Post-exposure prophylaxis with rVSV-ZEBOV following exposure to a patient with Ebola virus disease relapse in the UK: an operational, safety and immunogenicity report

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Summary: The rVSV-ZEBOV vaccine was used as post-exposure prophylaxis in individuals exposed to Ebola virus in the UK. It was rolled out rapidly and was generally well-tolerated. Side effects correlated with the magnitude of CD8+ T cell responses.
Abstract

Background
In October 2015, 65 people came into direct contact with a healthcare worker presenting with a late reactivation of Ebola virus disease (EVD) in the UK. Vaccination was offered to 45 individuals with an initial assessment of high exposure risk.

Methods
Approval for rapid expanded access to the recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine (rVSV-ZEBOV) as an unlicensed emergency medicine was obtained from the relevant authorities. An observational follow-up study was carried out for 1 year following vaccination.

Results
26/45 individuals elected to receive vaccination between October 10th and 11th 2015 following written informed consent. By day 14, 39% had seroconverted, rising to 87% by day 28 and 100% by 3 months, although these responses were not always sustained. Neutralising antibody responses were detectable in 36% by day 14 and 73% at 12 months. Common side effects included fatigue, myalgia, headache, arthralgia and fever. These were positively associated with glycoprotein (GP)-specific T-cell but not IgM or IgG antibody responses. No severe vaccine-related adverse events were reported. No-one exposed to the virus became infected.

Conclusions
This paper reports the use of the rVSV-ZEBOV vaccine given as an emergency intervention to individuals exposed to a patient presenting with a late reactivation of EVD. The vaccine was relatively well tolerated but a high percentage developed a fever ≥37.5°C necessitating urgent screening for Ebola virus and a small number developed persistent arthralgia.

Keywords: Ebola virus, rVSV-ZEBOV, vaccine, T cell
Introduction

The 2013-2016 Ebola virus (EBOV) outbreak in West Africa resulted in 28,646 reported cases of Ebola virus disease (EVD) and 11,323 deaths[1]. Healthcare workers were at particularly high-risk of infection with at least 500 deaths among 900 cases and amplified transmission of the disease in some healthcare settings. On the 29th December 2014, a nurse who had worked in a treatment centre in Sierra Leone was diagnosed with EVD on return to the UK[2]. Full protocols for the management of viral haemorrhagic fever (VHF) were instituted immediately. Of 3 individuals providing direct healthcare to the patient prior to transfer to the UK high level isolation unit, none were categorised as high-risk due to appropriate use of personal protective equipment (PPE). In contrast, when the same patient became unwell with a previously unreported complication of EVD reactivation associated with meningo-encephalitis between the 5th-9th October 2015 (the only reported late reactivation resulting in detectable viremia of 28,646 cases), 45 healthcare workers and household contacts were initially categorised as high-risk. An incident management team (IMT) was set up in order to consider post-exposure prophylaxis (PEP).

In October 2015, no licensed EBOV-PEP was available although vaccine responses had been shown to occur rapidly in macaques and humans. An interim phase III cluster randomised trial of the replication competent rVSV-ZEBOV vaccine, published in July 2015, indicated 100% efficacy at 10 days post-vaccination and an acceptable side effect profile[3]. In rhesus macaques, it was found to provide protection when given as little as 1 week prior to exposure[4] and had also been used successfully as PEP 49 hours after exposure in a laboratory worker following a high titre needlestick injury[5]. Another 6 individuals subsequently received the vaccine following exposure during the 2013-2016 outbreak and none developed EVD[6].

In view of the evidence of a rapid immune response in vaccinated individuals and the reported safety of the rVSV-ZEBOV vaccine, a decision was made to offer vaccination to those with the highest exposure risk. Vaccinated individuals were subsequently enrolled into the Glasgow Ebola Vaccine
Follow-up Study (GEVS). Primary outcomes included evidence of infection with EBOV, the immune response following vaccination and side effects.
Methods

Approval process: An international IMT including infection experts from Europe and the USA recommended that vaccination be offered to those with highest exposure risk on the 9th October 2015, following EVD diagnosis in the index case (Figure 1). 65 individuals were identified by the Greater Glasgow and Clyde public health team and designated as category 1, 2 or 3 depending on their level of exposure following national guidance (Supplementary Table 1). These cases were re-reviewed by 3 infectious diseases physicians, a public health physician and a clinical virologist, incorporating additional expert risk categorisation advice[7]. Those with a recent history of direct exposure to bodily fluids (vomit, diarrhoea, blood, sweat and/or cerebrospinal fluid) were recalled to an emergency vaccination clinic on 10th-11th October. 26/45 clinic attendees accepted the offer of vaccination with informed consent under local NHS emergency regulations for unlicensed treatments (Figure 2). The following day, the West of Scotland Research Ethics Committee approved a prospective observational follow-up study (15/WS/0251).

Vaccination: The vaccine clinic was staffed by 6 doctors, 4 nurses and a receptionist. Any attendee with a temperature of ≥37.5°C on arrival was immediately screened for EBOV by staff in full PPE (Tyvek suit, rubber boots, overshoes, FFP3 mask, visor, double gloves and apron) (Supplementary Figure 1). EBOV PCR was carried out within 6 hours of dispatch at Edinburgh Royal Infirmary.

Vaccination protocols (Supplementary Information)[3] and rVSV-ZEBOV vaccine were provided by WHO and maintained at -80°C. A single dose of 2x10^7 plaque-forming units (pfu)/ml was prepared using the PREVAIL pharmacy manual [8] and administered intramuscularly in the deltoid muscle.

Clinical follow-up: all individuals with a category 3 exposure were followed up with daily temperature screening for 3 weeks. Those with a temperature of ≥37.5°C were tested for EBOV infection by RT-PCR. Vaccinated individuals were followed-up at 30 minutes, 14 days and 1, 3, 6, 9 and 12 months post-vaccination. 20ml of blood, urine and sputum samples and a semen sample from males was obtained at each clinic visit.
Laboratory methods

**PCR:** Samples obtained during fever and at days 14 and 28 following vaccination were tested at Edinburgh Royal Infirmary using an adapted version of the Trombley PCR assay[9]. Blood, urine and semen were tested for the presence of the rVSV-ZEBOV vaccine using a VSV RT-PCR [10]. EAV was used as an internal control and had a detection limit of between 50-5 pfu/ml. Plasma, urine, sputum, serum, saliva, semen and whole blood were extracted using the NucliSens EasyMAG (bioMérieux, Hampshire, UK) according to manufacturer’s instructions. PCR was performed on 6μl of RNA extract with the Platinum RT-PCR mastermix kit (Invitrogen) on an ABI Prism 7500 SDS real-time platform (Applied Biosystems) in a 15μl reaction volume. The following thermal profile was used: 15min at 50°C and then 95°C for 15min, followed by 40 cycles of 95°C for 60s and 60°C for 60s.

**Immunological assays:** Antibody assays were carried out at days 14, 28 and 3, 6, 9 and 12 months post-vaccination and T-cell responses measured by IFNγ ELISpot and flow cytometry at 1, 3, 6, 9 and 12 months.

**Enzyme linked-immunosorbent assay (ELISA)**[11]
High binding microtiter plates were coated with 1μg/ml EBOV GP and incubated for 16-20 hours. Following washing (PBS/0.1% Tween20) and blocking (Casein), 1:200 dilutions of plasma sample were added and incubated for two hours. Polyclonal anti-human IgG-AP antibody (1:1000) with substrate (diethanolamine substrate buffer with 20 mg pNPP in 20ml ddH2O) was used to develop the reaction. Optical density (OD) was determined at 405 nm. Samples were analysed in duplicate and background subtracted from the mean of each sample. Plates were read using a predefined softmax template which fits a 4-parameter logistic model to the dose response data, IU/ml are based on the WHO International Reference Standard (NIBSC 15/220) which was used to quantify the internal standard.
Neutralisation assays: Neutralization assays were performed at biosafety level 4 at the Institute of Virology, Philipps-University Marburg, Germany as previously described[12]. Volunteer blood plasma was incubated at 56°C for 30 min for complement inactivation. After centrifugation at 13,000rpm for 10 min, sera were serially diluted from $2^3$-$2^{10}$ in Dulbecco’s modified Eagle’s medium (DMEM, Gibco) supplemented with 2% fetal calf serum (FCS, Gibco), penicillin (100U/ml), streptomycin (100mg/ml), and L-glutamine (2mmol/l) (Invitrogen) in 96-well culture plates. 100 TCID50 units of EBOV (Zaire, isolate Mayinga, AF086833) were added to the serum dilutions. Following incubation at 37°C for one hour, Vero cell suspension in DMEM containing 2% FCS was added and incubated at 37°C with 5% CO2. Cytopathic effects (CPE) were evaluated at seven days post infection. Neutralization titers were calculated as GMT of four replicates.

IFNγ-ELISpot assays: Peripheral blood mononuclear cell (PBMCs) were thawed using warm media and rested overnight at 37°C. The following day they were stimulated with overlapping EBOV glycoprotein peptides (MP1/MP2) as previously described[13]. Plates were counted using an S6 core analyser (Cellular Technology Limited) and results adjusted to spot forming units (SFU)/1x10^6 cells/ml. Analysis required detection of a positive control then subtraction of the non-peptide stimulated control from peptide-stimulated samples.

T-cell phenotyping studies: Intracellular cytokine staining (ISC) was performed as previously described[13]. Briefly, PBMCs were re-suspended in warmed media and rested overnight at 37°C. The following day, cells were adjusted to 1x10^6 cells/ml in media containing anti-CD28, CD49d and CD107a-PerCP cy5.5 (1 µg/ml). Cells were then untreated or stimulated with EBOV GP peptide pool, containing 187x15mer overlapping peptides at 2.5µg/peptide or 1µg/ml Staphylococcal Enterotoxin B peptide (SEB) for 16-18 hours. After two hours, brefeldin A and monensin (1µg/ml) were added to block cytokine secretion. The following day samples were washed and LIVE/DEAD dye added. Samples were washed, incubated with cell surface antibodies (CD3-APC 750, CD4-BV786, CD8-
AF700, CD19- BV510 and then CD14-BV510, CCR7- APC, CD95-BV395 and CD45RO-BV605), then washed, fixed and permeabilised then stained for intracellular cytokines using INFγ-AF488, TNFα-BV421 and IL-2-PE. Samples were analysed using a BD Fortessa machine and FACS Diva, FlowJo™, Pestle and SPICE software (see Supplementary Information).

**Statistical analysis**

Comparisons were made using parametric or non-parametric methods as appropriate using STATA v10. The sponsor of the study had no role in study design, data collection, analysis or writing of the report.
Results

Of 65 individuals designated as having had contact with the infected patient, 45 category 3 contacts were found to have had possible direct skin contact with contaminated bodily fluids (vomit, sweat, blood, urine or cerebrospinal fluid (CSF)). None had evidence of percutaneous exposure and all would be categorised as “intermediate” in a more recently proposed exposure risk stratification[7]. Of these, 26 elected to receive vaccination following written informed consent and agreed to be followed as part of the observational GEVS Study. The median age of those vaccinated was 40 (range 24-67). 15/26 (58%) were healthcare workers and 11/26 (42%) were household contacts. All individuals were followed up within the first 3 months following vaccination but attendance at subsequent follow-up clinics was incomplete due to movement of medical and nursing staff to other cities within the UK (Supplementary Table 2). No-one exposed to the virus became infected. All samples tested for EBOV and VSV were negative, including two febrile clinic attendees tested for EBOV prior to vaccination.

Antibody responses: IgG indirect ELISA results are presented in Figure 3a as seroconversion (a positive antibody response at any time during the follow-up period) and individual responses detected at each follow-up visit to assess longevity of the response. By day 14, 39% had seroconverted. This rose to 87% by day 28 and 100% by 3 months. Such responses were not always sustained; one 68-year old individual developed a positive IgG response at 14 days post-vaccination but the level descended below the detection threshold at all further timepoints (Supplementary Figure 2). This was not associated with the onset of any form of illness or immunosuppressive treatment during this time period. Detectable antibody responses fell to 73% by 12 months post-vaccination. Individual results are shown in Supplementary Figure 3. A positive anti-GP IgM response peaked at 14-28 days post-vaccination (Figure 3b) and negatively correlated with the emergence of neutralising antibody responses (Supplementary Figure 4). Neutralising antibody
responses were detectable in 6/16 (36%) individuals by day 14 and peaked at 9-12 months post-vaccination with a detectable response in 9/12 (73%; Figure 3c).

**T-cell responses:** IFNγ ELISpot responses to GP were detected at all timepoints, followed a similar pattern to neutralisation over time (Supplementary Figure 5) and peaked at 6 months post-vaccination (Figure 3d). Individual responses are shown in Supplementary Figure 6.

**Side effects:** Side effects were common but mild in the majority of cases and were characterised by a syndrome of fatigue, myalgia, headache and arthralgia (Table 1). The presence of one symptom was strongly associated with the presence of others (Fisher exact test, p<0.0001). During the first 72 hours of follow-up, 50% of individuals developed a fever ≥37.5°C, requiring in-hospital assessment and testing for EBOV. While the median duration of side effects was 0-1 days, a small number of patients developed long-standing symptoms of fatigue (up to 343 days), arthralgia (up to 261 days) and headache (up to 108 days). Two patients experienced long-lasting symptoms of arthralgia, one of whom had a diagnosis of osteoarthritis and flexor tendonitis thought to be unrelated to vaccination following specialist rheumatological review. Further details on cases of arthralgia are shown in Supplementary Table 3.
Symptoms of arthralgia, myalgia and fatigue occurring at the time of sampling were significantly associated with a higher proportion of CD8+ IFNγ and CD4+ IL2 secreting cells while headache was associated with higher CD4+ IL2 (Figures 4a-d) and IFNγ ELISpot response. No significant association with IgM, IgG or neutralising antibody responses was found (Supplementary Table 4).
Discussion

The risk of transmission of EBOV to household contacts and healthcare workers exposed to infected bodily fluids is high, particularly prior to diagnosis when the risks may not be fully appreciated. During the West Africa 2013-16 outbreak, several infected individuals travelled by air to other countries resulting in onward transmission. In Spain, a nurse became infected after caring for a patient transferred for specialist care and in the United States, two nurses became infected after contact with an undiagnosed infected traveller. In Nigeria, 20 people were infected (11 healthcare workers) following a single introduction[14]. No randomised studies on the use of PEP have been carried out in humans but vaccination and antiviral agents have been studied in exposed individuals on a case-by-case basis[6,7] and more recently in a large outbreak in DRC.

The rVSV-ZEBOV vaccine is a highly effective vaccine that rapidly protects mice, hamsters, guinea pigs, non-human primates and humans from infection with EBOV when administered prior to exposure. In humans, ring vaccination with rVSV-ZEBOV at a dose of 2x10⁷pfu was highly effective at preventing infection in contacts and contacts of contacts of individuals with EBOV infection in West Africa in a large phase III trial[15]. In this study, which initially involved an immediate and a delayed vaccine arm, no infections occurred 10 days after vaccination in any recipient (100% vaccine efficacy). As a result, randomisation was halted by an independent safety board and all subsequent participants in the study were offered immediate vaccination. Vaccination was carried out a median of 7.3 and 9.8 days following index patient symptom onset in the immediate and non-randomised vaccine rings respectively. Importantly, EBOV infection did occur in the 10-day period post-vaccination and this was not reduced compared with the delayed vaccination arm. This indicates that the timing of the use of the vaccine is likely to be critical and would need to stimulate a protective immune response early within the median 9-10 day incubation period.

In rhesus macaques (in whom infection is uniformly fatal with a more rapid onset of disease[6]), a single dose of the vaccine provides complete protection when given as little as 7 days before
challenge[4,16] and prevents infection in 50% when given as PEP 24 hours after infection[17]. Immunity is likely to be largely innate or antibody-dependent as depletion of CD4 or CD8+ cells post-challenge does not abrogate protection[18].

The first use of rVSV-ZEBOV in a human was reported in 2011 following a high-titre needlestick exposure in a laboratory[5]. In this case, a single dose of 5x10⁷ pfu was administered 48 hours after the accident. At least 6 other individuals have now also received the vaccine, given 1-3 days post-exposure, the majority having been exposed in Ebola Treatment Units (ETUs) during the 2014-2016 West Africa outbreak[5,19,20]. All of these individuals were given a higher dose of vaccine and all developed significant side effects although none became infected (Table 2).
In this intervention, the $2 \times 10^7$ pfu dose was selected as a balance between very high levels of reactogenicity found with the $1 \times 10^8$ pfu dose and the lower immune responses found in individuals treated with lower doses in phase I and II studies[10,12,21]. We detected a higher incidence of symptoms in our study compared with these trials[10] but lower than that found in the cases described in Table 2. The high incidence of symptoms may be related to variation in genetic background and high levels of psychological stress.

The risk of infection was likely to have been highest in those who had contact with body fluids from the index case. While blood and CSF tested positive by PCR, infectious virus was only isolated from the CSF where the titre was highest[22] (vomit, urine, saliva and rectal swabs all subsequently tested PCR-negative). In retrospect, the individuals with the highest potential risk of transmission were those exposed to CSF during the lumbar puncture procedure that took place 3 days before vaccination.

The mechanism of protection following vaccination with rVSV-ZEBOV may involve innate, T-cell mediated and/or B-cell mediated responses[15,23,24]. We assessed the immune response by indirect ELISA, neutralisation with live ZEBOV(Mayinga strain), ELISpot and flow cytometry. There are no definite surrogates of immunity but such responses have been associated with protection from infection in macaques and humans. IgM responses peaked at day 14 while IgG seroconversion occurred in 39% at 14 days post-vaccination increasing to 87% by day 28 and 100% of individuals by 3 months. The day 14 anti-GP seroconversion was lower than that found in rhesus macaques[4,25,26] and in human participants in pooled North American phase I studies which showed universal seroconversion by day 14[27]. In the phase II PREVAIL trials, 77-83% of 500 individuals seroconverted within a month of vaccination[8,28]. We found the number of individuals with positive neutralising antibody responses were similar to those with anti-GP responses evaluated by ELISA. 75% of individuals were anti-GP positive at 1 year after vaccination and 73% had
positive neutralisation results. This is in keeping with a long-lasting effect found in other studies[29]. T cell responses directed against GP were also detected as described previously[24].

Future use of rVSV-ZEBOV must be balanced against the risk of side effects. It is a live vaccine and fever in vaccinated individuals has been found to be associated with evidence of replicating rVSV-ZEBOV in blood[30]. The side effect profile of these Scottish vaccine recipients was similar to recipients in Switzerland with a higher prevalence of arthralgia than reported in phase I studies in Germany and Kenya. Arthralgia in Swiss participants lasted a median of 8 days (range 3-167 days; IQR:4-87 days)[12]. As in this study, symptoms were generally short-lived but were longer-lasting in 2 patients. Headache, fatigue, myalgia and arthralgia were associated with the magnitude of T-cell response to pooled GP peptides with higher CD4+ production of IL2 and CD8+ production of IFNγ but not with antibody responses.

There were several limitations to this study. Firstly, we cannot comment on efficacy of the vaccine as this was not a randomised controlled intervention following definitive virus exposure. However, we have demonstrated that Ebola vaccine used as PEP was immunogenic and relatively well-tolerated. Timing of administration is likely to be critical as some individuals did not develop a rapid immune response. While vaccination is a reasonable PEP strategy, other interventions such as the use of antiviral agents or newer vaccines may be warranted.
NOTES

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Conflicts of interest: Dr. Thomson and Dr Davis reported grants from Wellcome and the MRC during the conduct of the study. Dr. Carroll, Dr Hall and Dr Tipton reported a grant from the US Food and Drug Administration during the conduct of the study. FT, BW, CA, RG, SB, SS, TE, EP, AMHR, CS, JM, CJ, IJ, KT, LS, MZ, MK, SB, SF, TS had nothing to disclose.
References


FIGURE LEGENDS

Figure 1: Timeline of exposure period and vaccine delivery – following the recommendation to offer rVSV-ZEBOV vaccine by an expert panel, rapid approvals from the health board, MHRA and local ethics committee were obtained.

Figure 2: Selection of individuals for vaccination and follow-up study 65 contacts of the index patients were assessed by a team of healthcare specialists, 45 of whom were asked to attend an outpatient follow-up clinic based on exposure risk. Of these, 26 received the rVSV-ZEBOV vaccine.

Figure 3: Adaptive immune responses over time in vaccinated individuals Antibody responses measure by indirect ELISA, IgM, neutralisation and IFNγ ELISpot are plotted over time. Anti-GP seroconversion rates are shown with a cut-off of 0.03 IU/ml (3 x standard deviation of negative control). For antibody assays, negative control levels from unvaccinated individuals are plotted with a positive quality control (QC; dotted bars). Bars show the geometric mean with 95% CI. Numbers below the bars show the percentage of seroconverted people. Each dot is the average from two separate assays. For ELISpot, negative control represents unstimulated cells from vaccinated patients. P values < 0.05 (Mann Whitney U test) are highlighted.

3a. Total anti-GP responses over time measured by indirect ELISA
3b. Anti-GP IgM responses by ELISA over time
3c. Neutralisation responses over time
3d. T cell responses by IFNγ ELISpot to EBOV GP peptides over time

Figure 4: Side effects related to T cell response CD4+ and CD8+ IFNγ and CD4+ IL2 responses in individuals with arthralgia, headache, fatigue and headache are shown. P values < 0.05 (Mann Whitney U test) are highlighted.

4a. Arthralgia
4b. Myalgia
4c. Fatigue
4d. Headache
Table 1: Side effects associated with rVSV-ZEBOV vaccination

1a. Side effects specified in follow-up questionnaire

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Percentage (number)</th>
<th>Duration (IQR, days)</th>
<th>Severity (1-5) (IQR, days)</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>81% (21/26)</td>
<td>2 (1-5)</td>
<td>1 (1-2.5)</td>
<td></td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>69% (18/26)</td>
<td>2 (1-4)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>69% (18/26)</td>
<td>2.5 (1-4.5)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>69% (18/26)</td>
<td>2 (1-4)</td>
<td>1 (1-2)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>54% (14/26)</td>
<td>2.5 (1-17.75)</td>
<td>2 (1-2.75)</td>
<td>Two patients with long-lasting symptoms</td>
</tr>
<tr>
<td>Fever (≥37.5)</td>
<td>50% (13/26)</td>
<td>-</td>
<td>-</td>
<td>All tested negative for EBOV</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15% (4/26)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>8% (2/26)</td>
<td>18.5 (1-36)</td>
<td>2.5 (1-4)</td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>0% (0/26)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td></td>
</tr>
</tbody>
</table>

1b. Side effects volunteered during follow-up

<table>
<thead>
<tr>
<th>Other reported side effects</th>
<th>% (number)</th>
<th>Related to vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic shingles</td>
<td>3% (1/26)</td>
<td>Possible</td>
</tr>
<tr>
<td>Fractured neck of femur</td>
<td>3% (1/26)</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6% (2/26)</td>
<td>Likely</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3% (1/26)</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>3% (1/26)</td>
<td>Related (evaluated by ultrasound and too small for aspiration)</td>
</tr>
</tbody>
</table>
Table 2: Case reports/series of individuals treated with rVSV-ZEBOV vaccine

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exposure type</th>
<th>Setting</th>
<th>Timing of vaccination</th>
<th>Dose of vaccine</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunther et al 2011(^a)</td>
<td>High risk needlestick injury</td>
<td>Laboratory (BSL4)</td>
<td>48 hours</td>
<td>$5 \times 10^7$ pfu</td>
<td>Uninfected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Wong et al 2016(^a)</td>
<td>High risk injury with glass</td>
<td>Clinical (ETU)</td>
<td>3 days</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Wong et al 2016(^a)</td>
<td>Low risk needlestick injury</td>
<td>Clinical (ETU)</td>
<td>24 hours</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
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<td>Wong et al 2016(^a)</td>
<td>High risk injury with glass</td>
<td>Clinical (ETU)</td>
<td>27 hours</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
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<td>Symptomatic</td>
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<tr>
<td>Wong et al 2016; Lai et al 2015(^a,21)</td>
<td>High risk needlestick injury</td>
<td>Clinical (ETU)</td>
<td>43 hours</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
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<tr>
<td>Wong et al 2016(^a)</td>
<td>High risk needlestick injury</td>
<td>Clinical (ETU)</td>
<td>3 days</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
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<tr>
<td>Cnops et al 2015(^a)</td>
<td>High risk needlestick injury</td>
<td>Clinical (ETU)</td>
<td>2 days</td>
<td>$1 \times 10^8$ pfu</td>
<td>Uninfected</td>
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<td></td>
<td>Symptomatic</td>
</tr>
</tbody>
</table>

\(^a\)Same individual reported in two separate publications
Figure 1 v6

October 5th 6th 7th 8th 9th 10th 11th 12th

Symptoms

Hospitalisation

Vaccination

- Lumbar puncture: CSF EBOV positive
- Blood EBOV positive
- WHO agree to provide vaccine
- Outpatient clinic opened
- Submission to WoSREC for follow-up study
- Vaccine received from Geneva
- MHRA vaccine import license
- CCSC health board approved for use of unlicensed medicine
Figure 3a-d