patterns of ebolavirus infections have been observed, suggesting seasonal changes in factors such as climate maybe useful predictors of EVD outbreaks [9,10]. Examination of these factors may also provide some insight into why EVD had been limited to central parts of Africa in the past and why it has started to appear in West Africa. The objective of this study was to investigate the association between climatic conditions and EVD outbreaks in Africa that occurred between 1976 and 2014, and to discuss potential mechanisms to which climate may have an influence on ebolavirus infection in the natural host, intermediate hosts and humans.

TABLE 1

Characteristics of human ebolavirus disease outbreaks in five African countries included in analyses of the effect of climatic conditions, 1976–2014

Country	Area	Onset of first outbreak	End of last outbreak	Years of climate data analysed	Ebolavirus species	Mean temperature in °C (SD)	Mean absolute humidity in kg/m ³ (SD)
Guinea	Guékédou	Jan 2014	Ongoing	2013–2014 ^a	Zaire	25.53 (0.96)	16.50 (1.55)
	Macenta	Jan 2014	Ongoing	2013–2014 ^a	Zaire	24.79 (0.94)	15.22 (1.50)
	Kissidougou	Jan 2014	Ongoing	2013–2014 ^a	Zaire	25.31 (1.08)	15.70 (2.04)
Gabon	Andock	Dec 1994	Feb 1995	1993–1995	Zaire	26.50 (1.08)	20.10 (1.27)
	Mayibout II	Jan 1996	Apr 1996	1995–1996	Zaire	24.80 (0.94)	18.38 (0.62)
	Booué	Jul 1996	Jan 1997	1995–1997	Zaire	26.37 (0.93)	19.76 (0.88)
	Ogooué-Ivindo	Oct 2001	Mar 2002	2000–2002	Zaire	25.38 (1.06)	18.86 (0.74)
Democratic Republic of the Congo	Bumba	Sep 1976	Oct 1976	1975–1976	Zaire	24.94 (0.63)	18.17 (0.35)
	Tandala	Jun 1977	Jun 1977	1976–1977	Zaire	25.50 (0.70)	18.67 (0.57)
	Kikwit	Jan 1995	Jul 1995	1994–1995	Zaire	25.18 (0.57)	17.55 (1.54)
	Cuvette-Ouest	Dec 2002	Dec 2003	2001–2003	Zaire	24.93 (0.89)	18.49 (0.74)
	Kasai Occidental	May 2007	Oct 2007	2006–2007	Zaire	24.84 (0.53)	18.21 (0.80)
	Mweka	Nov 2008	Jan 2009	2007–2009	Zaire	24.81 (0.55)	18.21 (0.80)
	Luebo	Nov 2008	Jan 2009	2007–2009	Zaire	24.44 (0.61)	17.75 (0.96)
South Sudan	Isiro	Aug 2012	Oct 2012	2011–2012	Zaire	24.32 (1.36)	18.45 (0.97)
	Nzara	Jun 1976	Oct 1979	1975–1979	Sudan	24.27 (0.98)	15.95 (1.57)
Uganda	Yambio	Apr 2004	Jun 2004	2003–2004	Sudan	26.05 (1.18)	17.51 (1.73)
	Gulu	Aug 2000	Jan 2001	1999–2001	Sudan	24.69 (1.26)	15.27 (1.59)
	Masindi	Aug 2000	Dec 2000	1999–2000	Sudan	23.17 (0.87)	15.15 (0.87)
	Mbarara	Aug 2000	Jan 2001	1999–2001	Sudan	19.79 (0.66)	13.00 (0.75)
	Bundibugyo	Aug 2007	Dec 2007	2006–2007	Bundibugyo	18.76 (1.16)	13.02 (0.81)
	Luwero	May 2011	Nov 2012	2010–2012	Sudan	23.27 (1.26)	15.54 (0.95)
	Kibaale	Jul 2012	Aug 2012	2011–2012	Sudan	25.19 (0.99)	16.20 (1.82)

SD: standard deviation.

^a Climate data were available until 2012; climatic conditions in 2013 and 2014 were imputed from climate data during the previous three years.

Methods

Sources of data

A total of 28 reported EVD outbreaks in Africa were identified from records and references listed on the United States Centers for Disease Control and Prevention website [1]. These outbreaks have occurred in the Democratic Republic of the Congo, Congo, South Sudan, Gabon and Uganda since 1976, and recently in Guinea. Because this study is focused on emergence and local transmission of the viruses, two reports involving a medical professional who treated a case from an outbreak in Gabon and later travelled immediately to South Africa in 1996, and a scientist who performed an autopsy of a wild chimpanzee in Côte d'Ivoire in 1994 were excluded.

The onset of an outbreak is defined by the date of the first reported probable or laboratory-confirmed case. Climate data, including ambient temperature, vapour pressure and dew point, at the outbreak locations were obtained from the Climate Research Unit, University of

East Anglia, United Kingdom [11]. Absolute humidity was calculated using the conversion formula published by the National Aeronautics and Space Administration [12].

Statistical methods

A distributed lag non-linear model (DLNM) developed by Gasparrini et al. [13] was used in our analyses to examine the association between climatic factors and EVD outbreaks [7]. DLNM was used since it allows for a non-linear exposure–response relationship and provides flexibility in modelling the time structure of the relationship. The time structure is specified so that the log odds of an EVD outbreak can vary between each lag period following exposure of humans and intermediate host and natural host populations to certain climatic conditions at each outbreak area.

An earlier report of a detailed EVD outbreak investigation suggested exposure of the first cases to infected bats might precede detected outbreaks in humans by three months [7]. Lagged effects of one month, two months and three months were considered when our

FIGURE 1

Geographical distribution of human ebolavirus disease outbreaks included in analyses of monthly temperature and absolute humidity, 1976–2014



The red circles represent the outbreak areas.

models were fitted. The relationship between exposure variables (monthly temperature and absolute humidity) and the log odds of response (onset of an EVD outbreak in humans) were specified using first (linear) and second (quadratic) degree orthogonal polynomials in binomial regression models. Likewise, zeroth (uniform), first (linear) and second (quadratic) degree orthogonal polynomials were used to specify the time structure of the exposure–response relationship.

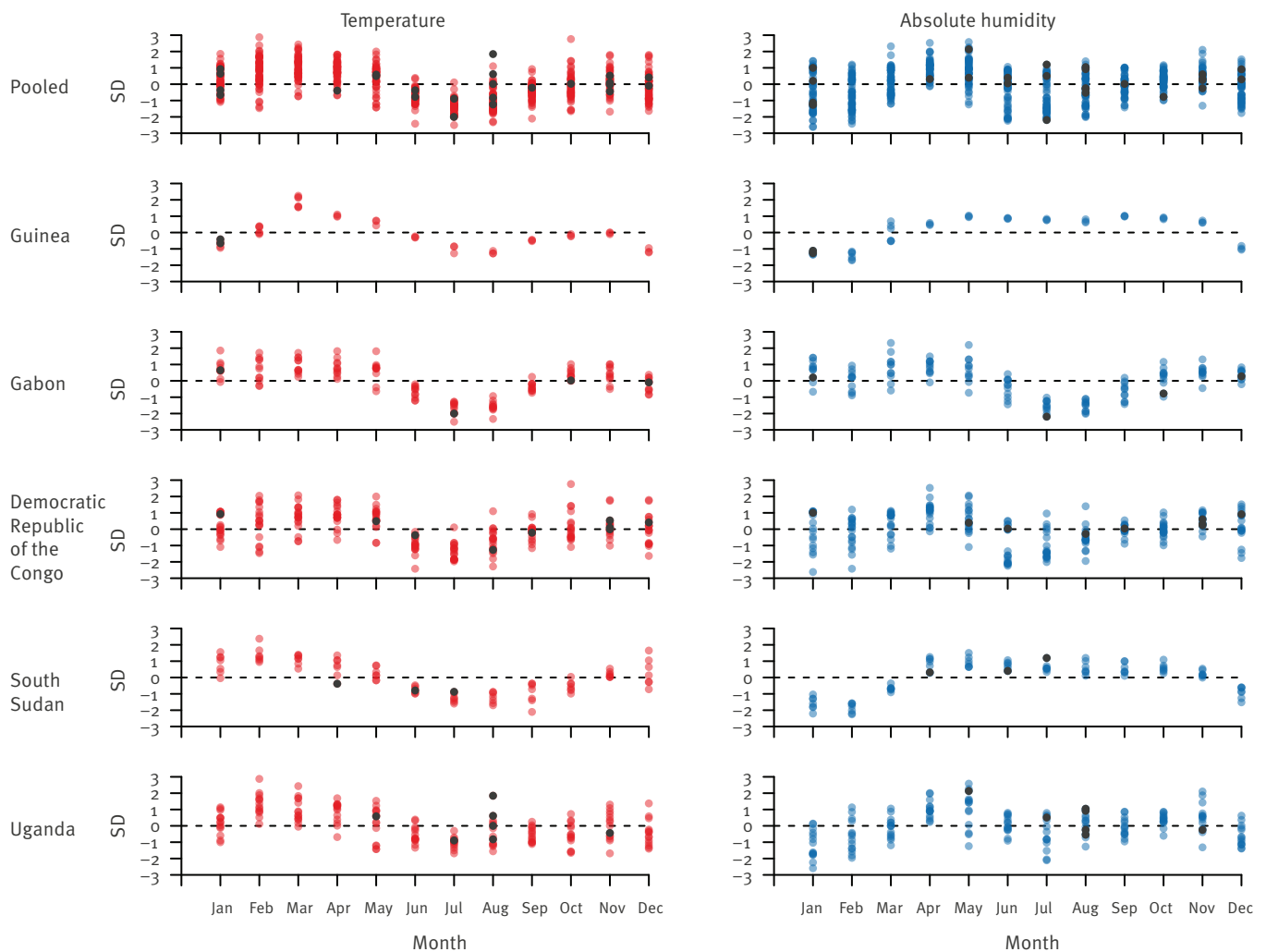
Climate data were available until 2012 and the monthly temperature and absolute humidity in 2013 and 2014 were imputed using the mean same month observations during the previous three years. Climate data for

Gabon was used for one outbreak that occurred at the border between Congo and Gabon.

Annual climate data from the year before the first outbreak to the year of the last outbreak at each outbreak area were analysed. Odds ratios of EVD outbreaks associated with deviation from mean climatic conditions over these years were calculated. The standardised monthly temperature and absolute humidity were visualised and variance inflation factors were calculated to inspect for multicollinearity between the two explanatory variables. The standardisation was carried out within each of the smallest geographical jurisdictions described in the outbreak reports. Separate models

FIGURE 2

Standardised monthly temperature and absolute humidity in five African countries with human ebolavirus disease outbreaks^a, 1976–2014



SD: standard deviation.

Standardised monthly temperature (red circles) and absolute humidity (blue circles) are shown.

The observations during onset months of ebolavirus disease outbreaks are highlighted as black circles. The mean and standard deviation of temperature and absolute humidity and the years of climate data included in the analyses for each outbreak area can be found in Table 1.

^a Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda. An outbreak occurring at the border of the Republic of Congo and Gabon was included here as an outbreak in Gabon.

were used for temperature and absolute humidity when evidence of multicollinearity was observed.

General estimating equations (GEE) [14] were used to adjust for correlations between multiple observations within the smallest geographical jurisdiction described in the outbreak reports. Both pooled and stratified analyses were performed for the five outbreak countries: the Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda. Quasilikelihood under the independence model criterion (QIC) is a modification of Akaike's information criterion (AIC) for models using GEE [15]. All model specifications were

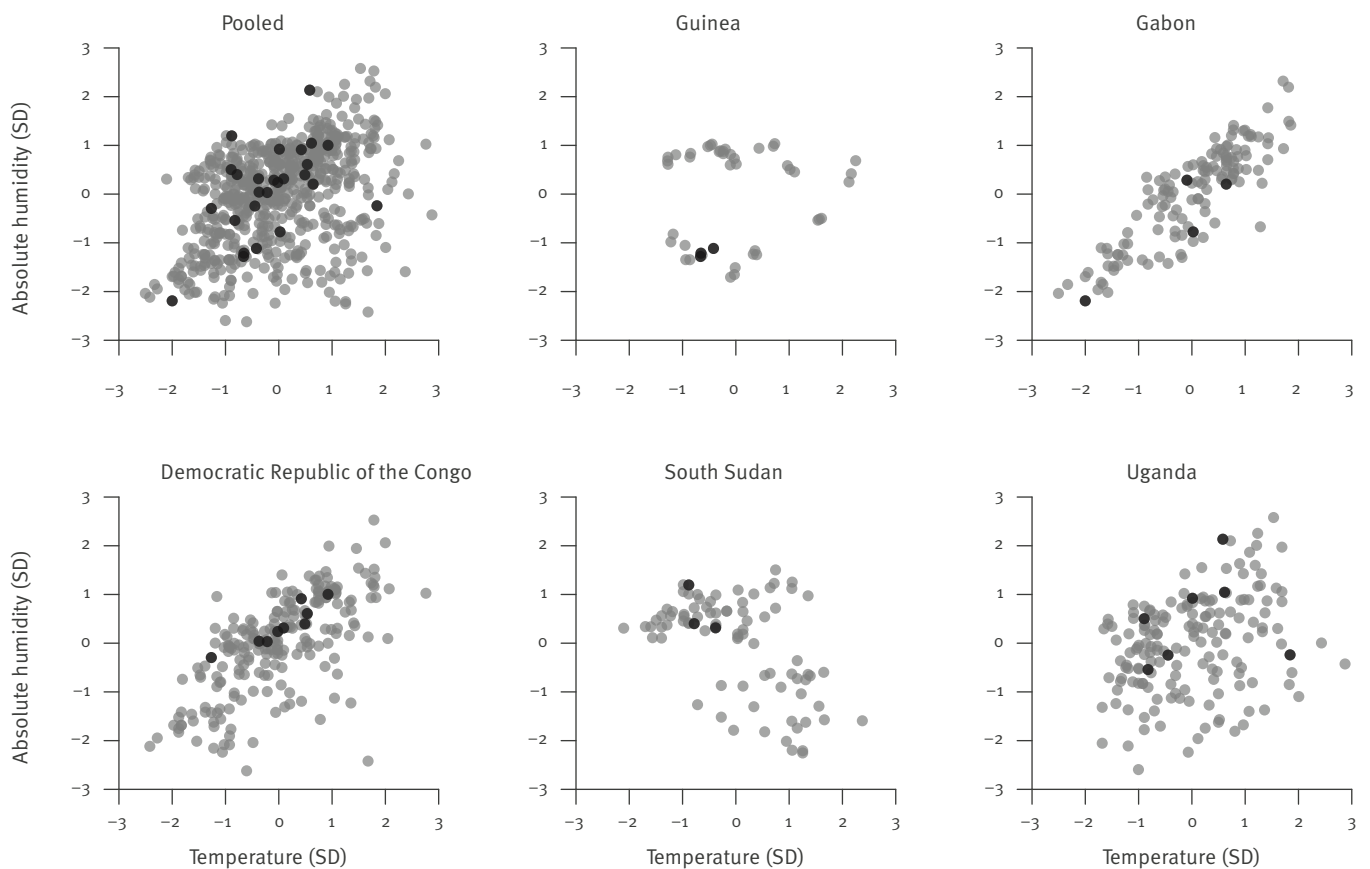
evaluated using QIC and the final models with the lowest QIC were selected.

Results

The geographical distribution of EVD outbreaks in the Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda is shown in Figure 1. The mean and standard deviation of monthly temperature and absolute humidity, causative ebolavirus species and outbreak period in each outbreak area are listed in Table 1 [1,6,16]. In Guinea, the mean temperature was rather similar to that of other areas with outbreaks of Zaire ebolavirus disease (in the Democratic Republic of the Congo and Gabon), while the mean absolute

FIGURE 3

Correlation between standardised mean monthly temperature and absolute humidity in five African countries with human ebolavirus disease outbreaks^a, 1976–2014



SD: standard deviation.

The correlation between standardised mean monthly temperature and absolute humidity is shown as grey circles. The observations during onset months of ebolavirus disease outbreaks are highlighted as black circles. The years of climate data included in the analyses for each outbreak area can be found in Table 1.

^a Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda. An outbreak occurring at the border of the Republic of Congo and Gabon was included here as an outbreak in Gabon.

humidity was lower, as in areas where previous outbreaks of Sudan ebolavirus disease occurred (Sudan and Uganda) [1]. Standardised monthly temperature and absolute humidity in the five countries analysed are shown in Figure 2. Consistent patterns in annual variation of temperature were observed across the five countries: June to August was generally cooler than the mean with February to April being the warmer months. The annual pattern of absolute humidity was, however, less consistent between countries. While the absolute humidity remained above the mean from April to November in Guinea and South Sudan, only March and April were more humid in the other three countries. In Gabon, July and August were noticeably drier, but this was not seen elsewhere. Since temperature and absolute humidity in the Democratic Republic of the Congo and Gabon were highly positively correlated (Figure 3), separate models were used in analysing their correlation with EVD outbreak onset. The variance inflation factors were low in Guinea, South Sudan, Uganda

and in the pooled analyses, therefore temperature and absolute humidity were included as covariates in the same models.

In the pooled analysis, the best-fitting model specified a uniform exposure–response relationship across the two months’ lag period for temperature and the three months’ lag period for absolute humidity (Table 2). Lower temperature and higher humidity (standard deviation) were found to log-linearly associate with increased risk of human EVD outbreak onset during each month in the lag periods. The estimated cumulative log odds ratio of human EVD outbreak onset at each month following exposure of humans and intermediate host and natural host populations to certain climatic conditions are shown in Figure 4. These associations were shown to be statistically significant across the entire lag period (Tables 3 and 4). Analyses stratified by country were underpowered and analyses only including areas with Zaire ebolavirus outbreaks

TABLE 2

Model specifications of the best-fitting models selected based on quasilikelihood under the independence model criterion, in five African countries with human ebolavirus outbreaks, 1976–2014

Country and outbreaks by ebolavirus species	Lag period following exposure ^a to temperature (in months)	Lag period following exposure ^a to absolute humidity (in months)	Degree of orthogonal polynomial used to specify the relationship between temperature and the log odds of EVD outbreak	Degree of orthogonal polynomial used to specify the relationship between absolute humidity and the log odds of EVD outbreak	How odds ratio vary across lag period following exposure ^a to temperature	How odds ratio vary across lag period following exposure ^a to absolute humidity
Country						
Pooled	2	3	1st	1st	Uniform	Uniform
Guinea ^b	–	–	–	–	–	–
Gabon ^c	2	NA	1st	NA	Uniform	NA
Gabon ^d	NA	2	NA	1st	NA	Uniform
Democratic Republic of the Congo ^c	2	NA	1st	NA	Uniform	NA
Democratic Republic of the Congo ^d	NA	1	NA	2nd	NA	Uniform
South Sudan	1	1	1st	1st	Uniform	Uniform
Uganda	2	3	1st	2nd	Uniform	Uniform
Ebolavirus species						
Zaire species outbreaks	2	3	1st	1st	Uniform	Uniform
Sudan species outbreaks	2	3	1st	1st	Uniform	Uniform
Bundibugyo species outbreaks ^b	–	–	–	–	–	–

EVD: ebolavirus disease; NA: not applicable.

^a Exposure of humans and intermediate host and natural host populations.

^b The analysis was not performed due to insufficient number of outbreaks.

^c Model including temperature as explanatory variable.

^d Model including absolute humidity as explanatory variable.

produced consistent conclusions (Figure 5). Stratified analyses for Sudan and Bundibugyo species were underpowered. The specifications of the best-fitting stratified models can be found in Table 2.

Discussion

Our analyses of human EVD outbreaks in Africa suggest that the onset of these outbreaks was associated with conditions with higher absolute humidity and lower temperature when their time-lagged effects are taken into account. This is one of the first studies to examine the association between climatic factors and EVD outbreaks in humans. Our findings are consistent with the prediction of previous ecological niche models that ebolaviruses are more likely to be distributed in areas of humid Afrotropic rainforests where the temperature is moderate [17]. Previous EVD outbreaks in humans have been observed in both dry and wet seasons [9,10,18–20]. This is consistent with our analysis (Figure 2), which shows that when the time-lagged effect of environmental exposure is not considered, EVD outbreaks do not have a clear association with temperature and humidity.

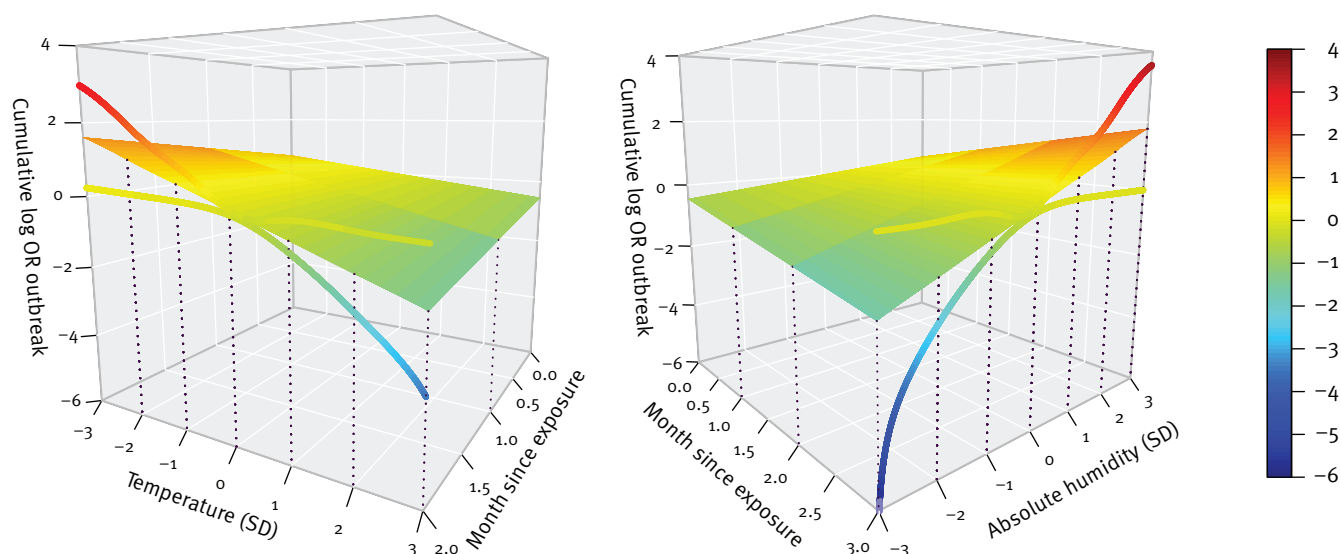
On the basis of knowledge of ebola-related viruses, there has been speculation that plants, arthropods,

bats and many other animals could be the natural host for ebolaviruses [21]. However, to date, evidence of potential ebolavirus persistence has only been found in bats [22]. Further animal virological studies are required to identify and verify all natural host species for ebolaviruses. Although seasonal patterns of ebolavirus infections among bats and other potential natural hosts have not been fully characterised, seroprevalence studies in bats have found the highest rates of seropositivity among adults and pregnant females [23]. This finding leads to the postulation that fighting and mating among bats may be associated with ebolavirus transmission [23]. These behaviours have been documented to be most frequent during rainy or wet seasons [24]: this may partly explain how climatic factors are associated with ebolavirus infection risk among bats, one of the potential natural hosts.

Viral persistence studies in EVD patients have found the virus to be more persistent in semen than in other bodily fluids and fomites [25]. Ebolavirus was found to remain detectable in semen for up to 91 days [26]. This finding highlights the relative importance of sexual transmission, if virus shedding in bats follows a similar pattern.

FIGURE 4

Estimated cumulative odds ratios of onset of human ebolavirus disease outbreaks at each month following exposure of humans and intermediate host and natural host populations to certain climatic conditions in five African countries with human ebolavirus disease outbreaks^a, 1976–2014



CI: confidence interval; OR: cumulative odds ratio; SD: standard deviation.

The lag period was two months for the effect of temperature and three months for absolute humidity. The OR was calculated with reference to ebolavirus disease outbreak onset risk at mean temperature/absolute humidity conditions. The 95% CIs for the estimated cumulative log OR at the end of the lag period are shown as the two lines enclosing the surface that shows the cumulative log OR. The mean and standard deviation of temperature and absolute humidity, and the years of climate data included in the analyses for each outbreak area can be found in Table 1. Numerical values for all ORs and 95% CIs can be found in Tables 3 and 4.

^a Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda. An outbreak occurring at the border of the Republic of Congo and Gabon was included here as an outbreak in Gabon.

TABLE 3

Estimated cumulative odds ratio of onset of human ebolavirus disease outbreaks at each month following exposure to temperature conditions^a, 1976–2014

Temperature (SD)	Same month	First month	Second month
	OR (95% CI)	OR (95% CI)	OR (95% CI)
-3	1.71 (1.08–2.70)	2.93 (1.17–7.29)	5.00 (1.27–19.68)
-2	1.43 (1.06–1.94)	2.05 (1.11–3.76)	2.93 (1.17–7.29)
-1	1.20 (1.03–1.39)	1.43 (1.06–1.94)	1.71 (1.08–2.70)
0	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
1	0.84 (0.72–0.97)	0.70 (0.52–0.95)	0.58 (0.37–0.92)
2	0.70 (0.52–0.95)	0.49 (0.27–0.90)	0.34 (0.14–0.85)
3	0.58 (0.37–0.92)	0.34 (0.14–0.85)	0.20 (0.05–0.79)

CI: confidence interval; OR: cumulative odds ratio; SD: standard deviation.

^a Estimated from the best-fitting model for the pooled analyses of outbreaks caused by Zaire, Sudan and Bundibugyo ebolaviruses in Guinea, Gabon, Democratic Republic of the Congo, South Sudan and Uganda. The outbreak areas and time period included in the analyses are described in Table 1. The best-fitting model included two months as the duration of the lag effect.

Seasonal migration of fruit bats may result in increased contact with humans and other animals [10]. An outbreak investigation in the Democratic Republic of the Congo in 2007 linked the first human case to migratory bats that stayed in the area during the migratory season [7]. Further investigation should be carried out to study whether disruption/change in migratory route or virus acquisition in other bat species with a different

geographical range would explain the first outbreak in West Africa. Bats host many viruses that are highly pathogenic in other mammals [27]. It has been hypothesised that flight activities maintain a high body temperature and metabolic rate, which may mimic the effect of a febrile immune response in limiting virulence of a virus that may otherwise be highly pathogenic [27,28]. Seasonal environmental and behavioural

TABLE 4

Estimated cumulative odds ratios of onset of human ebolavirus disease outbreaks at each month following exposure to absolute humidity conditions^a, 1976–2014

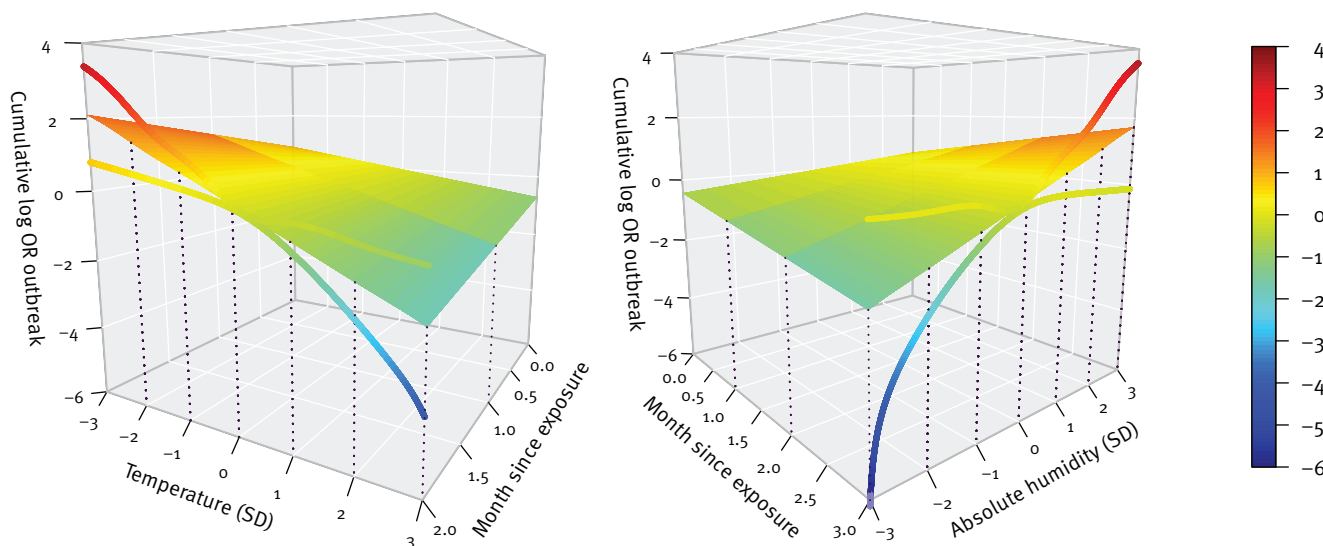
Absolute humidity (SD)	Same month	First month	Second month	Third month
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
-3	0.64 (0.40–1.00)	0.40 (0.16–1.00)	0.26 (0.07–1.00)	0.16 (0.03–1.00)
-2	0.74 (0.55–1.00)	0.55 (0.30–1.00)	0.40 (0.16–1.00)	0.30 (0.09–1.00)
-1	0.86 (0.74–1.00)	0.74 (0.55–1.00)	0.64 (0.40–1.00)	0.55 (0.30–1.00)
0	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
1	1.16 (1.00–1.35)	1.35 (1.00–1.83)	1.57 (1.00–2.47)	1.83 (1.00–3.34)
2	1.35 (1.00–1.83)	1.83 (1.00–3.34)	2.47 (1.00–6.11)	3.34 (1.00–11.18)
3	1.57 (1.00–2.47)	2.47 (1.00–6.11)	3.88 (1.00–15.11)	6.10 (1.00–37.37)

CI: confidence interval; OR: cumulative odds ratio; SD: standard deviation.

^a Estimated from the best-fitting model for the pooled analyses of outbreaks caused by Zaire, Sudan and Bundibugyo ebolaviruses in Guinea, Gabon, Democratic Republic of the Congo, South Sudan and Uganda. The outbreak areas and time period included in the analyses are described in Table 1. The best-fitting model included three months as the duration of the lag effect.

FIGURE 5

Estimated cumulative odds ratios of onset of human Zaire ebolavirus disease outbreaks at each month following exposure of humans and intermediate host and natural host populations to certain climatic conditions in three African countries with human Zaire ebolavirus disease outbreaks^a, 1976–2014



CI: confidence interval; OR: cumulative odds ratio; SD: standard deviation.

The lag period was two months for the effect of temperature and three months for absolute humidity. The OR was calculated with reference to Zaire ebolavirus disease outbreak onset risk at mean temperature/absolute humidity conditions. The 95% CIs for the estimated cumulative log OR at the end of the lag period are shown as the two lines enclosing the surface that shows the cumulative log OR. The mean and standard deviation of temperature and absolute humidity, and the years of climate data included in the analyses for each outbreak area can be found in Table 1. Numerical values for all ORs and 95% CIs can be found in Tables 3 and 4.

^a Democratic Republic of the Congo, Gabon, Guinea, South Sudan and Uganda. An outbreak occurring at the border of the Republic of Congo and Gabon was included here as an outbreak in Gabon.

factors such as long migratory flight may influence body temperature and metabolic rate in bats. This may result in altered susceptibility to and severity of ebolavirus infection. Reduction in susceptibility and severity may have bidirectional effects on ebolavirus transmission dynamics. While less severe infections may allow infected bats to remain active in transmitting the virus, reduction in susceptibility may reduce the overall infection rate among the bat population.

Peaks in mortality due to EVD in chimpanzees, gorillas and duikers (a type of antelope) were observed to coincide with some of the previous human EVD outbreaks [29]. EVD outbreaks in non-human primates have mostly been reported to occur at the end of rainy seasons [10,30,31]: however, it has been unclear whether this was due to earlier humid conditions or current dry conditions. As in bats, the behaviour of non-human primates and their exposure to bats may vary with the

season. A study of chimpanzees in Côte d'Ivoire found that they made a higher number of kills per day when hunting in the wet seasons [32]. This may lead to a sudden increase in consumption or contact with prey that is a natural reservoir of ebolaviruses. Furthermore, increased social mixing during wet seasons may also facilitate transmission of ebolaviruses among chimpanzees [24]. Similarly, human-to-human and human-to-animal contact patterns may have a seasonal effect on the risk of an EVD outbreak in humans.

While natural hosts such as bats can serve as a common source of cross-species transmission for humans and other primates, non-human primates can act as intermediate hosts in zoonotic events that result in human infections. Therefore, the time frame of the spillover effect of environmental exposure in the natural hosts may depend on the transmission chain of the zoonotic events and how these events are associated with climate. Environmental exposure may also have transient, immediate effects on the susceptibility to and severity of ebolavirus infection among natural hosts, intermediate hosts and humans. Previous experimental studies have found human exposure to low temperature may trigger changes in the immune response [33-36]. If these effects are conserved between these hosts, periods of suitable climatic conditions may provide windows of opportunity for cross-species transmission to occur. Serosurveillance studies in human populations in Africa have revealed a much higher prevalence of ebolavirus antibodies than the attack rate reported in previous EVD outbreaks [37,38]. This may suggest that exposure of humans to ebolaviruses or other cross-reactive pathogens was more prevalent than previously thought. In fact, a study of contacts of EVD patients has revealed that some ebolavirus infections can be mild or asymptomatic [39]. Tissue tropism of ebolaviruses has been studied: the viruses were found to target and infect immune cells including monocytes, macrophages and immature dendritic cells and to cause highly pathological immune responses [40,41]. Further studies should characterise how previously identified environmental effects on the immune response [33-36] may translate to ebolavirus infection outcomes. Since EVD cases with milder symptoms are more likely to be under-reported, the observed EVD outbreak pattern may in part be attributable to seasonal differences in EVD severity.

In the past, EVD outbreaks were confined to the central African countries and it is essential to understand why EVD has appeared in West Africa. This will have implications on how likely it is that EVD outbreaks will occur in the rest of the world. Climate has been found in our study to be associated with EVD outbreaks and, as discussed in this paper, there are a number of ways in which climate could be associated with the seasonal risk factors of EVD outbreaks. Further studies should investigate the potential impact of climate change on the geographical boundary of the virus and the time period in which EVD is likely to occur.

There are a number of limitations in this study. The initial identification of EVD outbreaks in Africa has mostly been reliant on the clinical manifestation of cases; however, some EVD cases presented with non-specific symptoms that can be easily confused with other diseases that are endemic in Africa [42]. Due to the limited resources and remoteness of some of the rural areas where human-animal contacts are most frequent, some EVD outbreaks might be under-detected. Delayed detection of EVD outbreaks should be expected and we addressed this by using distributed time-lag models. However, it is still difficult to interpret or construct the time structure of the exposure-response relationship since little information on reporting delays is available. The incubation period of EVD may be up to 21 days or more [43], and this has to be taken into account when interpreting time-lagged effects of environmental exposures. The choice of time structure of the exposure-response relationship is based on the model best fitting our data. Given that EVD outbreaks in humans are rather rare, our study may be underpowered to investigate a more sophisticated time structure of the exposure-response relationship and to detect a non-linear exposure-response relationship. The earliest few human cases are likely to be under-detected and our study may have excluded smaller EVD outbreaks that were unreported. While climatic variation can be a useful predictor, its association with EVD outbreaks may depend on other ecological and environmental factors, as well as on natural host species that vary between geographical areas. Our findings may therefore only apply to areas that share similar characteristics with the outbreak areas included in the analyses. It is most likely that ecological and environmental differences also exist between outbreak areas included in the analyses. Our country-specific analyses were unfortunately underpowered, as EVD outbreaks are rare. It is also possible that the association between climate and EVD is specific to ebolavirus species. Our study was only able to provide estimates for Zaire ebolavirus outbreaks since there were fewer outbreaks due to other ebolavirus species.

In order to understand the transmission dynamics of ebolavirus, current efforts in identifying the natural and intermediate hosts of ebolaviruses should be continued and supported. A better understanding of the chain of transmission from the natural reservoir to humans is essential for characterising the epidemiology of ebolavirus infections and directing public health preventive policies. Longitudinal serological and virological surveillance studies will help in identifying the event sequence and interfaces that are important for outbreaks in humans. Our study focused on the onset of EVD outbreaks, as we aimed to investigate environmental factors that are associated with cross-species transmission. To enable factors associated with human-to-human transmission to be investigated, current support to the outbreak countries in case detection and reporting should be continued.

Conflict of interest

BJC reports receiving research funding from MedImmune Inc and consults for Crucell NV. The authors report no other potential conflicts of interest.

Authors' contributions

SN, NEB and BJC have each participated in the conception, design, analysis and writing of the manuscript.

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Surveillance and Outbreak Response Management System (SORMAS) to support the control of the Ebola virus disease outbreak in West Africa

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In the context of controlling the current outbreak of Ebola virus disease (EVD), the World Health Organization claimed that ‘critical determinant of epidemic size appears to be the speed of implementation of rigorous control measures’, i.e. immediate follow-up of contact persons during 21 days after exposure, isolation and treatment of cases, decontamination, and safe burials. We developed the Surveillance and Outbreak Response Management System (SORMAS) to improve efficiency and timeliness of these measures. We used the Design Thinking methodology to systematically analyse experiences from field workers and the Ebola Emergency Operations Centre (EOC) after successful control of the EVD outbreak in Nigeria. We developed a process model with seven personas representing the procedures of EVD outbreak control. The SORMAS system architecture combines latest In-Memory Database (IMDB) technology via SAP HANA (in-memory, relational database management system), enabling interactive data analyses, and established SAP cloud tools, such as SAP Afaria (a mobile device management software). The user interface consists of specific front-ends for smartphones and tablet devices, which are independent from physical configurations. SORMAS allows real-time, bidirectional information exchange between field workers and the EOC, ensures supervision of contact follow-up, automated status reports, and GPS tracking. SORMAS may become a platform for outbreak management and improved routine surveillance of any infectious disease. Furthermore, the SORMAS process model may serve as framework for EVD outbreak modelling.

Introduction

The spread of the current outbreak of Ebola virus disease (EVD) in West Africa has slowed down in most affected areas, but daily case numbers are still high as of 11 March 2015 [1]. Even enhanced awareness and increasing international support did not prevent contacts of known cases from travelling to unaffected areas causing further spread. As a consequence, although the rise of new EVD cases slowed down, the number of foci has increased, causing new operational challenges for health officials and field epidemiologists [1]. The interruption of person-to-person transmission includes proactive case finding i.e., supervision of timely isolation, diagnosis and treatment, as well as identification and prospective monitoring of contact persons [2]. High population mobility, stigmatisation of persons considered infectious and fears of persons who had been in contact with them, require a large number of staff to reach out and maintain contact to patients and contact persons. At the same time, a large amount of rumours entering the public health service through a variety of channels and formats need to be validated. Existing surveillance systems are usually not built to address such challenges. In addition, uncertainty and delay of surveillance data due to different information sources and infrastructural hurdles such as irregular availability of communication or transportation services in the affected countries have led to limited reliability of epidemiological analyses. This was exemplified by the fact that the World Health Organization (WHO) needed to retrospectively correct the official outbreak reports in week 45/2014, resulting in 299 fewer cases than previously reported [3].

TABLE 1**User and system requirements for management systems to support the Ebola virus disease outbreak response**

Priority system requirements
Authorised persons should be able to immediately report on suspected EVD cases.
Reporting of case status including results from laboratory tests should be supported.
Monitoring of contacts and management of contact tracing activities should be supported.
Monitoring of infection prevention measures (e.g. decontamination, safe burials) should be enabled.
User requirements
Information on suspected EVD cases needs to reach simultaneously the health authorities in charge at district, state and national level and the Ebola Outbreak Emergency Operations Centre.
Changes in case status and changes from contact status to a suspected case need to be administered without generating new datasets.
Incoming information on suspected cases including unstructured information and unverified rumours and the respective decisions of further follow up need to be documented.
Status reports on cases, contacts and their respective classifications and follow up status need to be generated by the system automatically.
Reports should be compatible with reporting requirements of the International Health Regulations of the WHO [28], but should also allow for higher resolution epidemiological analyses via mapping, histograms etc. as exemplified by the current WHO and national situation reports on the EVD outbreak.
Variables included in existing standard forms on haemorrhagic fever as well as in the module for viral haemorrhagic fevers of EpiInfo [29] need to be reflected in the system.
The system needs to support supervisors in assuring that all contact persons are identified, documented and that their respective fever monitoring is executed without interruption.
The system needs to support supervisors in assuring that infection control measures and social mobilisation in affected districts have been carried out.
Technical requirements
Data exchange with existing surveillance systems is necessary, at least through a standardised output format to enable integration with the Integrated Disease Surveillance and Response System.
The system should be available as mobile application without a need for special configuration or installation.
Desktop applications for supervisors are required.
The system should be runnable on Android mobile devices (Jelly Bean Android OS, large touch screen interfaces or QWERTY keys).
Efficient network providers for mobile devices and tablets are required.
GPS tracking software for locating stolen devices is necessary.

EVD: Ebola virus disease; GPS: global positioning system; WHO: World Health Organization.

The first case of EVD was imported to Nigeria in August 2014 resulting in 19 additional secondary infections. Tremendous intensity, rigour, and timely control measures together with beneficial circumstances around the case identification led to the control of the outbreak and allowed WHO to declare the end of the Ebola outbreak for this country by 20 October 2014 [4].

Systematic analyses and review of the experiences of Shuaib et al. [5] revealed that a comprehensive management system needs to be in place already to ensure successful containment of similar emergencies even if they occur under less beneficial circumstances. At the time of the outbreak, the Ebola reporting tool, called Open Data Kit (ODK) [6] was established to document visits of contact persons, but it did not address case finding, bidirectional information flow and other aspects of outbreak response.

To address this need, a consortium of Nigerian and German public health and research institutions and a global software company have developed the Surveillance and Outbreak Response Management System (SORMAS). The objective of SORMAS is to ensure availability of validated real-time surveillance data and to manage the verification of cases as well as tracing and monitoring of their contacts as it is typically needed during an EVD and other disease outbreaks. This report describes the generic requirements, process models, and technical infrastructure of SORMAS.

Development of SORMAS

We identified the user requirements in Design Thinking [7] workshops and by reviewing the reports of Shuaib et al. [5]. Additionally, we took into account requirements identified in reviews and analyses on contact tracing, outbreak management and electronic surveillance systems for other diseases also, not only EVD [8-12]. The identified requirements to be addressed by an outbreak management system are listed in Table 1.

Specification of personas

By reviewing the processes of the EVD outbreak management in Nigeria, we identified the different SORMAS user types, i.e. personas, involved in the process. Regular staff or volunteers of different hierarchical levels and with different job descriptions may be summarised within one persona, if their respective role and interaction with SORMAS are the same [13]. We defined the role, the needs with respect to the system, the interaction with other personas and the required artefacts (e.g. checklists and forms) for each persona. We consider an artefact a specification of a physical piece of information that is used or produced by a software development process, or by deployment and operation of a system. By systematically analysing the processes and roles, we were able to condense the number of originally 15 personas to seven personas. Some of these represent officers with different professions and training background. The process of defining the personas and their system expectations allowed us to design SORMAS according to users' needs.

Table 2 depicts the identified and defined seven personas that are directly interacting with SORMAS. Additionally, there is the persona case officer who is involved in the process, but will not directly interact with SORMAS since they wear protective clothes and are thus unable to use a mobile device for entering

TABLE 2

Persona of SORMAS with their respective activities, artefacts and interactions

Persona	Activities	Artefacts	Interaction
Informant	Looks for disease rumours in the population Collects information on death or sickness among healthcare workers	<ul style="list-style-type: none"> • Checklist on standard operating procedures • Rumour information (demographics, travel, contact) 	Reports to surveillance officer
Rumour officer	Conducts initial triage on all incoming rumours on possible cases	<ul style="list-style-type: none"> • Checklist with required information on rumour • Rumour information 	Reports to the surveillance supervisor
Surveillance officer	Reports notifiable diseases to state epidemiologist, receives rumours on cases and forwards them to surveillance supervisor to decide on further investigation Conducts investigation to verify status of case, e.g. suspect or confirmed and is responsible for active case finding	<ul style="list-style-type: none"> • EVD active surveillance form • Checklist on rumour triage • Contact list of healthcare facilities • Rumour information 	Reports to surveillance supervisor Supervises informant
Surveillance supervisor	Coordinates the input from rumour officers and surveillance officers Supports rumour officer in deciding on the investigation on a new rumour	<ul style="list-style-type: none"> • Alert investigation form • Checklist for incoming rumours 	Reports to the heads of the unit (Epidemiology/Surveillance and Case Management) who are in turn reporting to the incident manager Supervises surveillance officer
Case supervisor	Coordinates all necessary steps of handling cases, e.g. triage, transport, laboratory tests, decontamination Forwards information about a suspected case to the contact and surveillance supervisor	<ul style="list-style-type: none"> • Checklist with tasks for case handling • Case investigation form / case report (available in folder artefacts) • Task list for case officers 	Reports to the heads of the unit (Epidemiology/Surveillance and Case Management) who are in turn reporting to the Incident manager. Supervises case officer
Contact officer	Conducts contact tracing within a particular district	<ul style="list-style-type: none"> • Contact list for the day / week • Daily report for contact supervisor • Case report relevant for currently followed contact • Suspected case information • Contact tracing form • Interview guide for contact interview • Meeting calendar • Contact list of new potential contacts to be traced 	Reports to contact supervisor
Contact supervisor	Coordinates the work of the contact officers Informs the case supervisor about suspected cases	<ul style="list-style-type: none"> • Information on traced contacts • List of contacts to trace and their details • List of contact officers • Task list for each contact officer • Meeting protocol from daily meeting with all contact officers • Daily reports from each contact officer • Information on suspected case 	Reports to case supervisor Supervises contact officers

EVD: Ebola virus disease; SORMAS: Surveillance and Outbreak Response Management System.

data. The complete listing of needs of the respective personas as well as the detailed process model is available at <http://www.helmholtz-hzi.de/sormas>.

Information flow and interactions between personas

Figure 1 indicates the interactions between the personas, the information flow and interactions in more detail, reflecting the information from the process model.

The informant can be a volunteer functioning as community informant, an Ebola focal person in a private healthcare facility, or a community healthcare worker. Therefore, the educational level and institutional

affiliation may differ widely. The rumour officer is part of the EOC team and collects all rumours on possible cases that come in through different channels, e.g. phone, mail, media reports etc. from citizen, healthcare workers, or indirectly via the hotline.

The surveillance supervisor may be a disease surveillance and notification officer (DSNO). They decide if and what kind of verification action is to be taken upon incoming rumours or notifications and direct this task to the surveillance officer in the field. They apply the criteria of the case definition and takes decision of the respective case classification based on available clinical epidemiological and laboratory data. Once a suspected case is identified by a rumour officer, the

surveillance supervisor informs the case supervisor to initiate isolation and treatment, laboratory confirmation and decontamination. Besides receiving hints on potential cases, the surveillance officer also reaches out to hospitals to assure zero reporting and may verify on site whether criteria of case definitions apply for a possible case.

The contact officer reports contacts as ‘suspected cases’ to the contact supervisor, as soon as the contact develops symptoms. Contacts or relatives of contacts who have issues with stigmatisation, rejection or are difficult to deal with are also referred to the case supervisor. The contact officers are often DSNOs, staff members from the Ministry of Health, graduates and residents from the Nigeria Field Epidemiology and Laboratory Training Programme, Red Cross Volunteers, or surveillance officers from WHO.

The case supervisor coordinates the activities of several case officers by assigning tasks such as clinical management of cases at the isolation facility, decontamination of residences and facilities, safe burial of corpses, psychosocial support of cases, contacts and relatives.

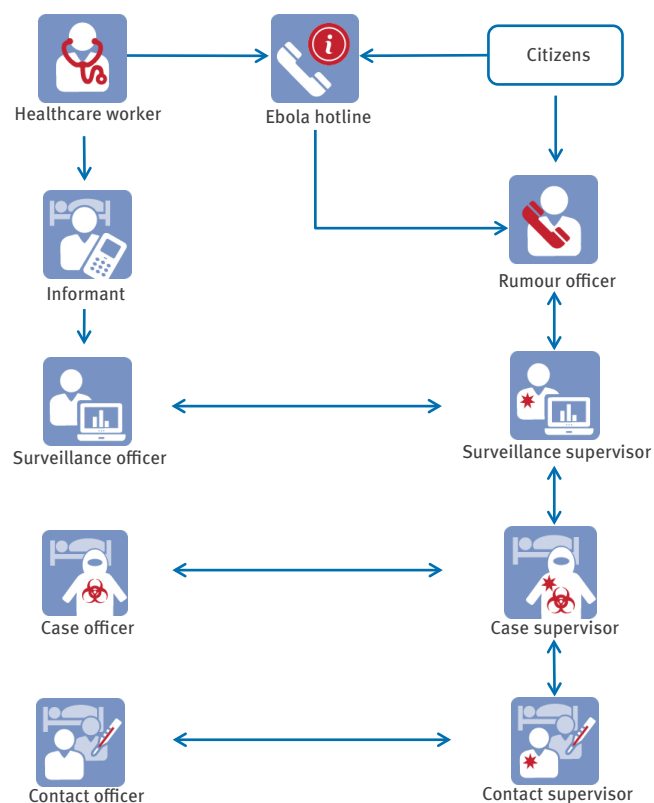
Technical infrastructure

We specified the technical infrastructure addressing the needs and tasks of the personas. We decided to focus on applications for mobile devices for the front end since the cellular network has become the first choice for Internet access in West Africa [14]. We further chose a scalable, cloud-based software architecture to allow non-dedicated computing resources on-site and to leave required maintenance to the cloud service provider.

The back end of the system is based on a cloud-based SAP HANA applying In-Memory Database (IMDB) technology [15]. A selected IMDB building block is the columnar database layout in order to enable real-time processing of analytical queries and lightweight data compression techniques. With the insert-only or append-only paradigm, IMDBs store the complete history of data changes to reconstruct the database state for any given point in time. Figure 2 depicts the software system architecture modelled as Fundamental Modelling Concepts block diagram [16]. Field workers use mobile devices to document acquired information directly in the cloud system. Available devices are registered in the cloud-based device management software SAP Afaria. The local cellular phone network provider provides data transfer to the Internet. All data exchange is encrypted using latest web standards, e.g. HTTPS protocol. All applications are configured by the cloud service provider and incorporate latest IMDB technology which allows storing all data in an encrypted format [17]. In case the mobile devices are to be used at times or in areas without mobile phone connectivity, the data entered will be automatically uploaded to the system as soon as connectivity is

FIGURE 1

Interactions between SORMAS users involved in the Ebola virus disease containment process



SORMAS: Surveillance and Outbreak Response Management System.

Arrows between personas represent the information flow.

available again. As a back-up option, data can also be downloaded from the encrypted SIM card.

User interface

The user interface was designed to fulfill all data collection and information needs of the seven personas, i.e. the artefacts have been implemented through corresponding screens. Bootstrap, a set of software tools for creating web applications based on HyperText Markup Language (HTML), Cascading Style Sheets (CSS), and JavaScript [18-20], has been used for this purpose. Some examples of screen shots for mobile devices are shown in Figure 3. The design of the icons, depicting the different personas and functions, went through six modifications to assure universally applicable, immediately understandable, and culturally sensitive design.

Comparison with other systems

The four main characteristics of SORMAS presented here are (i) its focus on the multilevel management functionality designed on the basis of systematic and in-depth analyses of the actual processes and personas involved in the successful EVD control in Nigeria,

(ii) its concept to ensure real-time synchronisation with surveillance systems already existing in many African countries such as IDSR and transfer interfaces to other EVD related database systems such as the EpiInfo Viral Haemorrhagic Fever application, (iii) its centralised back-end IT architecture using established software and database components with big data capacity, in combination with (iv) its mobile interface for bi-directional information exchange for staff in the field applicable on standard smart phones without any further configuration.

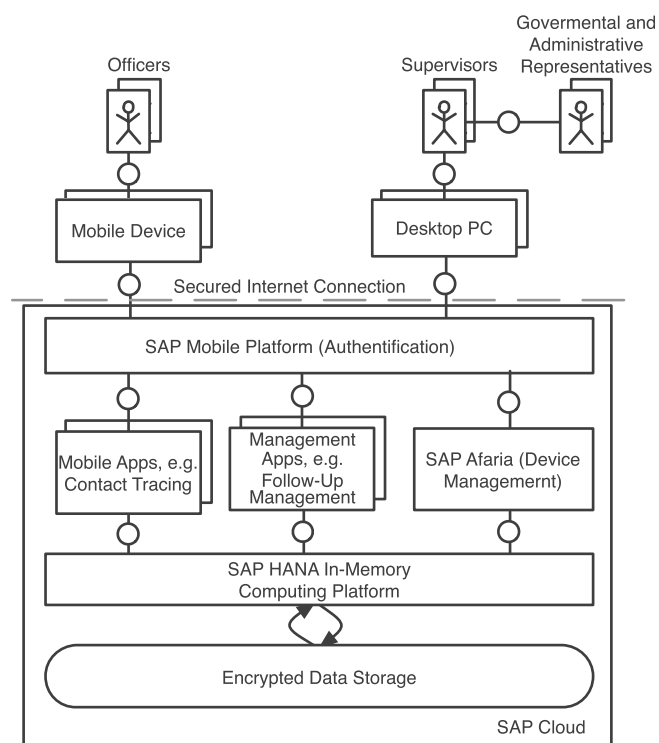
Through the combination of those four characteristics, SORMAS is distinct from various other tools aiming to support the control of the EVD and other outbreaks by means of mobile phone based applications. Detailed technical information on the existing systems is still available only to a limited extent. However, the existing tools do not support bidirectional information exchange and a task management as designed for SORMAS. For example, during the outbreak in Nigeria in August / September 2014, an Ebola reporting tool, called Open Data Kit (ODK) [6] was established running on Android phones. It allows reporting suspected cases, and sending of GPS data of cases/contacts, and integrated laboratory results with feedback to field workers. The ODK mainly digitised the data collection forms. ODK concentrated on contact tracing and follow-up. Only the contact officers had access to the system.

In contrast, SORMAS will be made available to several relevant personas, is more detailed and focuses on active case finding and surveillance.

The Centers for Disease Control and Prevention (CDC) developed a VHF module based on EpiInfo for contact tracing [21]. It provides support in case management, analysis, and reporting during outbreaks of EVD, Marburg virus, Lassa virus, Rift Valley Fever, and Crimean-Congo haemorrhagic fever. This module allows users to link cases with contacts and track those contacts continually over a 14- or 21-day follow-up window and to set up databases of patient information including names, sex, ages, locations, status, e.g. such as dead or alive, and case classification, for suspected case, confirmed case or no case. In contrast to SORMAS, the EpiInfo VHF module is not designed for bidirectional information exchange and does not address the challenge of information exchange.

The Ebola Care App supports contact tracing, patient data collection by ambulance teams, and Ebola education as well as observation and evaluation of children under quarantine [14]. Basing upon cloud data storage, it further gives decision makers real-time access to data from the field. It is currently tested by the Liberian government. CommCare is an open source mobile platform that supports a range of Ebola management needs. It has been developed and pilot tested to assist community healthcare workers [22,23]. CommCare operates through the use of Java-enabled phones or high-end Android smartphones. The system intends to provide a range of functions (some of them are still under development): household visit tracking, data collection, record keeping, day planning, and data exploration. Additionally, systems were developed that try to stimulate reporting by citizens or to provide citizens with information on prevention measures. EbolaTracks is an automated SMS system designed for monitoring persons potentially exposed to EVD, including travellers returning from Ebola-affected countries [24]. It enables monitoring of EVD contacts by SMS to inquire about development of symptoms.

FIGURE 2
SORMAS software architecture



SORMAS: Surveillance and Outbreak Response Management System; VM: virtual machine.

SORMAS, as well as most of the above mentioned IT-based tools to support the EVD outbreak control, makes use of the mobility and widespread availability of mobile phones in West Africa. This allows independence from variable wire-based IT and telecommunication infrastructure. In contrast to some of these approaches, SORMAS does not require any special configuration on the mobile devices which has proven to be a major obstacle when the ODK was used during the outbreak in Nigeria in August 2014. The use of SAP Afaria enables remote management of devices including their automated update as well as track and wipe of lost devices to ensure a high level of data security [25]. Using a cloud service provider also eliminates the need for local IT management. Data are uploaded to the cloud when an Internet connection is available. Otherwise SORMAS works in an offline mode where

FIGURE 3

Screenshots of the mobile SORMAS user interface



SORMAS: Surveillance and Outbreak Response Management System. The name of the person is fictitious.

data are stored locally until an Internet connection is available.

Discussion and conclusion

An advantage of SORMAS is the usage of the IMDB technology that was applied successfully in the analysis of big enterprise data and medical data, e.g. in supporting the identification of similar patient cases and the protection of markets from injecting pharmaceutical counterfeits [26,27]. We consider IMDB technology as a toolbox of IT building blocks enabling real-time analysis of big datasets [15]. IMDB technology also provides combined processing of structured data, e.g. relational database tables, and unstructured data, e.g. text documents. Furthermore, IMDB technology integrates statistical tools, such as clustering and machine learning algorithms. These functionalities would at a later stage allow development of complementary functionalities into SORMAS such as identification of social media messages and their linkage to reported cases.

Using such advanced IT technology might be perceived as a risk to acceptability and sustainability in countries in which computer systems may not work reliably due to lack of qualified maintenance or technical infrastructure. However, the use of a high performance architecture built with established components reduces the risk of break-down due to overload, allows flexible adaptation to country-specific needs and ensures a high level of data protection.

The process model has different dimensions:

1. centralised vs. field-based activities, carried out by respective personas who would in turn also use mobile devices vs desktop PC for their work.
2. the differentiation between

- intake of information (in form of rumours, notifications and reports of suspect cases),
- case verification,
- isolation management of the case, and
- identification and follow up of contacts of that case,
- monitoring of infection control measures (decontamination, safe burial) and social mobilisation.

SORMAS supports realising these control measures by providing reminders and check-lists to the user and confirming completed tasks. Standard operating procedures are thus automatised as much as possible. This will hopefully help reduce the time for action-taking and provide accountability. Another dimension of the process is the distinction between supervision and decision making (as represented by surveillance supervisor, case supervisor and contact supervisor) and the execution of these tasks by the respective personas.

Since the process model was based on the practical experience in the field it might serve as basis for epidemiological models on the impact of different intervention strategies.

One limitation is that SORMAS has not been used in the field yet. It remains to be seen until the foreseen pilot phase whether SORMAS can truly improve the control of EVD or other outbreaks. A table top prototype test based on two simulated scenarios was performed in February 2015 to evaluate the functionality of the system. A four-week pilot phase in Nigeria is planned for May 2015 to systematically evaluate SORMAS under field conditions. In order to allow proper piloting in the absence of EVD, we have identified alternative notifiable diseases and developed respective process models so that SORMAS will soon also contain functionalities

for surveillance and case management of additional epidemic prone diseases. In the Nigerian context, this would encompass measles, cerebrospinal meningitis, cholera, Lassa fever, rabies, acute flaccid paralysis, bloody diarrhoea/shigellosis, and Dengue fever. In order to realise this, the process model and data structures need to be redesigned taking existing public health guidelines and the respective surveillance processes into account.

Since SORMAS is designed to export information for integration in the IDSR forms, it may help to improve quality and efficiency of routine disease surveillance and control even in the absence of large epidemics. Possibly, SORMAS will only become available for implementation after the current EVD outbreak in West Africa has diminished in size. However, SORMAS is likely to be a very useful instrument to enhance routine surveillance of epidemic prone diseases as well as inhibiting the speed with which the disease is spreading. Currently we concentrate our work on adapting the system to surveillance tasks associated with other diseases such as measles and avian influenza A(H5N1). Beyond the actual system development, our work resulted in a better in-depth understanding of the processes and personas involved in the case management and surveillance tasks of EVD.

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Conflicts of interest

RR is employed by SAP, the provider of the platform used in this study. All other authors declare that there are no conflicts of interest.

Authors' contributions

Cindy Fähnrich, Kerstin Denecke and Gérard Krause drafted the manuscript. Cindy Fähnrich developed the process model and user interface, with contributions of Kerstin Denecke, Justus Benzler, Hermann Claus and Göran Kirchner, Olawunmi Olubunmi Adeoye, Sabine Mall, Daniel Tom-Aba, Gabriele Poggensee and Norbert Schwarz. Matthieu-P. Schapranow reviewed the process model. Cindy Fähnrich defined and specified the persona with contributions and discussions with Daniel Tom-Aba, Kerstin Denecke, Justus Benzler, Hermann Claus and Göran Kirchner, Olawunmi Olubunmi Adeoye, Sabine Mall, Gabriele Poggensee and Norbert Schwarz. Justus Benzler, Hermann Claus, Göran Kirchner and Kerstin Denecke developed the data model with contributions from Daniel Tom-Aba and Gabriele Poggensee. Ralph Richter, Matthieu-P. Schapranow and Matthias Uflacker designed the technical infrastructure. Kerstin Denecke discussed the results in comparison to related work. Gabriele Poggensee and Daniel Tom-Aba analysed the SORMAS requirements. Gérard Krause supervised the project and contributed to all

developments. All authors commented on the manuscript at all stages.

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Laboratory support during and after the Ebola virus endgame: towards a sustained laboratory infrastructure

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The Ebola virus epidemic in West Africa is on the brink of entering a second phase in which the (inter)national efforts to slow down virus transmission will be engaged to end the epidemic. The response community must consider the longevity of their current laboratory support, as it is essential that diagnostic capacity in the affected countries be supported beyond the end of the epidemic. The emergency laboratory response should be used to support building structural diagnostic and outbreak surveillance capacity.

As of 18 March 2015, the Ebola epidemic in West Africa has resulted in more than 10,194 deaths and more than 24,701 cases, however the most recent situation reports from the World Health Organization (WHO) [1] suggest that the weekly number of new cases in the first months of 2015 has been the lowest since June 2014. All indications therefore suggest that the epidemic has entered a second phase, making the end of the epidemic a real possibility. Importantly however, the feasibility of eradication of Ebola virus disease (EVD) in the human population in West Africa remains completely dependent on the sustained commitment of everyone involved in the response until all cases have been identified and transmission chains have stopped. This is illustrated by the slight increase in cases in Sierra Leone and Guinea reported in the first weeks of February [1].

One of the pillars of the response to this outbreak has been the provision of laboratory support that has facilitated the rapid testing of suspected cases [2,3]. The lack of laboratory capacity during the early stages of the epidemic will undoubtedly have been a contributing factor to the rapid expansion of the epidemic. With the aid of the international community, in-country laboratory capacity is no longer a significant limiting factor with respect to testing of patient samples and the turnaround time for samples in most areas is less than 24 hours, rather than several days as during the early days of the epidemic [4]. Given that the end of the epidemic is now a real possibility, we feel it is essential to begin active discussions with national agencies, the WHO and potential sponsors, regarding a 'post-Ebola

legacy' of laboratory support. Several countries have been involved in the deployment of in total 27 laboratories to provide rapid in-country testing for Ebola virus (EBOV) [1,4]. The laboratories deployed in the region are equipped to do molecular diagnostic testing, which has become the standard of care in clinical microbiology in other parts of the world. Therefore, the basic laboratory set-up currently provided in the EBOV response could be in the future extended to develop essential clinical and public health microbiology services also for other diseases.

With the decreasing number of patients in the EVD holding and treatment centres, the number of laboratory requests are falling rapidly, to the point that the conditions for laboratory testing need to be redefined. With the transition to the second phase of the EVD outbreak, a transition from acute testing for clinical triage to surveillance testing is needed, in which the threshold for the case definition should be lower, to demonstrate the absence of EBOV in the local population. In addition, it is widely accepted that the epidemic has had an impact way beyond the individuals infected with EBOV, the consequences of which will only become apparent long after the epidemic is over [5-7]. This impact is evident at many levels, including healthcare services and laboratory support for the detection of other circulating pathogens. Minor modifications of the procedures currently in use in the affected countries would make it possible to establish PCR-based diagnostic tests for a selected number of endemically circulating pathogens and could, as we enter the second phase of the epidemic, provide interim laboratory support to reduce the overall impact of the epidemic on public health by timely detection of endemic diseases enabling treatment and guiding control measures. If planned strategically, this could be a first step on the road to a sustained local laboratory infrastructure that will provide access to up-to-date facilities. Local laboratory experts took care of such activities with very limited resources before the start of the EVD outbreak; in the transition phase, it is therefore crucial to engage with these partners in order to discuss the way forward.

The international community must consider the longevity of their support, as it is essential that diagnostic capacity in the affected countries is supported beyond the end of the EVD epidemic. So far, the laboratories have largely been operated by teams of volunteers, flown in on a rotation of four to six weeks from research and public health laboratories around the world. With the outbreak ending, some laboratories will be closed in the coming months. We foresee an all too familiar pattern: equipment is left unused after an outbreak or even removed from the country because local staff lack the necessary training and affordable reagents and equipment are not available [8-10]. By building on the expertise in country and using the infrastructure currently present, the network of diagnostic and public health laboratories could be strengthened, strategically placed to facilitate reliable logistics as well as population coverage. Such a network should be capable of both routine and response modes and could be supported through telemedicine programmes, training programmes outside and within the country and international reference laboratories to provide improved access to additional laboratory services.

Rather than copying the workflows used in the United States and Europe, it is essential that fit-for-purpose diagnostic algorithms are developed, such as a combined laboratory package to diagnose sickle cell anaemia, infection with human immunodeficiency virus and hepatitis B virus, coupled with essential haematology and clinical chemistry as well as the ability to rule out EVD and Lassa fever in maternity clinics. A large advantage of the molecular era is that the division between clinical and public health work becomes blurred, creating an opportunity to kill two birds with one stone. It is time to step away from the 'one pathogen-one laboratory network' approach, which raises costs tremendously but is the standard set by international reference centres [11-15]. This is by no means an easy task, as it requires collaborative and out-of-the-box thinking. It also requires novel research to provide low-cost solutions and alternatives for the expensive assays that are currently available. The most commonly used EBOV laboratory test costs ca EUR 45 per patient (for diagnosis and pre-discharge testing). We invite suppliers and manufacturers of key laboratory equipment and reagents to suggest more affordable solutions that take into consideration the limited local cold chain capacity and to provide adequate regional technical support. Innovative solutions such as open source laboratory equipment may be one possibility to make equipment accessible.

The current epidemic and previous serological surveys [16] indicate that EBOV and other highly virulent pathogens are circulating in West Africa and will continue to do so beyond the end of the current epidemic. The reality is that EVD is likely to remain a problem in West Africa and this will not be the last epidemic we see in this area. The establishment of an integrated network of support laboratories would strengthen epidemic

preparedness and response capabilities for the inevitable introductions of highly pathogenic zoonotic pathogens in the local human population.

Conflict of interest

None declared.

Authors' contributions

All authors: design and writing of manuscript.

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Letter to the editor: Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014 – Eurosurveillance 17 September 2014

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To the editor:

In their article *Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014*, published on 11 September, Nishiura and Chowell estimated the effective reproductive number R_t for the mainly affected countries, Guinea, Liberia and Sierra Leone, to be consistently above 1 since June 2014, indicating that the outbreak is not yet under control [1]. Such studies are welcome and useful to understand and quantify the ongoing epidemic and to plan the response activities.

However, we would like to add a cautionary note to the interpretation of the surveillance data. Important detailed information may be missed by such general modelling approach. The study of the epidemic curves based on data retrieved by week and district of reporting, from the situational reports of the Ministry of Health of Liberia [2] shows very different patterns contributing to the overall observed dynamic at national level. Figure 1 shows the number of suspected, probable and confirmed cases reported by week in Liberia,

from calendar week 21 (starting on 19 May) to week 37 (starting on 8 September) 2014. Following the steep increase in the number of cases up to week 34, which was described by Nishiura and Chowell, a levelling off in the number of newly reported cases occurred between weeks 34 and 36 resulting in the flattening of the curve, followed by a new increase in week 37.

Figure 2 shows the distribution of newly reported cases by week for selected districts of Liberia. Only districts that reported more than five cases since the start of the epidemic are shown. The epidemic curves show markedly different patterns. The districts of Bomi, Bong, Grand Cape Mount, Margibi and Nimba experienced a relatively stable number of weekly cases, while the districts of Lofa and Grand Bassa reported an increase in the number of cases up to weeks 33 and 35, respectively, followed by a decrease in subsequent weeks. The district of Montserrado shows a continuous increasing pattern from week 29 up to week 37.

The presentation of aggregated data for Liberia at national level which shows a transient overall stabilising and even slightly decreasing trend in the number of newly reported cases between weeks 34 and 36 can therefore be misleading. The alarming trend in the district of Montserrado is compensated by a decreasing trend observed in the recent weeks in districts reporting fewer cases.

Furthermore, the observed dynamic based on available surveillance data can only be interpreted in the light of the performance of the surveillance system having generated them. There are reports from areas in the affected countries where hospitals have closed, health centres are overwhelmed, patients are treated at home and contact tracing and monitoring is inadequate. Caution is therefore necessary when interpreting the data, as a decrease in the number of newly reported cases could signify either a positive effect of the interventions to control the epidemic or a decrease in the

FIGURE 1

Distribution of suspected, probable and confirmed cases of Ebola virus disease by week of reporting, Liberia, week 21 (starting on 19 May) to 37 (starting on 8 September) 2014 (n=2,663)

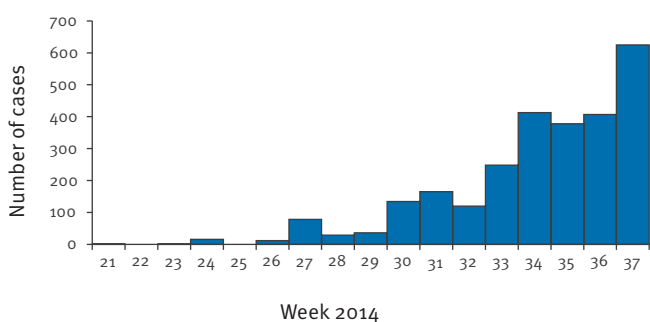
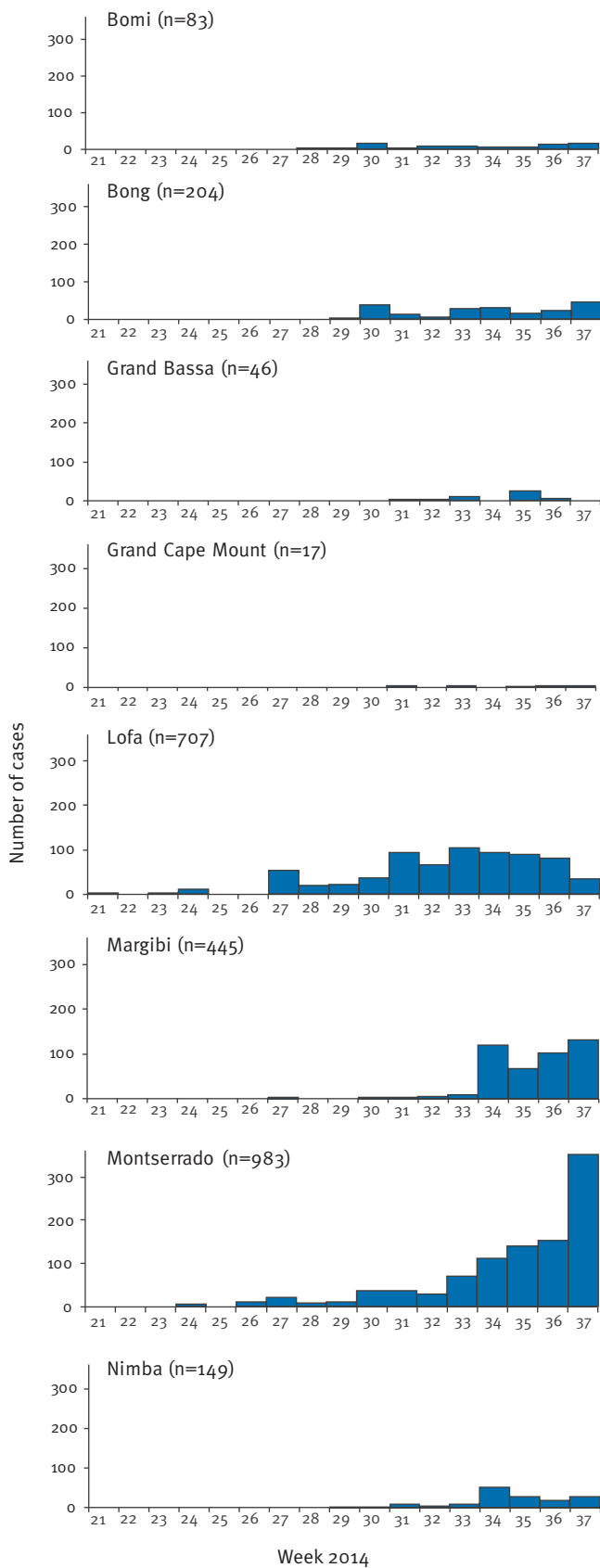


FIGURE 2

Distribution of newly reported cases of Ebola virus disease by week and selected districts, Liberia, week 21 (starting on 19 May) to 37 (starting on 8 September) 2014



performance of the surveillance system. Similarly, an increase in the number of cases could result not only from improved surveillance but also from increased transmission.

The use of surveillance data for setting priority intervention areas, for measuring their effectiveness and for planning resources on the basis of forecasting, needs to consider the performance of the surveillance system through which the data are generated. Simple surveillance quality indicators should be collected along with epidemiological data, such as the number of contacts identified and monitored. Moreover, studies assessing performance are a useful addition to allow better understanding of the limitation of surveillance data, e.g. capture-recapture studies, review of health-care facilities records or household visits in affected areas. In conclusion, ensuring efficient surveillance is essential for the effective response to this devastating outbreak.

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Authors' reply: Feedback from modelling to surveillance of Ebola virus disease

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To the editor:

We appreciate the comments from Plachouras et al. on our article published in *Eurosurveillance* a week ago [1,2]. Overall we fully agree with them on both points, i.e., (i) in that there is a need to account for the geographic heterogeneity of the ongoing Ebola epidemic to better understand the transmission dynamics and guide intervention strategies and (ii) in that caution must be exercised to interpret time-dependent changes in the reported coverage of cases captured by the surveillance systems. Here we further highlight these issues by providing feedback from a mathematical modelling point of view.

First, the most recent data points comprising the last three weeks of reported case counts (weeks 35-37) presented by Plachouras et al. were not incorporated in our analysis as these data were not available at the time of preparing our study. Indeed, these additional data points might have changed our interpretation of the most recent trends of the effective reproduction number. Second, our analysis was based on an approximate strategy in line with the available aggregated data. Consequently, we were not able to consider heterogeneous patterns of transmission within each country. With detailed spatial data, we could have detected an apparent slowdown in the incidence influenced by actual decline in incidence at several regions along with a steady increase in Montserrado. With such analysis of spatial data, we would have interpreted the most recent estimate of R_t for Liberia as the result of spatial dilution of differential growth rates by different regions, possible reflection of large local clusters of cases, or the presence of significant reporting delays in the most recent data. Real-time analysis of the ongoing public health crisis in West Africa deserves the consideration of the most detailed, accessible and accurate epidemiological data in order to capture the above-mentioned aspects and explicitly identify regional variations in transmission, which could be key to guide intervention efforts.

We take this opportunity to address two critically important issues in conducting modelling studies using surveillance data subject to limited reporting coverage. First, as discussed in light of our original findings [2], the reported case data are always accompanied by reporting delays. Suppose that the unbiased number of cases and the actual reported number of cases at calendar time t are given by c_t and r_t , respectively. Then we have the relationship,

$$c_t = r_t \frac{1}{H_{T-t}}$$

where H_{T-t} is the cumulative distribution function of the reporting delay (of length $T-t$) and T represents the most recent time of observation. This indicates that most recent incidence data might be underestimated (and should be adjusted by H_{T-t}). Nevertheless, this might not be a significant issue as long as H_{T-t} is independent of calendar time.

There is a second (and perhaps more serious) issue to consider, i.e., the potential for time-dependent changes in the reporting rate. This is highly relevant to the ongoing Ebola virus disease (EVD) epidemic as the number of new cases has been exponentially growing, which generates pressure on healthcare facilities to assist an extraordinary large number of cases beyond their expected capacity. Let the reporting fraction be s_t at calendar time t which could be estimated by carefully looking into the time-dependent change in the proportion of severe (or fatal) cases among all reported cases [3]. For instance, if the fraction of critically ill cases among total cases increases at a rate b per day, reflecting a decreasing ascertainment rate, we have

$$s_t = \frac{1}{b} s_{t-1}$$

and the unbiased number of cases at t , c_t , is calculated by dividing the reported number of cases n_t by s_t , i.e., $c_t = n_t / s_t$. For instance, a modelling study made a similar

adjustment to analyse data of the influenza A(H1N1) pdm2009 pandemic. In this study, the proportion of hospitalised cases among total reported cases was used as the input data to calculate s_t [3].

It is worth noting that several efforts have already been made to estimate the reproduction number of the ongoing EVD epidemic [2,4,5,6] based on the same publicly available country-wide data of reported cases as in our study.

Potential feedback from modelling studies to surveillance can be summarised as follows: (i) The geographic differences in the evolution of the Ebola epidemic highlighted by Plachouras et al. underscore the need to access high-resolution spatiotemporal data to detect heterogeneous levels in the spatiotemporal dynamics of the epidemic. At the same time, it is critical to exercise caution in the analysis of aggregated time-series data in the presence of significant levels of spatiotemporal heterogeneity. (ii) As a possible indicator of variations in the reporting fraction, monitoring well-defined severe cases would be useful, e.g., hospitalised cases, cases in the state of disseminated intravascular coagulopathy or shock, and deceased cases in order to calculate time-dependent changes in the fraction of the severe cases among the total number of reported cases. It might be also feasible to further account for the time delay from symptoms onset to developing severe manifestations in order to adjust the reporting delay. Surveillance and mathematical modelling are two complementary instruments in the toolbox of epidemiologists. Combining their strengths would be highly beneficial to understand epidemic dynamics and take public health actions. We are keen to contribute further by analysing more detailed epidemiological data of the Ebola epidemic.

Conflict of interest

None declared.

Authors' contributions

HN and GC drafted and revised the manuscript.

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Letter to the editor: Management of patients with Ebola virus disease in Europe: high-level isolation units should have a key role

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To the editor:

We read with interest the article by de Jong and colleagues, who provide an initial insight into European hospital preparedness level for the admission of a patient with Ebola virus disease (EVD) [1].

In the past, the rare imported cases of Ebola and Marburg in western European countries and the United States were managed in high-level isolation units (HLIUs) [2]. Subsequently, reported experiences indicate that strict contact-droplet isolation is enough for preventing transmission. From this hypothesis, the idea may derive that HLIUs are not strictly necessary for the management of EVD patients, who may be safely managed in non-specialised hospitals, as suggested by some international recommendations elaborated during the current Ebola outbreak in West Africa [3,4]. Even if we concur that strict contact-droplet isolation is enough to prevent transmission during routine care, we believe that HLIUs should have a key role in EVD containment in countries where such facilities are available. An HLIU is a healthcare facility specifically designed to provide safe, secure, high-quality, and appropriate care, with optimal infection containment and infection prevention and control procedures, for a single patient or a small number of patients who have, or who may have, a highly infectious disease [5].

In hospitals, breaches in infection control may occur; many healthcare associated infections could be prevented by standard precautions and contact isolation measures, but despite this, they continue to hit thousands of patients and to increase health-related costs [6]; measures for preventing needlestick and sharp injuries are well-known, but many of these accidents occur every day; hand hygiene alone may prevent many infections, but this simple procedure is often poorly applied [6]. We believe that such breaches are not acceptable when managing a disease with 50% of case fatality rate such as EVD. Data from de Jong and

colleagues, reporting that practical exercises have been performed in 28.4% of responding hospitals only [1], as well as the secondary transmissions that occurred in Spain and the United States, reinforce this position.

Indeed, establishing precautions is not equal to their adherence. Well-trained staff, awareness about personal protective equipment and other infection control procedures, continuous practice, appropriate supervision, and adequate logistics are needed; in other words, an established 'infection control culture and practice'. Moreover, rooms with special technical air-handling features are necessary for aerosol-producing procedures [7].

We believe that this unique combination of technical and logistic equipment, well-trained and experienced staff, and long-term established and updated procedures, is available within HLIUs only, thereby representing the safest place to manage EVD.

In Europe, an assessment of isolation capabilities for the management of highly infectious diseases was performed in 2009–2010 within the European Network for Infectious Diseases/European Network for Highly Infectious Diseases (EUNID/EuroNHID) projects coordinated by the National Institute for Infectious Diseases 'Lazzaro Spallanzani' in Italy [8]. The EuroNHID Consortium currently includes 47 isolation facilities identified by the national health authorities as referral centres for highly infectious diseases (including EVD), in 20 countries (Austria, Bulgaria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Norway, Poland, Portugal, Spain, Slovenia, Sweden and the United Kingdom). The survey results are being updated in 2014: complete data are available from 12 countries; from the remaining eight countries, partial data are available. According to currently available data, among

the 47 isolation facilities 17 HLIUs are present in nine European countries, with at least 92 beds available, 57 of which with intensive care capacity. Additional capacity may be present in other countries not participating to EuroNHID Consortium. This bed capacity (not expected to change significantly after the collection of pending data) is surely enough to effectively manage Ebola patients in Europe, in the current epidemiological situation.

In conclusion, we strongly believe that HLIUs should play a crucial role in management of patients, and preparedness plans should include referral of EVD patients to these facilities as early as possible.

Other members of EuroNHID Consortium are:

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Conflict of interest

None declared.

Authors' contribution

All authors equally contributed to manuscript concept and writing. All authors gave their final approval to the manuscript contents.

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Authors' reply: Management of patients with Ebola virus disease in Europe: high-level isolation units should have a key role

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Ippolito and colleagues suggest a key role of high-level isolation units (HLIUs) for patient management and containment of Ebola virus disease (EVD) in Europe [1]. In principle, we do agree with this notion, particularly in relation to repatriated or evacuated patients with confirmed EVD. However, realities are (i) that patients with (suspected) EVD who are in need of care may present at any hospital anywhere in Europe, and (ii) that the number and geographic distribution of HLIUs are limited which pose difficulties particularly in the unlikely event of multiple introductions or spread of EVD (or other highly infectious diseases) in Europe. For these reasons, preparedness for admission of suspected patients or procedures for transfer of such patients to other hospitals are essential, and this is what we sought to assess in our survey [2].

As noted by Ippolito et al., practical exercises of preparedness are important and were performed in only 28% of hospitals overall at the time of the survey. However, somewhat reassuringly, it should be noted that this percentage was substantially higher in hospitals that would admit suspected patients (46%). Also, it should be noted that this survey was initiated less than three weeks after the World Health Organization's Public Health Emergency of International Concern (PHEIC) declaration [3], and that preparedness activities, including exercises, will likely have intensified since then.

In conclusion, efforts to identify and address gaps in preparedness of European hospitals are essential to assess and manage the risk of possible spread of EVD or the next emerging highly infectious disease in Europe. Notwithstanding their importance, reliance solely on HLIUs for containment of EVD or other highly infectious diseases may be unrealistic.

Conflict of interest

None declared.

Authors' contribution

MDdJ, MK and HG wrote the letter.

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