

Sudan virus disease outbreak in Uganda: urgent research gaps

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ABSTRACT

The Sudan ebolavirus (SUDV) outbreak highlights our ongoing vulnerability to re-emerging high-consequence infectious diseases. Although the Minister of health in Uganda has initiated public health measures in collaboration with neighbouring countries and with support of the WHO, cases have continued to spread to several regions including the capital. The ongoing transmission, uncertain case numbers and no licensed vaccine or therapeutics available are a cause for concern. We searched four databases for SUDV research using the search terms “SUDV”, “Sudan Virus” and “Ebola Sudan”. Our analysis identified only 20 SUDV research studies. Most were implemented in the USA and only one in Uganda. Nine studies were on therapeutics, eight on vaccines, one on diagnostics, one in one health and one in social science. Our data highlight a lack of SUDV research and an urgent need for investment to identify an effective vaccine, and optimal supportive care and therapeutic strategies for all at risk groups as a key research priority. Research investments should be prioritised into vaccines and treatment strategies that will be accessible to high-risk populations in affected regions during the outbreak, to protect populations, improve individual outcomes and facilitate outbreak control.

BACKGROUND

On 20 September 2022, Uganda declared the first confirmed case of Sudan virus disease (SVD) in the current outbreak.^{1 2} By 12 October, there were 54 confirmed cases³ with 19 deaths, 4 of which were in health-care workers.^{4 5} Ebola is a severe disease, with high mortality risk, first identified in 1976 when two simultaneous outbreaks occurred in South Sudan and the Democratic Republic of Congo (DRC).⁶ Ebolaviruses belong to the viral family Filoviridae.^{1 7 8} There are six known ebolaviruses, four of which can cause human disease (Bundibugyo, Sudan, Tai Forest and Zaire viruses).^{7 8} Ebola outbreaks have most commonly been caused by the Zaire ebolavirus and Sudan ebolavirus (SUDV).^{9 10} Since May 2019, Ebola caused by the SUDV is known as SVD.^{1 2} Sudan and Uganda have predominantly been affected

SUMMARY BOX

- ⇒ Uganda is facing an Ebola outbreak caused by the Sudan ebolavirus (SUDV) in a health system currently responding to multiple emergencies.
- ⇒ The Sudan virus disease (SVD) mortality rate in previous outbreaks ranged from 41% to 100%.
- ⇒ Uganda has faced multiple Ebola outbreaks in the past, but a lack of vaccines and therapeutics against SVD plus cases in several regions, including the capital, is a cause for concern.
- ⇒ We provide an overview of up-to-date information on the SVD outbreak in Uganda and present the results from a rapid review of existing research on SVD and detail the existing vaccine candidates that have reached the point of human trials and ongoing research studies to inform research gaps.
- ⇒ Our data highlight a need for urgent investments into research on SUDV to identify effective vaccine and optimal treatment strategies and community engagement to support trial implementation.
- ⇒ The data also emphasise our vulnerability to infectious disease outbreaks and the need to strengthen our health systems and research response capacity and capability globally to manage concurrent emergencies, with a focus on resource-deprived settings.

by SUDV outbreaks.¹⁰ Uganda has had six previous ebolavirus disease outbreaks, four of which were SUDV outbreaks in 2000 and 2011 and two in 2012.^{1 9 10} The most severe of those was the 2000 outbreak with 425 recorded cases and 224 deaths.^{9 10} The aims of this article are to provide an overview of the SVD outbreak and response in Uganda and to present findings from our rapid analysis of existing research to identify research gaps to inform research response prioritisation.

EVOLUTION OF THE SUDV OUTBREAK IN UGANDA

Uganda declared an outbreak of SVD on 20 September 2022 with its first confirmed case in a 24-year-old man in the Mubende district.^{1 2 11} The case presented to two health-care facilities between 11 and 15 September before being referred to the referral regional hospital where he was diagnosed with SUDV



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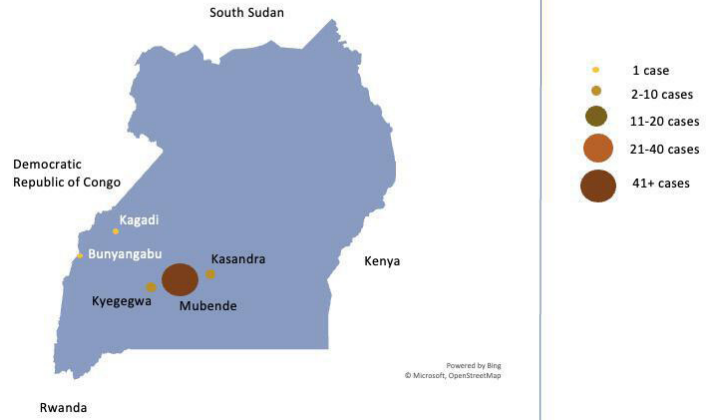


Figure 1 Geographical transmission of SVD cases in Uganda (25 September–2 October 2022). The map shows the total number of confirmed and probable cases of SVD reported from Uganda by district. Data source: WHO Regional Office for Africa Weekly Bulletin on Outbreaks and Other Emergencies,^{2 12} created in Microsoft Excel. SVD, Sudan virus disease.

on 19 September.^{1 2} It is estimated that SUDV has been circulating in the Mubende district for 3 weeks prior to this first case being detected, with reports of unexplained community deaths during the first 2 weeks of September and traditional burials for those who died.^{1 2}

By 25 September, 36 cases were reported (18 confirmed and 18 probable) from three districts with 35 of these admitted to the hospital.² The median age of these cases were 26 years old (range 1–63 years old). By 2 October, the case reports had increased to 43 confirmed cases from five districts (figure 1).¹² The Mubende district remains the most heavily affected with 36 confirmed cases.¹² By 10 October, the Uganda Ministry of Health reported 48 confirmed cases and a death from SUDV in its capital, Kampala, by an individual who did not isolate after a relative died in an affected district, but instead visited a traditional healer.^{4 13 14} By 12 October, there were 54 confirmed cases and 19 deaths reported.³ The rise and geographical spread of the cases are a cause of concern.⁹

This outbreak initially predominantly affected gold miners, who are a highly mobile population, which may increase the risk of spread to other districts and bordering countries.² One of the affected districts (Bunyangabu) borders the DRC.^{12 15} The transmission into several districts highlights a need to strengthen preparedness and readiness activities across the country and in collaboration with neighbouring countries.¹²

TRANSMISSION, CLINICAL PRESENTATION AND CASE FATALITY

Ebolaviruses are primarily transmitted to humans through close contact with blood, secretions, organs or other bodily fluids of infected humans or animals and contaminated surfaces and materials.¹⁶ The incubation period ranges from 2 days to 21 days.¹⁶ An increase in population size, the rise of urbanisation and the interconnectedness of travel can expand the spread of filovirus disease beyond endemic regions.¹⁷

The symptoms of Sudan and Zaire ebolavirus are similar.¹ Patients generally present with fever, fatigue, muscle pain, headache and sore throat, followed by vomiting, diarrhoea, rash, and/or symptoms of impaired kidney and liver function.^{16 18} More severe illness can include internal and external bleeding, multiorgan failure, encephalopathy, respiratory distress, shock and spontaneous abortion in pregnant women.¹⁶ Diagnosing SVD can be challenging as the initial symptoms resemble other common infectious diseases including malaria.⁶ Diagnosis can be made using reverse transcriptase–PCR.^{1 6 19} More novel laboratory tests also exist, such as OraQuick Ebola rapid antigen test approved by the US Food and Drug Administration.¹⁹ This test detects antigens from viruses in the *Ebolavirus* genus but cannot differentiate between viruses¹⁹ and is deemed not sensitive enough to detect SUDV.²⁰

The average Ebola case fatality rate is estimated around 50% with rates varying from 25% to 90% in past outbreaks.⁶ The case fatality for SVD ranged from 41% to 100% in past outbreaks.¹ Early data from the ongoing outbreak of SVD in Uganda showed a case fatality rate of 46% based on 63 confirmed and probable cases, with 29 deaths and 4 recoveries at the time of the estimation.¹² Healthcare workers are at high risk of exposure; by 5 October, there were four reported healthcare worker deaths from SUDV in Uganda.⁵

Currently, there are no licensed vaccines or therapeutics for SUDV.¹ There are monoclonal antibodies (mAB114 and REGN-EB3, also known as Ansuvimab or Ebanga and Inmazeb, respectively) licensed for treatment of Ebola caused by the Zaire ebolavirus but not for SUDV.²¹ Merck’s (MSD) rVSV-ZEBOV (ERVEBO) vaccine is ready to be deployed for outbreaks of Zaire ebolavirus; however, Zaire ebolavirus is genetically distinct from Sudan virus, and available evidence suggests that it will not provide cross protection against SUDV.^{1 11 18} The

Johnson & Johnson's Zabdeno/Mvabea vaccine is a two-dose vaccine, with the first dose priming and the second dose boosting the immune response against the Zaire ebolavirus.¹⁸ Additional antigens, including Sudan virus, are present in the second dose and may provide protection based on available evidence from a non-human primate model; however, it has not been tested against SUDV in humans, and due to the second dose being administered after 56 days, it is less ideal for outbreak response.^{1 18}

With a lack of vaccines and therapeutics, access to optimal supportive care guided by physiological monitoring and treatment of secondary complications are key for improving survival rates.¹ The prolonged Ebola outbreak caused by Zaire ebolavirus from 2013 to 2016 in West Africa allowed for the evaluation of supportive care.²² This included evaluating care such as volume resuscitation, symptom control, monitoring of glucose, electrolyte levels and organ dysfunction, and treatment of coinfections.²² This data informed the WHO 2019 guideline on optimised supportive care for Ebola.²² In August 2022, the WHO released a linked guideline specifically focused on therapeutic treatment recommendations for the Zaire ebolavirus.²³ It is not yet known if these treatments are effective against SUDV.

SUDV RESEARCH

Limited research on SUDV exists partly because outbreaks have been sporadic.⁹ The GloPID-R research and policy team conducted a rapid search of the World RePORT, European Union Clinical Trials Registry, Pan African Clinical Trial Registry (PACTR) and WHO International Clinical Trials Registry Platform databases using search terms "SUDV", "Sudan virus" and "Ebola Sudan".²⁴⁻²⁶ No time restrictions were applied to the search to rapidly identify any existing research related to SUDV. Our searches identified 20 studies as of 15 November 2022; 9 were focused on therapeutics, 8 on vaccines, 1 on social sciences, 1 on diagnostics and 1 on one's health. There

were no trials registered in PACTR as of 20 October 2022 (online supplemental appendix 1).

Of the nine studies that related to therapeutics, eight were focused on monoclonal antibodies and one at ebolavirus cell entry inhibitors. Only two studies focused on therapeutic development specific to SUDV; the remaining seven aimed to develop therapeutics that covered a broad spectrum of ebolaviruses. Eight studies were based in the USA; the other was a collaborative study with seven countries involved, including Uganda.

Of the eight studies that related to vaccines, two had conducted human studies. One of these, led by the University of Oxford, was a phase I and Ib study which began enrolment of participants in the UK in November 2021 and Tanzania in March 2022. It aimed to determine the safety and immunogenicity of the bivalent CHAdOx1 vectored vaccine. The other was a completed phase I clinical trial evaluating the safety, tolerability and immunogenicity of two doses of an Ebola Sudan chimpanzee adenovirus vector vaccine led by the Sabin Vaccine Institute. The remaining six studies identified were all focused on supporting the development of broad-spectrum vaccines. Four of these studies were based in the USA; one was a collaboration between Canada and the USA; and one was a collaboration between the UK and the USA (online supplemental appendix 1).

The WHO R&D blueprint team have been tracking progress of SUDV vaccine research. So far, they have registered 24 SUDV vaccine candidates (as of 28 September 2022).²⁷ These are indicated at different stages of development (clinical (n=1), phase I (n=2) and preclinical (n=21)).²⁷ Four vaccine candidates have progressed to the point where human trials have begun or can begin soon, including the two described earlier (table 1).²⁸⁻⁴⁰ The WHO has stated that three of these (cAd3, cAdOX1 and rVSV SUDV GP) are under consideration for clinical trials in Uganda.³⁷ The cAd3 vaccine is a single-dose vaccine developed partly by the US National Institute of Allergy and Infectious Diseases and now licensed to the

Table 1 SUDV vaccine candidates that have or are rapidly progressing to human trials as of 15 November 2022

| Vaccine name | Studies conducted | Lead institution |
|----------------------------------|--|---------------------------------|
| cAd3-EBO S (VRC-EBOADC086-00-VP) | Phase I clinical trials in Uganda and USA, completed Planning phase II trial | Sabin Vaccine Institute (NIAID) |
| ChAdOx1 biEBOV | Phase I clinical trials in the UK and Tanzania (currently recruiting) | University of Oxford |
| rVSV SUDV GP | Preclinical phase, rapidly preparing for phase I trial and efficacy studies | MSD |
| Ad26.ZEBOV, MVA-BN-Filo | Phase III clinical trial in Sierra Leone, completed Vaccine approved by the European Medicines Agency (EMA) | Johnson & Johnson |

*The Johnson & Johnson vaccine is a two-dose regimen with the second dose providing protection against SUDV. The second dose is administered after 56 days of the first dose.¹

EMA, European Medicines Agency; MSD, Merck; NIAID, National Institute of Allergy and Infectious Diseases; SUDV, Sudan ebolavirus.

Sabin Vaccine Institute.^{9 27-29 32 33} It has shown protection against SUDV in non-human primates.^{9 29} One hundred doses of this vaccine are being shipped to Uganda with advice to prioritise vaccination for healthcare workers.^{9 33} The cADOX1 vaccine is another single-dose vaccine developed by the Jenner Institute at the University of Oxford.³² The rVSV SUDV GP vaccine developed by MSD is a single-dose vaccine specific to SUDV, using a replication-competent, live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine construct similar to that used for ERVEBO (Ebola Zaire Vaccine, Live). The rVSV SUDV vaccine has shown efficacy in non-human primates.^{38 39 41} MSD aims to deliver 50 000 doses to Uganda by the end of 2022 via the International AIDS Vaccine Initiative, a non-profit scientific research organisation, for phase I and efficacy studies.^{38 39}

These data highlight an urgent need for research investments into trials to identify vaccines and therapeutics for SVD, as well as optimal supportive care strategies. It also highlights the need for broader research studies relating to the wider understanding of SVD, including epidemiology and social science aspects. Access to

effective vaccines, together with stringent public health and hospital infection control methods, is key for outbreak control, including therapeutics and supportive care for improving survival rates.

National public health response

Multiple task forces including the Uganda MOH and WHO have been holding regular meetings since the 2022 SUDV outbreak was declared and have visited the affected districts to evaluate and orientate response activities.¹² Epidemiological investigations in the affected districts identified 884 contacts with 60% of these followed up as of 2 October.¹² Mobile laboratory clinics set up at Mubende Regional Referral Hospital are processing samples.^{9 12} Uganda are training staff in SUDV reporting, contact tracing and infection, prevention, control procedures and safe burials, and have initiated community awareness campaigns via media (figure 2).¹²

WHO risk assessment

The WHO has assessed the public health risk of SUDV in Uganda as very high at the national level, high at

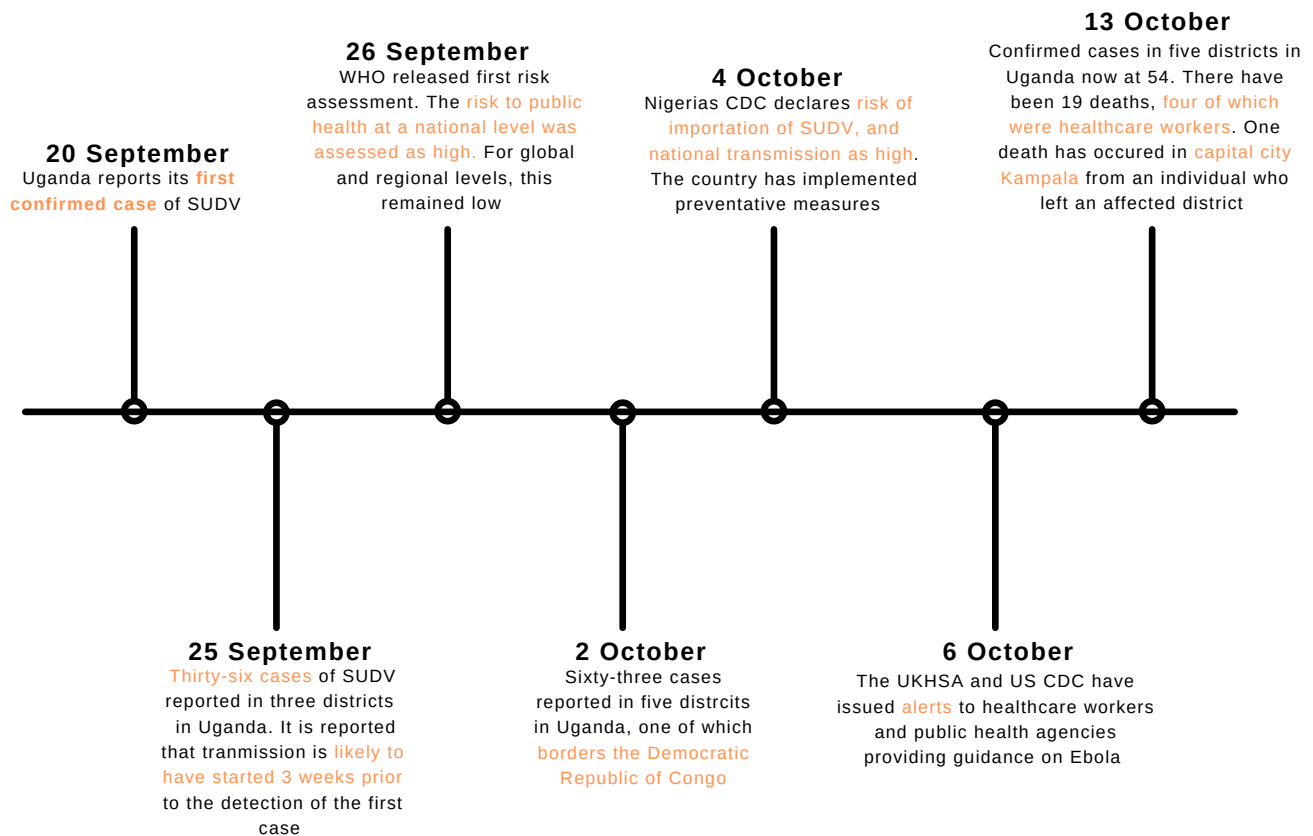


Figure 2 An overview of the early public health response. CDC, Centers for Disease Control and Prevention; SUDV, Sudan ebolavirus; UKHSA, UK Health Security Agency.

the regional level and low at the global level as of 10 November 2022.⁴² This is based on the following⁴²:

- ▶ Lack of an authorised vaccine for SUDV.
- ▶ SUDV has affected a highly mobile population group, and cases have spread to multiple districts with high populations.
- ▶ Health clinics where patients presented had limited infection prevention and control measures.
- ▶ The possibility for missed contact cases.
- ▶ Community engagement in affected districts reported as challenging.
- ▶ Uganda has local capacity and resources for an effective response to SUDV; however, the country is dealing with multiple emergencies, including COVID-19, anthrax, yellow fever, food insecurity and flooding. If cases continue to rise and spread to other districts, the system could be overwhelmed.

Regional and international alerts

No cases have been identified in other countries to date. However, internationally, some countries have issued advice to public health providers and healthcare workers to be alert to risk of travel imported cases, with guidance on identification and diagnostics, and advising on travel history in patients presenting with Ebola/SUDV symptoms.^{43 44} Based on the international risk assessment, the risk to other countries is low, and there are currently no recommendations on travel restrictions by WHO. Many countries have initiated travel-related guidance. The USA has implemented screening of passengers arriving from Uganda.

The Nigeria Centre for Disease Control (NCDC) declared a high risk of importation of SUDV and impact on national health on 4 October.⁴⁵ The high risk of importation assessment was based on high travel volume between Nigeria and Uganda, and the risk of onward transmission nationally due to upcoming large gatherings and religious festivals.⁴⁵ The NCDC has put preventative measures in place, including development of an incident action plan, risk communication and engagement, trained rapid response teams put on standby and follow-up of passengers from Uganda up to 21 days after their arrival in Nigeria.⁴⁵ The NCDC has advised avoiding non-essential travel to Uganda.⁴⁶

The government of Uganda, the Africa Centres for Disease Control and Prevention and WHO hosted a high-level emergency meeting on cross-border collaboration for preparedness and response to Ebola disease outbreaks in Kampala on 12 October.³ Ministers of Health and government representatives from nine African countries agreed on joint measures to stop the potential spread of the ongoing outbreak in Uganda and beyond its borders.³ These include disease surveillance, contact tracing and monitoring, prompt alert notification, information sharing, joint trainings of emergency responders and simulation exercises to enhance preparedness and response.³

CONCLUSION

The re-emergence of SUDV in Uganda with rapid transmission into multiple districts with high mortality rate re-emphasises our global vulnerability to re-emerging infections and reinforces the need for investments to strengthen our preparedness to combat high-consequence infectious diseases. Without effective treatments, supportive care guided by evidence and physiological monitoring is key for improving survival rates.

The regional response to SUDV has been swift in implementation of public health control; however, despite previous outbreaks, our data highlight a lack of prior and active SUDV research, and a need for urgent investments to identify effective vaccines and therapeutics to improve outcomes. There are certain research activities which can only be undertaken while a virus is circulating in the human population, such as therapeutic and vaccine trials, evaluation of public health measures and community perceptions, and understanding transmission dynamics and epidemiology. Optimising surveillance and evaluation of point of care diagnostics and research across these areas now need to be rapidly activated.^{47 48}

Our data highlight our global vulnerability to re-emerging infectious disease outbreaks and the need to improve our preparedness for high-consequence infectious diseases through investments into global research capacity, medical countermeasure platforms and strategic clinical research networks with capacity to respond at the outset of outbreaks, with a focus on deprived resource settings, to protect populations, health systems and improve epidemic outcomes.

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Contributors AN, LS and SK conceptualised the review. SK, LS and DN conducted a rapid review of research related to Sudan virus disease. SK led on writing the initial manuscript with input from LS, KT, DN and AN. All authors revised the manuscript and gave their approval for it to be published. LS and AN are joint senior authors.

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Appendix 1: SUDV research studies registered as of 15 November 2022

| Project title | Start date | End date | Funder | Director | Country | Research theme |
|--|------------|-----------|----------------|--|---|-----------------|
| World RePORT database | | | | | | |
| Thermostabilized Subunit Glycoprotein Vaccine Platform: Immune Characterization of an Emulsified | Dec. 2020 | Nov. 2022 | NIH | Donini, O | USA | Vaccines |
| A "Trojan Horse" bispecific antibody strategy for broad filovirus therapeutics | Jul. 2017 | Jun. 2022 | NIH | Chandran, K | USA | Therapeutics |
| Rationally Designed Pan-Ebolavirus Vaccine | Jun. 2017 | May 2022 | NIH | Qiu, X; Aman, MJ | Canada; USA | Vaccines |
| Preclinical Development of a Thermostable Trivalent Filovirus Vaccine | Jun. 2017 | May 2022 | NIH | Lehrer, AT; Bedwell G | USA; UK | Vaccines |
| Evolution of anti-filovirus B cell responses and mechanisms of protection | Apr. 2017 | Mar. 2022 | NIH | Aman, MJ | USA | Vaccines |
| Engineered, multispecific antibodies as broad anti-filovirus therapeutics | Jan. 2017 | May 2021 | NIH | Lai, J | USA | Therapeutics |
| Remodeled glycoprotein for broad protection against ebolaviruses | Jan 2018 | Dec. 2020 | NIH | Aman, MJ | USA | Vaccines |
| Broadly Protective Bispecific Antibodies for Treatment of Ebola Virus Disease | May 2016 | Jun. 2020 | NIH | Aman, MJ | USA | Therapeutics |
| Consortium for Immunotherapeutics Against Viral Hemorrhagic Fevers | Mar. 2014 | Feb. 2019 | NIH | Nykiforuk, K; Lobel, B; Lutwama; Khan; Saphire; Happi | Canada, Israel, Argentina, Uganda, Sierra Leone, USA, Nigeria | Therapeutics |
| Development of CM-SV1, a monoclonal antibody treatment for Sudan Virus | Feb. 2018 | Jan. 2020 | NIH | Guyre, P | USA | Therapeutics |
| Transcriptomics of immunity and disease in African Fruit Bats- important zoonotic reservoirs | Jan. 2017 | Dec. 2019 | NIH | Reeder, DA; Geoffrey, A | USA; Uganda | One Health |
| SSHAP response to Ebola outbreak in DRC and neighbouring countries | Nov. 2018 | Nov. 2019 | Wellcome Trust | Bedford, J | UK | Social Sciences |
| Optimization of Ebola Virus Entry Inhibitors | Jan. 2018 | Oct. 2019 | NIH | Mccormack, KJ | USA | Therapeutics |
| Mammalian and Plant-derived Antibody-based Therapies against Sudan Ebolavirus | Jan. 2014 | May 2019 | NIH | Dye, JM | USA | Therapeutics |
| Preclinical characterization of a multivalent killed Filovirus/Rabies vaccine | Jan. 2013 | Jan. 2019 | NIH | Neubert, A; Schnell, MJ | USA; Germany | Vaccines |
| Structure-guided redesign of monoclonal antibodies targeting conserved filovirus epitopes | Jan. 2016 | Jun. 2017 | NIH | Aman, MJ | USA | Therapeutics |

| | | | | | | |
|--|--------------------------------------|------------|--------------------------------------|------------|----------------------------|--------------|
| Recombinant antigen diagnostics for filoviruses | Jan. 2010 | May 2017 | NIH | Boisen, LM | USA | Diagnostics |
| Direct sequencing of serum antibodies after infection | Feb. 2017 | Oct. 2018 | NIH | Guthals, A | USA | Therapeutics |
| WHO ICTRP database & EU clinical trial register | | | | | | |
| A Phase I & Ib Study to Determine the Safety and Immunogenicity of a Bivalent ChAdOx1 Vectored Vaccine Against Zaire and Sudan Ebola Virus Species in UK & Tanzanian Healthy Adult Volunteers <i>*Note: This was registered as two separate studies on WHO ICTRP database (Phase I in UK and Phase Ib in Tanzania). Here we have combined them.</i> | Nov. 2021 (UK); Mar. 2022 (Tanzania) | Recruiting | University of Oxford (UKRI) | Olotu, A | UK; Tanzania | Vaccines |
| A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3- EBO S), in Healthy Adults | Jul. 2019 | Completed | NIAID, Sabin Vaccine Institute (NIH) | Unknown | Uganda | Vaccines |
| A Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of the V920 (rVSV?G-ZEBOV-GP) Ebola Virus Vaccine Candidate in HIV-Infected Adults and Adolescents | Aug. 2017 | Unknown | Dalhousie University (Unknown) | Tremly, C | Canada + two African sites | Vaccines |
| Pan African Clinical Trial Registry | | | | | | |
| No trials registered | | | | | | |