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Evaluation of the UK Vaccine Network Project 1.0 (NIHR207661)

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Disclaimer

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1 Rationale for case study selection

The study team set out to develop case studies to illustrate outcomes and impacts of the UKVN 1.0. The overarching rationale for case study selection was based on ensuring a balanced view of projects covering the diverse portfolio of investments. The selection criteria were based on:(1) funding size, delivery partner and research competitions; (2) type(s) of organisations involved; (3) type(s) of outcomes and impact as set out in the ToC; (4) Coverage of evaluation questions; (5) Availability of evidence and access to key informants; and (6) type(s) pathogens involved.

A long list of case studies was developed by the study team and iterated with DHSC. This iteration allowed for an assessment of case study strengths and feasibility, in particular relation to criteria (5): availability of evidence and access to key informants. The final list of case studies is shown in Table 1 below.

Table 1 Final list of case studies

Delivery Partner	Case study title
BBSRC	One Health and accelerating Vaccines for Ebola and Lassa (OVEL)
	Bunyavirus Immunity Consortium
EPSRC	FVMR Hub: Successful vaccine platform transfer sparks wider collaboration with Vietnam
	Scaling Innovation: Advancing affordable glycoconjugate vaccine production through Vax-Hub
NIHR (CCF)	Electronic Data Capture to support rapid epidemiological research and response during epidemics
	Anthropological exploration of facilitators and barriers to vaccine deployment and administration during diseases outbreaks
	Vaccine Efficacy Evaluation for Priority Emerging Diseases
NIHR (NESTCC)	Advanced development of a safe and effective Rift Valley fever vaccine for livestock
	Phase I studies of a novel chimpanzee adenovirus MERS
	Phase I studies of a novel chimpanzee adenovirus Rift Valley fever vaccine
Innovate UK	Supporting vaccine R&D through serological standards and animal models
	Assessment of persistence of immunity in multiple viral-vector Ebola vaccines, and response to a booster dose of Ad26.ZEBOV
	Development of a new vaccine against Plague

	A phase I study of recombinant poxvirus Zika vaccines
	Vaccine against mosquito-borne diseases
	Rapid, accessible, globally distributed RNA vaccine manufacture on demand
	Development of an economically viable CCHF virus vaccine
	Novel multivalent vaccines against haemorrhagic fevers

NIHR CCF refers to 'Central Commissioning Facility' and NIHR NETSCC refers to 'Evaluation, Trials and Studies Coordinating Centre'.

The final list consists of 18 case studies that vary in depth, focus area and project stage. Case studies from projects funded via BBSRC, EPSRC and NIHR (CCF) showcase activities related to One Health approaches for vaccine development, vaccine manufacturing and epidemiology for vaccinology. Case studies from projects funded via NIHR (NETSCC) and Innovate UK cover various stages of vaccine research and development, ranging from early-stage discovery to pre-clinical and clinical phases. Collectively, these case studies provide evidence of outcomes and impact across multiple elements of the UKVN's Theory of Change.

2 Case studies

2.1 One Health and accelerating Vaccines for Ebola and Lassa (OVEL)

Summary

Lassa fever and Ebola virus disease are haemorrhagic fevers caused by rapidly mutating RNA viruses. Developing vaccines that remain effective over time is challenging, as new variants emerge in animal reservoirs and when they infect humans. The £1.5 m UKVN/BBSRC-funded "One Health and accelerating Vaccines for Ebola and Lassa (OVEL) project (2018-2023), led by Prof Jonathan Heeney, University of Cambridge, set out to address the issue of strain diversity, viral mutation and the potential for virus reactivation in individuals after recovery from infection, crucial information to underpin development of broadly protective vaccines.

Sampling of rodents showed that LASV prevalence and the range of carrier species both expand during human outbreaks, pointing to shifts in rodent populations as drivers of spill-over to humans. The findings highlighted the value of ongoing animal monitoring to predict and control LASV outbreaks. In parallel, OVEL's immunological studies showed that Lassa fever survivors produce virus-neutralising antibodies that recognise genetically diverse LASV strains - pointing to the possibility of a broadly protective 'universal' vaccine. To support project OVEL, the team developed Sentinel, a survey app for gathering data from Lassa fever survivors and their contacts. This later evolved into a predictive platform for disease outbreaks, using machine learning and climate, human, and animal case data.

Based on the OVEL datasets, as well as data collected on the Ebola Sudan and Marburg viruses, the team then used a computational tool to select conserved viral segments and inserted these into the viral Modified Vaccinia Ankara (MVA) vector. The resulting trivalent vaccine candidate, HFVac3, was fully protective in animal challenge studies. To further develop HFVac3, the university spun out a company, DIOSynVax.

The next phase is to advance HFVac3 development into Phase I clinical trials. The company has secured UKVN2.0 funding to develop the vaccine's GMP manufacturing processes. In addition, the team plans to apply for further funding to conduct clinical trials and to optimise the vaccine platform for broader use against other high-priority pathogens.

The project also helped strengthen Nigeria's epidemic preparedness by training local laboratories in advanced immunology and engaging communities on rodent control and stigma, thereby expanding in-country capacity for vaccine research and outbreak response. The team is now preparing for clinical testing in LMICs and, via a partnership with the African subsidiary of a CDMO, is building local GMP manufacturing capacity to contribute to the goal of producing vaccines "in Africa, for Africa."

Haemorrhagic fevers caused by RNA viruses with high mutation rates

A disproportionately large share of emerging or re-emerging diseases are caused by RNA viruses[1]. These viruses are particularly challenging to combat because of their high mutation rates, which lead to high genetic variability as they replicate and evolve within animal reservoir populations (species that naturally carry the virus without developing the disease).

Both Lassa Fever and Ebola Virus Disease (EVD) are caused by RNA viruses. Rodents are the main reservoir for the Lassa Virus (LASV)[2] while bats are thought to be the natural hosts of the

[1] Heeney JL. Zoonotic viral diseases and the frontier of early diagnosis, control and prevention. J Intern Med. 2006;260(5):399-408. doi:10.1111/j.1365-2796.2006.01711.x

[2] World Health Organization. Lassa fever key facts. Published December 5, 2024. Accessed May 9, 2025. Available here.

Ebola virus.[3] Occasionally, these viruses can cross over from animals to humans – a process known as spill-over – and cause serious outbreaks. EVD and Lassa fever are both primarily found in West Africa. The 2014–2016 Ebola outbreak in West Africa resulted in over 28,000 cases and 11,000 deaths (WHO, 2016).[4] The estimated number of LASV infections in this region varies, with a recent estimate of up to 2 million infections and 5,000-10,000 deaths annually.[5]

Developing vaccines that remain effective over time is challenging, as new variants emerge in animal reservoirs and when they infect humans. Moreover, vaccine candidates currently under development are based on virus strains from human outbreaks in the 1960s and 70s, which may not reflect the full genetic diversity of variants circulating in animal reservoirs. In case new variants spill over into human populations, these vaccines may only provide low level of protection.

Project "One Health and accelerating Vaccines for Ebola and Lassa" (OVEL)

Researchers from the University of Cambridge launched the "One Health and accelerating Vaccines for Ebola and Lassa (OVEL)" project to address the issue of strain diversity, viral mutation and the potential for virus reactivation in individuals after recovery from infection. It was funded through a £1.5m award from the BBSRC's One Health Competition between 2018 and 2023.[6] The project was led by Professor Jonathan Heeney at the University of Cambridge, in collaboration with investigators from the University of Oxford, the London School of Hygiene & Tropical Medicine (LSHTM), and Redeemer's University in Nigeria.

OVEL aimed to collect and analyse Ebola viruses and LASVs directly from animal reservoirs and create a sequence database to understand their genetic diversity. The research team then planned to combine the viral sequences with antibody data from survivors and use a computational tool to identify viral proteins that a) trigger an immune response and b) remain stable despite viruses mutating. Based on this data, the tool would design vaccines that not only block initial infection by a broad range of viral strains, but also elicit strong, durable immune responses capable of clearing hidden viral reservoirs in survivors, thus preventing post-infection re-emergence and transmission.

The computational tool – the EVAC (Emerging Viral Vaccine Antigen Construct) platform – had previously been developed at the University of Cambridge under the leadership of Professor Heeney, supported by a UKVN / Innovate UK SBRI grant.[7] The research was expected to provide insights and learning beyond vaccines against Ebola virus and LASV, informing approaches to vaccine design more broadly.

Surveillance and immune profiling to inform outbreak response and vaccine design

The OVEL project advanced our understanding of immunity to and transmission of Ebola and Lassa viruses, informing vaccine development.

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[3] World Health Organization. Ebola disease key facts. Published December 5, 2024. Accessed May 9, 2025. Available here.

[4] World Health Organization. Ebola outbreak 2014–2016 – West Africa. Updated 2020. Accessed April 28, 2025. Available here.

[5] Olayinka AT et al. (2022) Analysis of sociodemographic and clinical factors associated with Lassa fever disease and mortality in Nigeria. PLoS Glob Public Health 2:e0000191. doi:10.1371/journal.pgph.0000191

[6] Gateway to Research. One Health and Accelerating Vaccines for Ebola and Lassa (OVEL) Project. Biotechnology and Biological Sciences Research Council (BBSRC). Published 2018. Accessed April 28, 2025. Available here.

[7] Heeney JL. Emerging Viral Vaccine Antigen Insert Consortium (EVAC) Project. Innovate UK, SBRI, £498,379, Aug 2016-Oct 2017. Accessed April 28, 2025. Available here.

A key discovery was that both, Lassa fever survivors and individuals exposed to the virus but asymptomatic, exhibited similar T-cell and antibody responses; however, only the survivors had developed detectable virus-neutralising antibodies, which are thought to be crucial for long-term protection against LASV.[8,9] These antibodies were able to recognise and respond to genetically diverse LASV strains, indicating the possibility of developing a broadly protective 'universal' vaccine. The team also identified specific regions of the LASV glycoprotein and nucleoprotein that activated broad T-cell immune responses. In particular, strong T-cell responses to the virus's nucleoprotein were associated with protection from severe illness. These regions provide key targets for vaccine development.

Both T-cell and antibody responses in Lassa fever survivors persisted for up to 2 years after infection but were no longer detectable in blood samples after ten years. This finding suggests that both types of immunity decline over time and that booster vaccinations may be needed to maintain protection.

The research team also studied the spread and variety of LASV strains in rodents during outbreaks in human populations in Nigeria, sampling over 900 rodents across two Nigerian states.[10] The number of rodents testing positive for LASV increased during epidemic periods, and a larger number of rodent species acted as hosts for the virus during outbreaks, suggesting that changes in rodent populations and host species diversity may influence LASV transmission to humans. Understanding these patterns can improve strategies to predict and control future Lassa fever outbreaks and highlight the importance of animal surveillance in disease prevention. The researchers also found that kidney, spleen, and testes are reliable tissues for detecting LASV in small rodents. The findings informed recommendations to test at least three tissue samples, rather than in only in blood samples where the virus may be short-lived.

To support project OVEL, the team developed Sentinel, a smartphone app-based survey initially designed to improve data collection from Lassa fever survivors, their contacts, and uninfected individuals. Sentinel later evolved into a broader platform for disease research and surveillance, utilising machine learning and seasonal climate change and human and animal case data to develop a predictive system for infectious disease outbreaks.[11]

Additionally, project OVEL contributed to capacity building and training. Laboratory teams at Redeemer's University in Nigeria were trained in immunological techniques critical for vaccine development, enabling them to perform key tests analysing immune responses. In addition to technical skills, the project worked closely with local communities to raise awareness about rodent control and disease transmission, while also addressing social barriers such as the stigma often associated with Lassa fever. These combined efforts have strengthened local healthcare infrastructure and enhanced Nigeria's ability to contribute to vaccine development.

A trivalent, broadly protective vaccine against LASV, SUDV and MARV strains

[8] Ugwu C, Olumade T, Nwakpakpa E, et al. Humoral and cellular immune responses to Lassa fever virus in Lassa fever survivors and their exposed contacts in Southern Nigeria. Sci Rep. 2022;12(1):22330. Published 2022 Dec 25. doi:10.1038/s41598-022-26045-w

[9] Heinrich ML, Boisen ML, Nelson DKS, et al. Antibodies from Sierra Leonean and Nigerian Lassa fever survivors cross-react with recombinant proteins representing Lassa viruses of divergent lineages. Sci Rep. 2020;10(1):16030. Published 2020 Sep 29. doi:10.1038/s41598-020-72539-w

[10] Happi AN, Olumade TJ, Ogunsanya OA, et al. Increased Prevalence of Lassa Fever Virus-Positive Rodents and Diversity of Infected Species Found during Human Lassa Fever Epidemics in Nigeria. Microbiol Spectr. 2022;10(4):e0036622. doi:10.1128/spectrum.00366-22

[11] https://www.ucl.ac.uk/news/2021/jun/project-helping-prevent-future-pandemics-wins-global-prize

The project's findings have supported the development of a vaccine candidate, Trivalent Haemorrhagic Fever Vaccine (HFVac3), designed to protect against three deadly viruses: Sudan Ebola (SUDV), Marburg (MARV), and LASV.

Guided by LASV immunological data from project OVEL, the team focussed on targeting a nucleoprotein antigen - a departure from the approach of most research groups, which have been targeting a LASV glycoprotein from a strain isolated nearly 50 years ago. Using their computational platform, the Digital Immune Optimised Synthetic Vaccines (DIOSynVax), the team designed a broadly reactive T-cell vaccine antigen and showed that it was protective in guinea pigs challenged with LASV (in collaboration PHE, now UKHSA). Similarly, drawing on lessons learned from the West African Ebola outbreak, the team developed broadly reactive glycoprotein antigens from the larger family of Ebola viruses that cause haemorrhagic fever diseases in sub-Saharan Africa.

The vaccine candidate that arose from the early project OVEL work, HFVac3, combined the engineered antigens from SUDV, MARV and LASV and inserted them into the Modified Vaccinia Ankara (MVA) viral vector. Because MVA is in itself a licensed vaccine for Mpox (a virus widely spreading in Africa and abroad), this vaccine candidate has the potential to protect against four different human virus diseases that plague Africa each year.

To clinically translate this vaccine, the team spun out a biotechnology company from the University of Cambridge called DIOSynVax. Development was supported by another UKVN 1.0 grant of £2.35 million, which aimed to validate the vaccine candidate in preclinical models and conduct a first-in-human clinical trial to assess safety and immune responses[12]. The animal studies yielded encouraging results, showing that the vaccine provided protection against all three diseases.[13]

Enablers and Challenges

A key enabler of the project was the strong collaboration between the University of Cambridge, University of Oxford, LSHTM, and Redeemer's University in Nigeria. This collaboration enabled the exchange of technical skills, scientific expertise, and local knowledge, which was essential for advancing research and building in-country capacity in Nigeria for epidemic preparedness and vaccine development.

The project faced several challenges during implementation:

- **COVID-19 Pandemic**: The pandemic caused project delays and disruptions. Lockdowns hindered follow-up with study participants and delayed data collection. Travel restrictions and supply chain interruptions made it difficult to source laboratory materials internationally. Additionally, the original partner, PHE, was unable to conduct the planned animal studies due to the UK's national COVID-19 response. Instead, the Public Health Agency of Canada (PHAC) stepped in to complete the high-containment studies.
- **Security Concerns**: Security challenges around the Irrua Specialist Hospital in Edo State, Nigeria, particularly the presence of kidnapping groups, posed risks that impacted participant recruitment. As a result, the data collected mainly reflects the situation in two sites flanking this region, Abakaliki Ebonyi State and Owo, Ondo State, in Southern Nigeria, with some limitations of the study's geographic scope and representativeness.

[12] https://gtr.ukri.org/projects?ref=971616

[13] Pfranger M et al Immunogenicity of a trivalent haemorrhagic fever vaccine candidate against Sudan Ebola virus, Marburg virus and Lassa Fever virus in a Mpox vaccine. 34th Annual Meeting of the Society for Virology, 11 Nov 2024; and J General Virology (under review)

- **Genomic Sequencing Challenge**: The project aimed to sequence 100 full Lassa virus genomes from rodent samples. However, this target was not met due to the presence of non-viral RNA from other pathogens in the tissue, which interfered with sequencing. Nonetheless, over 3,500 rodent tissue samples were successfully analysed, significantly exceeding the initial expectations in terms of sample processing and data generation.

Next steps – clinical trials and manufacturing in Africa

Project OVEL's success in implementing in-country surveillance and generate insights into the protective immune responses of certain individuals exposed annually to LASV and EBOV have resulted in the development of a promising vaccine candidate with strong potential to benefit human health. The candidate's safety and immunogenicity results in animal models are encouraging.

The next phase of the project is to advance HFVac3 development into Phase I clinical trials. Through a UKVN2.0 grant, Innovate UK is providing DIOSynVax with £1.78m to develop the vaccine's GMP manufacturing process.[14] The team plans to apply for additional funding to conduct clinical trials, and to optimise the vaccine platform for broader use against other high-priority pathogens.

To ensure sustainable impact, the team is currently preparing for the next stage of clinical testing in developing countries and strengthening partnerships with health institutions and researchers in LMICs. This includes a collaboration with the African subsidiary of the contract development and manufacturing organisation ProBioGen, MiGenTra.[15] The collaboration aims to build local GMP manufacturing capacity and thus contribute to the long-term goal of manufacturing vaccines in Africa, for Africa.

[14] https://gtr.ukri.org/projects?ref=10087890

[15] ProBioGen and DIOSynVax partner to manufacture groundbreaking multivalent vaccine for hemorrhagic fever. ProBioGen AG. March 27, 2024. Accessed April 29, 2025. Available here.

2.2 Bunyavirus Immunity Consortium

Summary

Crimean-Congo haemorrhagic fever virus (CCHFV) is a tick-borne virus with no licensed vaccine or treatment, placing an estimated three billion people, particularly in low- and middle-income countries, at risk. The UKVN/BBSRC-funded the £1.1 million project "Delineating the immune response against CCHFV and other Nairoviruses to aid effective vaccine design" (2018-2022), led by Professor Teresa Lambe at the University of Oxford, to generate the immunological data and research tools needed for vaccine development.

The team developed a set of assays capable of detecting and differentiating antibody responses to CCHFV and related nairoviruses like NSDV, which enable a more detailed understanding of the immune response. These tools, along with data on immune targets and antibody cross-reactivity, are important to understand which immune responses are protective and how to reliably measure them - a prerequisite for designing, evaluating, and advancing effective vaccines. The results were disseminated in four peer-reviewed publications. The project also fostered international collaborations with institutions such as ILRI in Kenya and The Pirbright Institute, strengthening global capacity to address CCHFV and related diseases.

Building on the project outputs, the Oxford team constructed and tested a viral vector vaccine, ChAdOx2 CCHF. This vaccine candidate provided full protection in mice and is now in Phase I human trials, showing strong early immune responses. In addition, the CCHF assays underpinned fieldwork in Uganda, funded by Wellcome and the MRC, which revealed high rates of CCHFV exposure in both humans and livestock and identified key behavioural risk factors, e.g. regular contact with livestock, and handling or even eating engorged ticks. This information can now support future trial design and inform public health interventions.

Going forward, the team will continue to develop the ChAdOx2 CCHF vaccine candidate through clinical trials, and participate in a collaboration funded by the UK-US Ecology and Evolution of Infectious Diseases programme to investigate whether people in areas with low CCHF cases are protected by cross-reactive immune responses to other viruses.

CCHFV causes severe haemorrhagic fever, placing three billion people at risk

Crimean-Congo haemorrhagic fever virus (CCHFV), a member of the *Nairoviridae* family in the order of Bunyavirales, is a tick-borne virus causing viral haemorrhagic fever (VHF). Spreading to humans mainly from livestock, it is classified as a biosafety level 4 (BSL-4) pathogen due to its high mortality rate (up to 40% during outbreaks), its potential for human-to-human transmission, and the lack of a licensed vaccine or effective treatments.[16,17] As a result, the World Health Organization (WHO) has designated CCHFV a major emerging threat and placed it on the WHO priority list for Research and Development (R&D).[18]

It is estimated that between 10,000 and 15,000 people are infected with CCHFV worldwide each year, causing around 500 fatalities.[19,20] However, the actual numbers are likely to be higher as many cases may be unrecognised, and globally, three billion people are believed to be at risk of infection. CCHFV is endemic across a wide geographic range, including regions in

[16] https://gow.bbsrc.ukri.org/grants/AwardDetails.aspx?FundingReference=BB/R019991/1

[17] https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever

[18] https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts

[19] https://www.gov.uk/guidance/crimean-congo-haemorrhagic-fever-origins-reservoirs-transmission-and-guidelines

[20] ECDC Factsheet for health professionals about Crimean-Congo haemorrhagic fever. Updated Dec 2023. https://www.ecdc.europa.eu/en/crimean-congo-haemorrhagic-fever/facts/factsheet

Africa, Asia, Eastern and Southern Europe, and Central Asia, affecting many low- and middle-income countries (LMICs), especially farm workers.[21] Its distribution mirrors that of the principal tick vector, Hyalomma ticks. Recently, Hyalomma ticks have been detected in previously unaffected areas, e.g. as far North as southern Germany and the Czech Republic, potentially due to climatic changes, with Spain reporting a fatal case of CCHF in 2022, and Portugal confirming its first case in 2024.[22] This geographic expansion underscores the need for protective vaccines and treatments.

Another member of the *Nairoviridae* family, Nairobi sheep disease virus (NSDV), poses a threat to livestock health, with mortality rates of nearly 90% in sheep and goats.[23] Smallholder farmers in LMICs are especially vulnerable to economic losses during NSDV outbreaks due to decreased productivity and trade restrictions. For instance, in Kenya, NSDV outbreaks have historically resulted in severe losses among small ruminant herds, directly impacting rural livelihoods reliant on these animals.

A key challenge in developing effective vaccines for CCHFV is the limited understanding of which immune mechanisms provide protection in humans and animal models, e.g. the level of antibody-mediated and T-cell mediated responses.[24] In addition, the virus' genetic diversity and variability in surface proteins (antigens), the need for high-containment laboratories, and the complexity of field surveillance in endemic regions present additional hurdles. NSDV is closely related to CCHFV but carries a low risk for humans making it a useful comparative model for studying immune responses to nairoviruses more broadly, without the need for BSL-4 containment.

People who have had CCHFV in the past are not known to get infected again, and NSDV outbreaks usually occur when animals with no prior exposure are moved into areas where the virus is present.[25] This suggests that previous infection may provide protection. However, the breadth and repertoire of immunity needed to develop protective immunity following CCHFV/NSDV has not been fully delineated, and antigenic targets on the viral surface have not been defined.

The Bunyavirus Immunity Consortium

The UKVN project "Delineating the immune response against CCHFV and other Nairoviruses to aid effective vaccine design" was funded with £1.1m from April 2018 to March 2022 via the 2017 BBSRC OneHealth competition (BB/R019991/1), led by Professor Teresa Lambe, University of Oxford. The project focussed on the development of critical tools and immunological data including the development of assays (blood tests), essential for measuring immune responses in both human and animal studies.

The project was part of a wider research effort to accelerate vaccine development for CCHF. Consortium partners were also funded by separate UKVN 1.0 awards, to the Pirbright Institute led by Prof Bryan Charleston via a NIHR NETSCC competition[26], and the to UK Health Security

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[21] https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever

[22] Celina SS et al (2023) Mapping the potential distribution of the principal vector of Crimean-Congo haemorrhagic fever virus Hyalomma marginatum in the Old World. PLoS NTD, https://doi.org/10.1371/journal.pntd.0010855

[23] Krasteva S et al (2020) Nairobi Sheep Disease Virus: A Historical and Epidemiological Perspective. Front Vet Sci 7:419. doi: 10.3389/fvets.2020.00419.

[24] Ahata B & Akçapınar, GB (2023) CCHFV vaccine development, current challenges, limitations, and future directions. Front. Immunol 14: doi.org/10.3389/fimmu.2023.1238882

[25] https://gtr.ukri.org/projects?ref=BB%2FR019991%2F1

[26] 16/107/06, NIHR NETCC, Bryan Charleston, Pirbright, 9/1/2016 - 2/1/2021, £2,468,495 "Advanced development of a safe and effective CCHF vaccine for livestock and humans"

Agency led by Prof Miles Carroll via an InnovateUK SBRI grant[27]. While the Oxford-led team focussed on the development of a novel adenoviral-vectored CCHF vaccine, ChAdOx2 CCHF, the Pirbright Institute and UKHSA were jointly pursuing development of a viral-vector vaccine based on the Modified Vaccinia Ankara virus, MVA-GP, which had already been tested in animal studies prior to the UKVN 1.0 award.[28] The consortium hence brought together expertise in virology, immunology, veterinary science, and research under high-containment conditions, from The Jenner Institute at the University of Oxford, The Pirbright Institute and UKHSA.

The primary aim of the "Delineating the immune response against CCHFV and other Nairoviruses to aid effective vaccine design" project was to characterise immune responses after exposure to CCHFV in humans and NSDV in animal models. This included:

- Identifying which CCHFV and NSDV antigens are targeted by the immune system
- Assessing the strength and level of protection of these responses
- Exploring whether immune responses to one nairovirus could recognise others, which has implications for both, the potential of vaccine cross-protection and the accuracy of diagnostic tests.

Generating data and tools to enable CCHFV vaccine development

The researchers developed assays to support diagnostics, differentiating between different nairoviruses, and defined the immune response to infection.

Specific outputs included:

- Assays capable of detecting antibodies against two specific CCHFV antigens in livestock. Compared to the commercially available test, these assays provide a more detailed understanding of the immune response and potentially increase diagnostic precision, e.g. by reducing cross-reactivity between related viruses.[29] As the assays were also crucial for progressing the MVA-GP CCHF vaccine candidate, the teams collaborated on this task.
- An assay that detects a specific NSDV antigen but does not react with CCHFV or related viruses.[30]
- Mapping of which antibodies specifically detected CCHFV proteins, and which cross-reacted with NSDV. Cross-reactivity highlighted both challenges for differential diagnostics and opportunities for cross-protective vaccine strategies.[31]

[27] 972213, SBRI Innovate Uk, Miles Carroll, UKHSA, 10/1/2016 - 8/30/2024 (ongoing), £1,041,860, Phase I Study of a Modified Vaccinia Ankara (MVA) based vaccine for Crimean Congo Haemorrhagic fever

[28] Buttigieg KR et al (2014) A novel vaccine against Crimean-Congo Haemorrhagic Fever protects 100% of animals against lethal challenge in a mouse model. PloS One 9(3):e91516 . DOI 10.1371/journal.pone.0091516

[29] Belij-Rammerstorfer S et al (2022) Development of anti-Crimean-Congo hemorrhagic fever virus Gc and NP-specific ELISA for detection of antibodies in domestic animal sera. Frontiers in Veterinary Science 9:913046. DOI: 10.3389/fvets.2022.913046

[30] Maze EA et al (2023) Generation and Characterisation of Monoclonal Antibodies against Nairobi Sheep Disease Virus Nucleoprotein. Viruses 15(9):1876. DOI: 10.3390/v15091876

[31] Maze EA et al (2025) Serological cross-reactivity between Crimean-Congo haemorrhagic fever virus and Nairobi sheep disease virus glycoprotein C. Front Immunol 15. https://doi.org/10.3389/fimmu.2024.1423474

The project findings were disseminated in four peer-reviewed publications.[32],[33],[34],[35] In addition, instructions (SOPs) for the immune response assays against NSDV and CCHFV were shared beyond the research team, e.g. with the International Livestock Research Institute (ILRI) in Kenya and with the developer of another UKVN-supported CCHF vaccine (Oxford Expression Technologies).

Underpinning progress: UKVN outputs inform vaccine design and trials

Building on the assays and data from the UKVN1.0/BBSRC-funded project, the team continued research to progress the development of vaccines against CCHFV:

Based on immunological data gathered, the team constructed, manufactured, and tested a viral vector-based vaccine, ChAdOx2 CCHF, in mice, funded by a UKVN1.0/InnovateUK SBRI grant.[36] They showed that ChAdOx2 CCHF triggered strong immune responses and fully protected animals against the disease.[37] As Prof Lambe explained: "*Those assays and the knowledge [immunological data] have helped us identify the targets that we want to be hitting in our next generation vaccine. We've now generated those vaccines and we have tested them in small animals. So we know which targets to go for*." The team is currently testing the ChAdOx2 CCHF vaccine in a Phase I clinical trial in humans. Early results indicate that the vaccine triggers very strong T-cell responses and robust antibody responses[38].

The Oxford team conducted field studies in Uganda, funded by Wellcome Trust and UK Medical Research Council grants, in collaboration with Professor Robert Tweyongyere at Makerere University Kampala and Professor Emma Thomson at the University of Glasgow.[39] These helped to understand better the prevalence of CCHFV in humans and animals – important data for planning vaccine trials - , and risk factors associated with CCHFV infections. The study found that 28% of humans, 92% of cattle, 75% of goats and 56% of dogs in farming communities had CCHFV antibodies. Regular contact with livestock and ticks was a major factor in CCHFV infection risk, while dog ownership and certain behaviours, e.g. handling or even eating engorged ticks, were also linked to significantly higher exposure. Findings can now guide public health measures focussed on this setting.

The collaborations initiated through the BBSRC-funded project have continued to strengthen and expand. Working with the Pirbright Institute, Prof Lambe is involved in veterinary vaccine trials for CCHF/NSDV[40]. The research team recently secured follow-on funding to identify risk factors of disease through the UK-US Ecology and Evolution of Infectious Diseases (EEID) programme, with Prof Thomson, Glasgow University, as lead applicant and Prof Lambe as co-

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[32] Belij-Rammerstorfer S et al (2022) Development of anti-Crimean-Congo hemorrhagic fever virus Gc and NP-specific ELISA for detection of antibodies in domestic animal sera. Frontiers in Veterinary Science 9:913046. DOI: 10.3389/fvets.2022.913046

[33] Maze EA et al (2023) Generation and Characterisation of Monoclonal Antibodies against Nairobi Sheep Disease Virus Nucleoprotein. Viruses 15(9):1876. DOI: 10.3390/v15091876

[34] Maze EA et al (2025) Serological cross-reactivity between Crimean-Congo haemorrhagic fever virus and Nairobi sheep disease virus glycoprotein C. Front Immunol 15. https://doi.org/10.3389/fimmu.2024.1423474

[35] Gilbride C et al (2021) The Integration of Human and Veterinary Studies for Better Understanding and Management of Crimean-Congo Haemorrhagic Fever. Front Immunol 12:629636. doi: 10.3389/fimmu.2021.629636

[36] 971519, InnovateUK SBRI, 4/1/2017 - 3/31/2018, £350,780, https://gtr.ukri.org/projects?ref=971519

[37] Saunders, J E et al (2023) Adenoviral vectored vaccination protects against Crimean-Congo Haemorrhagic Fever disease in a lethal challenge model. eBioMedicine, Volume 90, 104523, https://doi.org/10.1016/j.ebiom.2023.104523

[38] Prof T Lambe, personal communication, 6 June 2025

[39] Atim SA et al (2022) Risk factors for Crimean-Congo Haemorrhagic Fever (CCHF) virus exposure in farming communities in Uganda. The Journal of Infection 85(6):693-701 DOI: 10.1016/j.jinf.2022.09.007

[40] Prof T Lambe, personal communication, 6 June 2025

investigator. The award will enable the collaborators to test whether people in areas with low CCHF cases are protected by cross-reactive immune responses to other viruses. The UKVN 1.0 / BBSRC project also helped to establish new collaborations, including with ILRI in Kenya, to enable future animal challenge studies and clinical trial planning.

As Prof Lambe commented: "*The findings, tools and collaborations we established have subsequently allowed my team to set up a clinical trial. […] So the assays that we developed through that project are now being used in clinical trials. We also established new relationships, for example with ILRI in Kenya for animal challenge studies.*"

Next steps

Building on the immunological data, diagnostic tools, and collaborative networks established through this project, the research team continues to advance the ChAdOx2 CCHF vaccine through Phase I clinical evaluation. Concurrently, international collaborations - such as those with The Pirbright Institute and ILRI in Kenya and partners on the EEID-funded programme - will investigate cross-reactive immunity and the interplay between viral family members.

2.3 FVMR Hub: Successful vaccine platform transfer sparks wider collaboration with Vietnam

Summary

The Future Vaccine Manufacturing Research (FVMR) Hub supported the transfer of a vaccine production platform, the MultiBac baculovirus expression vector system (BEVS), from Professor Imre Berger's laboratory at the University of Bristol to Vabiotech, one of Vietnam's leading vaccine manufacturers.

The project was originally designed to enable the production of influenza and rabies vaccines in Vietnam using BEVS, but its scope shifted when COVID-19 emerged. Through the collaboration, Vabiotech successfully established baculovirus-based vaccine production under Good Manufacturing Practice (GMP) conditions. Collaborating with FVMR Hub experts, the company successfully developed a COVID-19 vaccine, scaled up manufacturing, and showed effectiveness in animal studies. Vabiotech is now in a position to quickly initiate and scale up vaccine production using the baculovirus system as and when needed.

Work on influenza and rabies vaccines continues post-COVID and as part of the FVMR Hub2.0, including research on a second type of vaccines, protein nanoparticles. Going forward, the Bristol group and Vabiotech are also planning to collaborate outside the FVMR Hub on innovative animal vaccines.

In addition to the long-term partnership between UK groups and Vietnamese researchers, the FVMR Hub collaboration nucleated a wider partnership between Bristol and Vietnam: In 2022, the University of Bristol and two Vietnamese universities signed a Memorandum of Understanding (MoU), creating a student visit programme and research collaborations.[41]

The Baculovirus Expression Vector System (BEVS) for vaccine production

The Future Vaccine Manufacturing Research (FVMR) Hub aimed to advance research and development across multiple vaccine manufacturing platforms, including the Baculovirus Expression Vector System (BEVS). BEVS is a well-established approach for producing recombinant proteins in insect cells.[42] The platform can produce complex proteins at scale, which many other systems struggle with, in simpler, lower-cost facilities. It thus has potential to support local vaccine production in low- and middle-income countries (LMICs), with the system's adaptability to emerging diseases, enhancing regional pandemic preparedness and reducing dependence on foreign suppliers. FVMR Hub co-investigator Professor Imre Berger from the University of Bristol is a leading expert in protein expression using BEVS, and had developed a BEVS platform, MultiBac, designed for efficient and scalable production of complex multiprotein assemblies.[43]

Vabiotech is a state-owned company located in Hanoi, Vietnam.[44] In 2016, at the start of the FVMR Hub, baculovirus-based vaccines had already demonstrated success in the global market, with examples such as the Human Papillomavirus vaccine, Gardasil.[45] However,

41 https://www.bristol.ac.uk/news/2022/july/bristol-vietnam-mous.html . Accessed 2 May 2025

42 Sari D, Gupta K, Thimiri Govinda Raj DB, et al. The MultiBac Baculovirus/Insect Cell Expression Vector System for Producing Complex Protein Biologics. *Adv Exp Med Biol*. 2016;896:199–215. doi:10.1007/978-3-319-27216-0_13.

43 Gupta K, Tölzer C, Sari-Ak D, et al. MultiBac: baculovirus-mediated multigene DNA cargo delivery in insect and mammalian cells. *Viruses*. 2019;11(3):198. doi:10.3390/v11030198

44 https://vabiotech.com.vn/en/home-page/. Accessed 2 May 2025.

45 Yousefi Z, Aria H, Ghaedrahmati F, et al. An update on human papilloma virus vaccines: history, types, protection, and efficacy. *Front Immunol*. 2021;12:805695. doi:10.3389/fimmu.2021.805695

Vietnam lacked the technological capability to produce these vaccines domestically. Vabiotech expressed strong interest in acquiring BEVS technology to improve their vaccine production capabilities. This kicked off a collaboration with Professor Berger's group, with the aim of transferring the technology to Vabiotech. The activity was funded by the FVMR Hub with approximately £1m.[46]

Building capacity: Vabiotech implements BEVS technology and co-develops vaccine candidate

The collaboration's initial focus was on avian influenza and rabies vaccines, two major public health concerns in Vietnam.[47,48,49] Visits by Prof Berger and his team members to Vietnam and by Vabiotech scientists to the UK provided the company with training in baculovirus-based protein expression using the MultiBac platform developed by the Berger group at Bristol University. Vabiotech then focussed on adapting the platform for industrial-scale manufacturing.

With the onset of the COVID-19 pandemic, Vabiotech decided to pivot and develop a baculovirus-based COVID-19 vaccine.[50,51] Working in collaboration with Prof Berger and Prof Shattock (Imperial College London), Vabiotech successfully developed a vaccine candidate based on the SARS-CoV-2 spike protein, and transferred laboratory-scale production of the vaccine candidate to its industrial-scale facility in Vietnam. The Vabiotech team then focused on scaling up, refining purification methods, and establishing quality control measures to meet regulatory requirements, including under Good Manufacturing Practice (GMP) conditions. To test immune responses and safety, the company trialled the vaccine candidate in animal models, demonstrating a strong immune reaction and confirming its effectiveness. However, plans for a Phase I clinical trial were halted when several globally authorised vaccines became widely available.

The development of manufacturing processes for the COVID-19 vaccine under GMP conditions advanced Vabiotech's capabilities in baculovirus-based vaccine production, setting the foundation for future vaccine development in Vietnam. As Prof Berger summarised: "*Vabiotech didn't have a baculovirus platform [when we started]. Now they have a baculovirus platform and they are as good as anybody else in terms of producing vaccines with that technology. They have expanded it all the way to GMP scale production. The project worked out completely*."

In terms of research impact, the collaboration demonstrated the feasibility of using BEVS for vaccine production in LMIC settings. Protocols and processes are in place to respond rapidly and effectively when an outbreak occurs. This will enable Vietnam to become less reliant on foreign vaccine manufacturers and strengthened the country's pandemic preparedness.

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46 Personal communication, Prof Imre Berger. 6 March 2025

47 FVMR Hub proposal document. May 2017

48 Watts J. Vietnam needs cash to stave off future outbreaks of bird flu. *Lancet*. 2005 May 21–27;365(9473):1759–60. doi:10.1016/S0140-6736(05)66565-8. PMID:15915564; PMCID:PMC7137749

49 National Program for Rabies Control and Elimination in Viet Nam in the period from 2017 to 2021. Hanoi: Ministry of Agriculture and Rural Development; Ministry of Health; 2016 Dec. Available from: https://rr-asia.woah.org/app/uploads/2020/03/national-program-for-rabies_vietnam.pdf

50 Closure Report FVMR Hub. Dec 2023

51 Personal communication, Prof Imre Berger. 6 March 2025

Bristol University group benefits from strong collaboration with Vabiotech

The collaboration quickly moved beyond a simple technology transfer into a dynamic scientific partnership and led to ongoing joint projects, iterating modifications to the platform between academic and industry settings. Existing BEVS platforms often encounter reduced yields during scale-up (a factor that caused a delay in the development of the Novavax COVID-19 vaccine).[52] Prof Berger's group aimed to address this challenge by modifying the MultiBac system and testing iterations at the laboratory scale in the UK. Funded by the FVMR Hub, promising candidates were then tested by Vabiotech under industrial scale-up conditions. In this way, the collaborators developed an improved platform that successfully produced a baculovirus-based rabies vaccine at the pilot scale. As Prof Berger described: "*This was more than just transfer, it turned into a really great collaboration, which was also beneficial for us*. […] *If I compare it with my other collaborations, it was not really different working with somebody in Europe*." Thus, the project also provided insights into the opportunities and challenges of vaccine manufacturing in LMIC settings, and the role LMIC companies can play in process development.

Continued and expanded research and education partnership, beyond the FVMR Hub

Work on the influenza and rabies vaccines, along with platform improvements for industrial-scale manufacturing, continue as part of FVMR Hub 2.0.[53] This includes production scale-up of a second vaccine approach, a nanoparticle vaccine developed in the Berger lab. Going forward, the Bristol group and Vabiotech also plan to collaborate on the development of animal vaccines outside the FVMR Hub, and are currently applying for funding. Vabiotech has introduced the BEVS platform to other developers and manufacturers in Vietnam and aims to commercialise products using the technology in the future.[54] The company is committed to commercialising products produced by this technology in the future.

In addition to the long-term partnership between UK groups and Vietnamese researchers, the FVMR Hub collaboration catalysed a wider partnership between Bristol and Vietnam.[55] The interactions as part of the FVMR Hub led to the signing of a Memorandum of Understanding in 2022 between the University of Bristol and two Vietnamese universities. This created a student visit programme and the basis for broader research collaboration.

Key enabling factors – strong commitment and UKVN funding

Several factors contributed to the project's success and underpinned continued collaboration between the Bristol group and Vabiotech.[56]

Vabiotech were fully committed to establishing the baculovirus system at its facility. Throughout the collaboration, Prof Berger was impressed by the staff's professionalism and commitment to advancing local vaccine manufacturing. The company's laboratories were well equipped, and Vabiotech invested in the platform to make it operational.

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52 King ML. How manufacturing won or lost the COVID-19 vaccine race. *Vaccine*. 2024;42:1004–1012. doi:10.1016/j.vaccine.2023.12.031

53 Personal communication, Prof Imre Berger. 6 March 2025

54 Personal communication, Dr Do Tuan Dat. 12 March 2025

55 https://www.bristol.ac.uk/news/2022/july/bristol-vietnam-mous.html. Accessed 2 May 2025

56 Personal communication, Prof Imre Berger. 6 March 2025

A collaborative research approach ensured that knowledge was effectively exchanged between partners, enhancing the overall impact of the initiative. Vabiotech had selected the BEVS for transfer, and the company was fully engaged - and played a crucial role - in innovation and refinement of the platform for industrial use. Both partners view the ongoing collaboration positively, as Dr. Tuan Dat Do, Senior Advisor at Vabiotech, commented: "*The collaboration with the UK researchers is great, we were able to translate academic research to industrial applications*."

UKVN funding was instrumental in enabling the transfer of technology and adoption by the LMIC partner. The project also benefitted from a flexible funding approach that allowed it to pivot towards COVID-19 vaccine development when needed. As Prof Berger commented: "*I wouldn't see a way Vabiotech could have built this up without [the UKVN]. […] The hub opened the doors for Vabiotech to pick up the capabilities, the funding was absolutely critical.*" As a result of the collaboration, Vabiotech are now a partner in cutting-edge technology development with world-leading academic experts.

In conclusion, the UKVN-funded project successfully adapted the MultiBac system for vaccine production in an industrial setting, and developed a vaccine candidate that proved effective in animal studies. The collaboration enhanced Vietnam's vaccine manufacturing capabilities and epidemic preparedness, and led to a sustained research partnership which continues to benefit both UK and LMIC stakeholders.

2.4 Advancing affordable glycoconjugate vaccine production through Vax-Hub

Summary

Vax-Hub played a key role in advancing the work of Professor Brendan Wren at the London School of Hygiene & Tropical Medicine (LSHTM) in developing a platform for vaccine manufacturing against a range of bacterial diseases. Wren had pioneered a method for producing glycoconjugate vaccines in *Escherichia coli*, with substantially reduced manufacturing costs compared to traditional chemical approaches. Collaborating with Professor Martina Micheletti at University College London (UCL), an expert in bioprocess engineering, the team took this work further towards scale-up, developed an automated screening platform for vaccine candidates, generated high-yield *E. coli* strains, and achieved larger-scale production.

Vax-Hub expanded Wren's research from lab-based discovery to include applied research -vaccine manufacturing - and connected him with manufacturing experts. The experience and network he gained through Vax-Hub have helped him secure multiple follow-on grants, from funders including Wellcome, the BBSRC and the EPSRC, to develop vaccines against a range of bacterial diseases. Vax-Hub's outputs now underpin the further development of a scalable, low- and middle-income country (LMIC)-adapted vaccine production platform in the follow-on hubs, VaxHub Sustainable and VaxHub Global. Crucially, retaining control of the platform outside industry ensures that glycoconjugate vaccine production will remain accessible to LMICs.

Making glycoconjugate vaccines more affordable

Many pathogenic bacteria have polysaccharide (glycan) coats, which can be used in vaccines. However, on their own, glycans elicit weak immunity, especially in young children whose immune systems are still developing. To overcome this challenge, the bacterial glycans can be linked to a protein carrier (forming a glycoconjugate), which boosts immune

recognition and induces lasting immunity.[57,58] Glycoconjugate vaccines are currently available against some types of bacteria causing meningitis, pneumonia and typhoid fever.

Traditionally, glycoconjugate production involves linking the glycan and protein by chemical methods.[59] This process requires multiple steps using complex techniques, is prone to batch-by-batch variation, and is expensive. For example, pneumonia caused the deaths of 2.6 million people in 2017, even though an effective vaccine against *Streptococcus pneumoniae* was on the market. One of the reasons for this was the high price of the vaccine - $169 per dose. In addition, differences in bacterial glycoproteins between geographic areas limited protection by available vaccines.

A novel production method, Protein Glycan Coupling Technology (PGCT), offers a promising solution. PGCT uses purpose-engineered bacterial cells, such as *Escherichia coli*, to link the glycan and protein.[60] This bioconjugation process uses standard microbial fermentation rather than chemical linking, which lowers production costs and facilitates scale-up. In addition, genetic engineering of bacterial cells enables different combinations of proteins and glycans to be generated and tested quickly. This can accelerate development of vaccines against emerging bacterial threats and is particularly useful for tailoring vaccines to specific bacterial strains as and when outbreaks occur. Another advantage of PGCT over traditional chemical approaches is that any protein carrier can be used in the coupling reaction. Traditional approaches largely rely on coupling to a single carrier protein, called CRM, the repeated use of which dampens the immune response in subsequent vaccinations that also use CRM. The flexibility of PGCT avoids this as it allows coupling of different proteins and glycans. In addition, vaccines can be developed where the protein and glycan each trigger an immune reaction, against different pathogens - so called 'double-hit' vaccines.[61]

Vax-Hub co-investigator Professor Brendan Wren, based at the London School of Hygiene & Tropical Medicine (LSHTM), pioneered PGCT in the early 2000s when he and colleagues discovered a bacterial pathway linking glycans to proteins.[62] Wren then showed that engineering this pathway into *E. coli* enabled targeted production of glycoconjugates. In the following years, he further refined and developed this bioconjugation platform, improving its overall efficiency and versatility.[63,64]

Scaling production: Interdisciplinary collaboration through Vax-Hub

57 Adamo R. Glycoconjugate vaccines: classic and novel approaches. *Glycoconj J*. 2021 Aug;38(4):397–398. doi:10.1007/s10719-021-09997-5

58 Kay E, Cuccui J, Wren BW. Recent advances in the production of recombinant glycoconjugate vaccines. *npj Vaccines*. 2019;4:16. doi:10.1038/s41541-019-0110-z

59 Samaras JJ, Mauri M, Kay EJ, et al. Development of an automated platform for the optimal production of glycoconjugate vaccines expressed in *Escherichia coli*. *Microb Cell Fact*. 2021;20:104. doi:10.1186/s12934-021-01588-1

60 Kay E, Cuccui J, Wren BW. Recent advances in the production of recombinant glycoconjugate vaccines. *npj Vaccines*. 2019;4:16. doi:10.1038/s41541-019-0110-z

61 https://www.birmingham.ac.uk/research/immunology-immunotherapy/research/bactivac/funded-pump-priming-projects-awardees/prof-brendan-wren. Accessed 2 May 2025

62 Wacker M, Linton D, Hitchen PG, et al. N-linked glycosylation in *Campylobacter jejuni* and its functional transfer into *E. coli*. *Science*. 2002;298:1790–1793. doi:10.1126/science.298.5599.1790

63 Dow JM, Mauri M, Scott TA, Wren BW. Improving protein glycan coupling technology (PGCT) for glycoconjugate vaccine production. *Expert Rev Vaccines*. 2020;19(6):507–527. doi:10.1080/14760584.2020.1775077

64 Abouelhadid S, Atkins ER, Kay EJ, et al. Development of a novel glycoengineering platform for the rapid production of conjugate vaccines. *Microb Cell Fact*. 2023;22(1):159. doi:10.1186/s12934-023-02125-y

With a primary research focus on bacterial pathogenesis, Wren did not have experience in manufacturing processes beyond the laboratory scale.[65] Joining Vax-Hub enabled Wren's team to collaborate with bioprocess engineers at University College London (UCL), Professor Martina Micheletti's group. The partnership provided Wren with access to bioprocess engineering expertise and bioreactors, crucial for scaling of production. Vax-Hub provided £700,000 in funding to support this work.

Optimising glycoconjugate vaccine production requires the right *E. coli* strain for each vaccine and efficient coordination of key production processes to maximise yield. To enable rapid screening of large numbers of vaccine candidates, the Wren and Micheletti groups developed an automated platform for microscale glycoconjugate vaccine production in *E. coli*.[66] The platform enables precise control over fermentation conditions, real-time monitoring of process parameters, and rapid optimisation of production yields in small volumes. The team used the platform on a test case, a pneumococcal vaccine, identifying the best *E. coli* strain and genetic constructs and optimising culture conditions. The work demonstrated the platform's ability to speed up early-phase research.

Scaling up from small lab flasks to industrial bioreactors adds complexity, and requires downstream processing and analytical validation to ensure the vaccine's composition is correct. As part of Vax-Hub, the collaborators developed an upscaled PGCT production process, including an analytics platform that monitors both vaccine yield and quality throughout production. Through interactions with experts in LMICs, particularly in African countries, Wren ensured that the production process was designed to be adaptable to the local conditions and available resources in these regions.[67] In addition, interactions with the Vax-Hub team at the University of Oxford, including Professor Sarah Gilbert, provided valuable insights into scaling vaccine production and preparing for GMP manufacturing. This informed, scaling of production from laboratory (1L) to bioreactor volumes (50L). However, as the process was more complex than anticipated, production under GMP conditions could not be achieved within the Vax-Hub timeframe.[68]

Research partially funded by Vax-Hub also developed *E. coli* strains that are safer for therapeutics manufacturing ('detoxified') and with improved glycoconjugate production (e.g. by removal of competing glycan synthesis pathways). These strains are deposited in a major repository of micro-organisms, the Belgium Co-ordinated Collection of Microorganisms (BCCM), and are freely available to researchers.[69] In 2023, the strains received an award from BCCM as the most requested strains from the collection that year, demonstrating broad interest and applicability in PCGT technology by the research community.[70]

Opening up the field: Vax-Hub outputs enable glycoconjugate vaccines to bacterial diseases

65 Personal communication, Prof Brendan Wren. 5 March 2025

66 Samaras JJ, Mauri M, Kay EJ, et al. Development of an automated platform for the optimal production of glycoconjugate vaccines expressed in *Escherichia coli*. *Microb Cell Fact*. 2021;20:104. doi:10.1186/s12934-021-01588-1.

67 Personal communication, Prof Brendan Wren. 5 March 2025

68 Personal communication, Prof Brendan Wren. 5 March 2025

69 Kay EJ, Mauri M, Willcocks SJ, et al. Engineering a suite of *E. coli* strains for enhanced expression of bacterial polysaccharides and glycoconjugate vaccines. *Microb Cell Fact*. 2022;21:66. doi:10.1186/s12934-022-01792-7.

70 EP/R013756/1. Outcomes, Research Tools and Methods. UK Research and Innovation. Available from: https://gtr.ukri.org/projects?ref=EP%2FR013756%2F1.

Underpinned by the *S. pneumoniae* work funded through Vax-Hub, Wren's group have produced novel recombinant glycoconjugate vaccine candidates against a range of bacterial diseases, including *Campylobacter*, Group A and Group B *Streptococcus*, *Shigella*, *Francisella*, and several animal pathogens including *Brucella* and *Streptococcus suis*.[71,72]

Underpinned by the *S. pneumoniae* work funded through Vax-Hub, Wren's group have produced novel recombinant glycoconjugate vaccine candidates against a range of bacterial diseases, including *Campylobacter*, Group A and Group B *Streptococcus*, *Shigella*, *Francisella*, and several animal pathogens including *Brucella* and *Streptococcus suis*.[15,16]

As Wren commented: "*The technology has really opened up the field. There are just three [chemically linked] glycoconjugate vaccines against bacterial pathogens in current use, after four decades of development. But now we have the chance of making glycoconjugate vaccines against most bacterial pathogens including against multi-antibiotic-resistant strains*."

Through Vax-Hub, Wren gained experience in scaling production and access to a wide network of manufacturing experts he can consult or collaborate with. This has given funders confidence in the impact and real-world applicability of his work, and he has attracted multiple grants from various organisations (approx. £19m in total consortium funding, e.g. £11m from the BBSRC for the GlycoCell Initiative (2024-2029) and £5.2m from Wellcome for the Campylobacter Control Campaign, with approx. £4.5m going to LSHTM)[73,74,75,76,77]. Latter includes a work package on capacity-building to support LMICs in producing and testing glycoconjugate poultry vaccines.[78] Building on Vax-Hub's work, LSHTM also spun out ArkVax in early 2023, a start-up company focussed on glycoengineering for veterinary vaccines.[79]

Vax-Hub was instrumental in securing follow-on support and underpinning further development. As Wren explained: "*We have funding to make prototype vaccines for a lot of different diseases now. Being part of Vax-Hub has been invaluable; it means that we don't stop at the prototype. We have the capability and expert network to move candidates further along the production pathway.*"

Future directions: Towards GMP production and global impact

Building on the success of Vax-Hub, Wren continues to work on glycoconjugate vaccine production as co-PI of Vax-Hub's follow-on consortia:

71 https://www.lshtm.ac.uk/research/centres-projects-groups/wrenlab; https://gtr.ukri.org/projects?ref=BB%2FY008472%2F1#/tabOverview . Accessed 2 May 2025

72 Personal communication, Prof Brendan Wren. 5 March 2025

73 EP/R013756/1. Outcomes-Further Funding. UK Research and Innovation. Available from: https://gtr.ukri.org/projects?ref=EP%2FR013756%2F1.

74 https://www.lshtm.ac.uk/newsevents/news/2024/ps2m-funding-develop-novel-glycocell-vaccine-hub. Accessed 2 May 2025

75 https://www.lshtm.ac.uk/research/centres/vaccine-centre/news/418156/lshtm-researchers-part-new-collaborative-develop-strep-vaccine. Accessed 2 May 2025

76 https://wellcome.org/grant-funding/people-and-projects/grants-awarded/campylobacter-control-campaign. Accessed 2 May 2025

77 Personal communication, Prof Brendan Wren, 14 March 2025

78 https://www.lshtm.ac.uk/research/centres/vaccine-centre/news/447031/ps14m-funding-vaccine-development-protecting-against-foodborne-bacteria. Accessed 2 May 2025

79 https://www.lshtm.ac.uk/aboutus/people/wren.brendan#research. Accessed 2 May 2025

- VaxHub Sustainable is funded with £12m by the EPSRC (2023-2030).[80] As co-PI of VaxHub Sustainable, Wren is collaborating with Prof Katherine Green (University of Oxford) and Prof Micheletti (UCL) to scale up bioconjugate vaccine production towards GMP and clinical trials for two exemplar vaccines (*Francisella tularensis*, a biothreat; *S. pneumoniae* serotype 1, a multi-antibiotic resistance threat).[81]
- VaxHub Global is funded with £10m by the UKVN (DHSC) with contribution from the EPSRC.[82] Here, Wren focusses on adapting the technology for use in LMICs, drawing on input from collaborators in African countries to ensure processes can be implemented under local conditions.

Reducing reliance on big pharma and ensuring greater global vaccine equity has been a key driver of Wren's work. Glycoconjugate vaccines are also currently being developed by GlycoVaxyn/GSK, and are being tested in Phase I, II and III clinical trials.[83] However, developing the PGCT vaccine production platform 'in parallel' with Vax-Hub support, and without industry involvement, has allowed Wren and collaborators to maintain control over the technology. As Wren explained: "*If 'big pharma' took over, we might lose the option of delivering the technology to LMICs. Keeping control of our platform allows us to ensure that vaccines reach those who need them most*." For example, the team published several patents on the process.[84]

Challenges and lessons learned

While the project achieved significant milestones, such as the development of the automated screening platform and glycoconjugate production in 50L bioreactors, Wren noted that scaling up vaccine production had been more complex than he had anticipated. Yield optimisation required extensive process development, and production under GMP conditions was not achieved within the Vax-Hub timeframe. However, the experience gained through Vax-Hub is now informing further process development carried within VaxHub Sustainable and VaxHub Global, with the aim of moving glycoconjugate vaccine candidates into GMP manufacturing while tailoring production methods to LMICs.[85,86]

Vax-Hub proved to be key for fostering interdisciplinary collaboration, connecting biologists, engineers, and industry experts accelerated problem-solving and innovation. This was particularly important for Wren who had not worked on upscaling of bioprocesses and GMP-compliant manufacturing prior to Vax-Hub. The collaboration with bioprocess engineers at UCL and Oxford provided the expertise and infrastructure needed. Without Vax-Hub, Wren thought it was unlikely that he would have got involved in this type of research. As he explained: "*I never thought I'd be involved in understanding the later stages of manufacturing pathways, but Vax-Hub got me thinking that way*." Insights from the collaborations now guide Wren's early-stage research from the outset, ensuring it aligns with requirements for scalability and

80 https://gtr.ukri.org/projects?ref=EP%2FX038181%2F1; https://vaxhubsustainable.com. Accessed 2 May 2025

81 VaxHub Sustainable Annual Report 2024. Available at: https://vaxhubsustainable.com/wp-content/uploads/sites/3/2024/12/VaxHubSustainable%20Annual%20Report%202024.pdf

82 https://vaxhubglobal.com/. Accessed 2 May 2025

83 https://www.gsk.com/en-gb/media/press-releases/gsk-strengthens-early-stage-vaccine-pipeline-with-acquisition-of-glycovaxyn-ag/. Accessed 2 May 2025

84 Patent 11278610: Glycosylation method, March 22, 2022; and Patent 11179454: Whole cell vaccines, November 23, 2021. End Report Vax-Hub, 2023.

85 https://vaxhubsustainable.com/research-programme/. Accessed 2 May 2025

86 https://vaxhubglobal.com/research-programme/ Accessed 2 May 2025

regulatory compliance, e.g. rigorous documentation and the selection of appropriate growth media.[87]

Conclusion

Vax-Hub was instrumental for progressing PGCT to scalable vaccine production methods. The collaboration with bioprocess engineers at UCL, other members of Vax-Hub and new academic and industrial collaborators, provided the expertise and infrastructure needed to improve production, automate screening, and scale up vaccine yields, paving the way for future GMP production. Beyond technological advancements, Vax-Hub provided Wren with experience in process development and connection to a network of experts, which have contributed to his success in securing additional funding from Wellcome, BBSRC, MRC and Right Foundation for continued vaccine development. Through follow-on projects such as VaxHub Sustainable and VaxHub Global, Wren is further adapting the technology to enable vaccine production in LMICs, ensuring greater global vaccine equity. As Wren summarised: *"In the longer term, this will be the achievement of Vax-Hub: that these vaccines will be far simpler to make in any resource setting."*

87 Personal communication, Prof Brendan Wren. 5 March 2025

2.5 Electronic Data Capture to support rapid epidemiological research and response during epidemics

Summary

During disease outbreaks, unlicensed vaccines may be deployed to mitigate the spread of infections. A major challenge in these situations is obtaining timely, reliable data on vaccine safety and efficacy. A £539,000 UKVN grant enabled researchers from the London School of Hygiene and Tropical Medicine to address this challenge by developing a rapidly deployable electronic data collection platform to support outbreak response.

The project 'Electronic Data Capture to support rapid epidemiological research and response during epidemics' (EDK) built on an existing open-source system to create new software and methods for real-time data collection. These tools played an important role in the 2018-20 Ebola virus disease outbreak in the Democratic Republic of the Congo:

- The platform supported the collection of safety and efficacy data from over 260,000 recipients of the unlicensed vaccine (VSV-ZEBOV-GP)
- The team introduced biometric cards for offline data capture, which is critical for tracking vaccination in remote areas. This innovation eliminated the need to manually process more than 15 million paper records of vaccination data

By delivering an electronic data collection system for use in health emergencies, the EDK project strengthened research capabilities and contributed to more effective public health responses during an outbreak.

Electronic data collection systems for vaccination during outbreaks

Ebola virus disease (EVD) is a highly contagious and fatal infectious disease[88], first discovered in 1976 following outbreaks in South Sudan and the Democratic Republic of the Congo.[89] A 2014 EVD outbreak in West Africa led to 11,000 deaths and increased poverty rates in affected economies as well as in neighbouring countries.[90][91][92] Vaccination is crucial in mitigating the impact of EVD and other disease outbreaks, however vaccine development is challenging due to the unpredictable nature of outbreaks and the logistical complexities of conducting clinical trials.

During emergencies, unlicensed vaccines are often administered under compassionate use agreements, requiring follow-up to assess vaccine safety and effectiveness. Accurate and timely data collection is thus essential to evaluate the effect of vaccination on controlling outbreaks. Data collection includes participant consent to vaccination, eligibility records, vaccination details, geographical tracking and multiple safety follow-ups. Collecting data in remote or conflict-affected regions with limited infrastructure is highly challenging. Traditional methods involving paper records are slow and error prone. While electronic systems for data

[88] Goeijenbier, M. et al. (2014). Ebola virus disease: A review on epidemiology, symptoms, treatment, and pathogenesis. Neth. J. Med. 72(9), 442–448.

[89] World Health Organization (2023). Ebola virus disease. WHO. Available at: https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease [Accessed 24 Feb 2025].

[90] Cenciarelli, O. et al. (2015). Ebola virus disease 2013-2014 outbreak in West Africa: An analysis of the epidemic spread and response. Int. J. Microbiol. 2015(1), 769121. https://doi.org/10.1155/2015/769121

[91] Gov.uk (2023). Ebola: Overview, history, origins, and transmission. Gov.uk. Available at: https://www.gov.uk/government/publications/ebola-origins-reservoirs-transmission-and-guidelines/ebola-overview-history-origins-and-transmission [Accessed 24 Feb 2025].

[92] United Nations Development Programme (2016). Socio-economic impact of the Ebola virus disease in West Africa. UNDP. Available at: https://www.undp.org/africa/publications/socio-economic-impact-ebola-virus-disease-west-africa [Accessed 24 Feb 2025].

collection exist, they are not always user-friendly, affordable and able to function without an internet connection (offline).[93] Thus, there is a critical need to develop and adapt electronic data collection systems for emergency settings.

Developing LSHTM's ODK system for rapid electronic data collection

Since 2009, the London School of Hygiene and Tropical Medicine (LSHTM) has developed and maintained electronic data capture tools to support global health research, based on the open-source data platform 'Open Data Kit' (ODK).[94] By 2017 the LSHTM tools supported data collection for over 100 projects in 50 countries. In 2018, researchers at LSHTM identified the need to further develop the LSHTM's ODK system, to enable collection of different types of data crucial for epidemiological studies and for rapid responses to outbreaks. This culminated in the 'EDK' project (Electronic Data Capture to support rapid epidemiological research and response during epidemics).

Running from April 2018 to March 2022, the EDK project received approximately £539k in funding from the UK Vaccine Network 1.0 through the UK's National Institute for Health and Care Research (NIHR)'s 'Epidemiology for Vaccinology' funding competition.[95] The overarching aim of the EDK project was to further develop LSHTM's ODK system into a rapidly deployable platform for electronic data collection to support responses to outbreaks and other humanitarian emergencies. Led by Prof Dr. Chrissy Roberts and co-applicants from the LSHTM, the project sought to improve the software and expand LSHTM's ODK applications, such as web surveys, geospatial data collection and automated data analysis. In addition, the project aimed to test the improved system in a simulated disease outbreak.

Deploying electronic data collection tools during outbreaks

A few months into the project, EVD cases were reported in the Democratic Republic of the Congo (DRC), leading to a two-year EVD outbreak (2018-20), the second largest on record[96]. This event, along with the COVID-19 pandemic in 2020, strongly shaped the project's activities.

In 2018, the EDK project team collaborated with the World Health Organization (WHO) R&D Blueprint team to support data collection to monitor the EVD outbreak in the DRC. A ring vaccination approach was used by the DRC's Ministry of Health to combat the outbreak, using the unlicensed EVD vaccine 'VSV-ZEBOV-GP'.[97] To assess safety and effectiveness of the vaccine, the EDK team adapted the LSHTM ODK tools to collect follow-up health data from vaccinated individuals. The hybrid system using analogue and digital technology enabled offline collection of follow-up health data for over 260,000 individuals in conflict-affected locations. This system was further developed in 2019 for a Phase III clinical trial of the two-dose EVD vaccine regimen 'Ad26.ZEBOV' and 'MVA-BN-Filo', conducted in collaboration with CEPI,

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[93] Hossmann, S. et al. (2017). Data management of clinical trials during an outbreak of Ebola virus disease. Vaccine. https://doi.org/10.1016/j.vaccine.2017.09.094

[94] https://getodk.org/

[95] The competition provided Official Development Assistance (ODA) funding for the development of epidemiological models, tools and research to assist with the deployment and clinical trialling of vaccines in outbreak situations in LMICs.

[96] World Health Organization (2025). Ebola virus disease – Democratic Republic of the Congo. WHO. Available at: https://www.who.int/emergencies/situations/Ebola-2019-drc- [Accessed 24 Feb 2025].

[97] Ring vaccination is a strategy that involves vaccinating individuals at high risk of exposure and those around them to create a protective 'ring' and contain the spread of a disease

DRC's National Institute of Biomedical Research, Médecins Sans Frontieres and Janssen Pharmaceuticals. To enable and streamline robust data collection, even at vaccination units without internet access, the EDK project team developed biometric cards. Each trial participant received a biometric card that recorded their progress through the trial using an analogue system similar to punch cards. The data was simultaneously digitalised (including offline-capable methods) for reporting and analysis.

Adapting and enhancing data collection tools for epidemic response

In parallel to the support provided during the EVD outbreak, new open-source methods and protocols were created for the LSHTM ODK system, including software for tracing vaccine trial participants using a low-cost USB fingerprint reader device.[98] In collaboration with the UK-funded 'AViD' project[99] the EDK team also developed a toolkit to support social science research during outbreaks, with automated extraction of key themes from text data using emerging natural language processing methods.

In light of the COVID-19 pandemic, project activities and tools were pivoted to support the response in the UK. Analytical tools developed by the EDK team helped to investigate the effectiveness of airport screening in reducing infections. Surveys were conducted in the UK to monitor public experiences with lockdown measures and government trust during the pandemic. In collaboration with the WHO, the EDK team also supported crowd-sourcing data activities to obtain insights about local and regional non-clinical interventions to combat the pandemic.

The EDK project led to 24 peer-reviewed articles and open-source software for the LSHTM ODK system, including biometrics solutions[100], optical mark recognition for paper surveys[101] and geofencing GPS data[102]. Throughout the project, the EDK team conducted several activities to disseminate knowledge and engage stakeholders. They developed training resources, which contributed to a community-driven WHO toolkit to investigate outbreaks[103] and to informal training with global health agencies. Workshops and other educational activities were delivered to engage external agencies; for example, LSHTM co-hosted an outbreak analytics workshop at the Wellcome Trust with 150 delegates from public health organisations, such as the Nigeria Center for Disease Control.[104]

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[98] Roberts, C. & Stott, C. (2021). LSHTM-ORK/ODK_Biometrics. Github [Data Collection]. Available at: https://github.com/LSHTM-ORK/ODK_Biometrics

[99] The AViD project (Anthropological exploration of facilitators and barriers to vaccine deployment and administration during disease outbreaks) was led by LSHTM as part of the NIHR's Epidemiology for Vaccinology competition

[100] Roberts, C. H. (2020). ODK Biometrics. Github. Available at: https://github.com/LSHTM-ORK/ODK_Biometrics [Accessed 24 Feb 2025]

[101] Roberts, C. H. (2021a). OMR LSHTM. Github. Available at: https://github.com/chrissyhroberts/OMR_LSHTM [Accessed 24 Feb 2025]

[102] Roberts, C. H. (2021b). ODK Geofencing. Github. Available at: https://github.com/chrissyhroberts/ODK_Geofencing [Accessed 24 Feb 2025].

[103] World Health Organization (2025). Outbreak Toolkit. WHO. Available at: https://www.who.int/emergencies/outbreak-toolkit [Accessed 24 Feb 2025].

[104] EMPHNET (2019). EMPHNET Participates in Workshop on Data collection and Analytics in Humanitarian Health Emergencies and Outbreaks. Available at https://emphnet.net/en/resources/news/2019/emphnet-participates-in-workshop-on-data-collection-and-analytics-in-humanitarian-health-emergencies-and-outbreaks/ [Accessed 24 Feb 2025].

Building research capacity through open-source innovation

The EDK project expanded and enhanced the LSHTM ODK system's functionality, as well as generated key findings during the EVD outbreak and the COVID-19 pandemic. Peer-reviewed publications resulting from the project have accumulated over 1,000 citations, indicating strong uptake by the research community. Software and methodological developments for the ODK system are available as open-source resources. These resources provide reliable electronic data collection capabilities beyond global health, as the ODK system is used in various sectors, including farming and energy. While it's not possible to ascertain the exact number of ODK users benefiting from the open-source resources developed by the EDK team, improvements to the ODK system as a whole are likely to result in tangible benefits for many of its 2m annual users worldwide.[105] The software for tracing vaccine trial participants using fingerprints can also contribute to electoral voting, with several countries introducing biometrics in elections.[106]

The EDK project played a key role in fostering a critical mass of experts in electronic data collection, epidemiology and public health research. The project team provided support, training and service access to users of the LSHTM ODK system at universities, non-governmental organisations and government agencies. The methods and protocols for using the ODK tools have been incorporated into LSHTM's postgraduate programmes, with over 1,000 researchers receiving training to use them. Around 400 projects have benefited from the developed tools, of which approximately 300 received one-to-one support and advice from the EDK team. As LSHTM maintains a leading position in global health research and provides education to international postgraduate students from over 150 countries - with many graduates working in public health agencies - the outcomes of the EDK project are expected to continue advancing data science knowledge in public health worldwide.[107]

Strengthening vaccine trials and outbreak response

The innovative solutions developed in the EDK project supported vaccine trials and improved government coordination in emergency response efforts, resulting in substantial health impact for LMICs.[108] The Ebola vaccine VSV-ZEBOV-GP was administered to approximately 300,000 individuals during the DRC Ebola epidemic, and the EDK project played an important role in facilitating this effort. Analysis of the vaccine's effectiveness suggests it provides strong protection against EVD, likely preventing deaths in the DRC and neighbouring countries.[109,110]

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[105] ODK website (2025). Available at https://getodk.org/ [Accessed 24 Feb 2025].

[106] International Institute for Democracy and Electoral Assistance (2017). Introducing biometric technology in elections. IDEA. Available at: https://www.idea.int/sites/default/files/publications/introducing-biometric-technology-in-elections-reissue.pdf [Accessed 24 Feb 2025]. See also https://www.aratek.co/news/how-biometrics-is-becoming-a-norm-of-elections-in-africa

[107] LSHTM (2022). LSHTM financial statement 2021/22. Available at https://www.lshtm.ac.uk/files/financial-statement-2021-22.pdf [Accessed 24 Feb 2025].

[108] Marks M et al., (2021). Electronic data management for vaccine trials in low resource settings: Upgrades, scalability and impact of ODK. Available at https://www.medrxiv.org/content/10.1101/2021.02.08.20191908v1.full.pdf [Accessed 24 Feb 2025].

[109] Coulborn R. et al., (2024). Case fatality risk among individuals vaccinated with rVSVΔG-ZEBOV-GP: a retrospective cohort analysis of patients with confirmed Ebola virus disease in the Democratic Republic of the Congo. *The Lancet Infectious Diseases,* Volume 24, Issue 6, 602 - 610

[110] World Health Organization (2019). Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: An example

By removing the need to process over 15 million paper records of vaccination data during the EVD outbreak, the EDK team made it possible to track trial participants' health over time in an active emergency in a conflict-affected region, a task that would have otherwise been near-unfeasible. This outcome supported the assessment of safety and effectiveness of the VSV-ZEBOV-GP vaccine, ultimately leading to licensing of the first-ever EVD vaccine. The hybrid data collection system also supported further safety trials of the two-dose EVD vaccine regimen 'Ad26.ZEBOV-MVA-BN-Filo'. Both vaccines are recommended by WHO's Strategic Advisory Group of Experts on Immunization for use in different scenarios, including a 2021 recommendation to stockpile 500,000 doses of the VSV-ZEBOV-GP vaccine to prepare for outbreaks.[111]

During the COVID-19 pandemic, analytical tools developed by the EDK project supported the UK government's response to the COVID-19 pandemic, helping to understand the effectiveness of public health countermeasures and the number of cases based on reported deaths. Project team members provided input as experts in the UK's Scientific Advisory Group for Emergencies (SAGE) during the COVID-19 pandemic.[112] In addition, collaboration with the WHO during the EDK project to identify non-clinical interventions to for COVID-19 resulted in the creation of a global database of public health and social measures.[113] Led by Dr. Chris Grundy, this work received funding from the WHO[114].

Challenges and lessons learned

The EDK project successfully adapted its initial objectives to support two public health emergencies of international concern. A key enabler to this success was the use of an agile approach to develop the software and tools for the ODK system. The project also benefited from over 40 researchers from LSHTM's network worldwide. They provided informal contributions to support the rapid development of the ODK tools for the EVD outbreak. In addition, the NIHR supported the EDK team by promptly assessing and approving necessary project changes, enabling the project to adapt in response to the health emergencies. While the project achieved its objectives, the COVID-19 pandemic posed challenges to maintain field work in LMICs. The project team had to redirect its focus to the UK response to the crisis, and a few activities including publication of findings are still being finalised.

The EDK project directly contributed to all five outcomes of the UKVN's Theory of Change, in particular (1) Protocols and processes for trialling outbreak vaccines; and (2) New technologies to accelerate vaccine responses to an unknown pathogen; and (3) UK R&D community is ready and able to support future health emergencies. The project demonstrated impact by

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of integration of research into epidemic response. WHO. Available at: https://www.who.int/publications/m/item/preliminary-results-on-the-efficacy-of-rvsv-zebov-gp-ebola-vaccine-using-the-strategy-in-the-control-of-an-ebola-outbreak [Accessed 24 Feb 2025].

[111] World Health Organization (2024). Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: Conclusions and recommendations. WHO. Available at: https://iris.who.int/bitstream/handle/10665/378109/WER9927-355-362.pdf?sequence=1 [Accessed 24 Feb 2025].

[112] Gov.uk (2022). List of participants of SAGE and related sub-groups. Gov.uk. Available at: https://www.gov.uk/government/publications/scientific-advisory-group-for-emergencies-sage-coronavirus-covid-19-response-membership/list-of-participants-of-sage-and-related-sub-groups [Accessed 24 Feb 2025].

[113] World Health Organization (202). WHO Public Health and Social Measures Initiative. WHO. Available at: https://www.who.int/initiatives/who-public-health-and-social-measures-initiative [Accessed 24 Feb 2025].

[114] London School of Hygiene & Tropical Medicine (2020). LSHTM awarded over £2.5m in new grants to tackle COVID-19 pandemic. LSHTM. Available at: https://www.lshtm.ac.uk/newsevents/news/2020/lshtm-awarded-over-ps25m-new-grants-tackle-covid-19-pandemic [Accessed 24 Feb 2025].

playing a pivotal role in controlling the EVD 2018 outbreak, and tools and knowledge gained through the project are likely to contribute to rapid and effective responses to future outbreaks.

UKVN funding provided stability to researchers to develop the tools and support health crisis responses. Given the competitive nature of research funding for development of methods and tools, UKVN funding was essential to enable the testing and the improvement of critical systems to respond to emergency settings.

A key lesson from the EDK project is the missed opportunity to leverage its findings in the UK government's response to the COVID-19 pandemic. The systems developed to register and track vaccine trial participants during the EVD outbreak could have been quickly adapted at the onset of the pandemic to understand disease transmission early on. This highlights the need to improve the communication of UKVN project findings to policymakers, towards more effective adoption of solutions.

Conclusion

Work to improve methods, train researchers and maintain the network of LSHTM ODK users has continued unfunded due to the challenging landscape post COVID-19 pandemic. Further improvements to the LSHTM ODK system to maximise its use in outbreaks and global health research more widely will require long-term funding. Despite this, the tools created by the EDK team have been pivoted for other projects. For example, the COVID-19 Surveillance Intensification in Ghana Network is an international collaboration coordinated by LSHTM and funded by the European Union. The network benefited from the tools developed in the EDK project to strengthen surveillance for COVID-19 and support response in Ghana.[115]

[115] LSHTM (2025). COVID-19 Surveillance Intensification Ghana Network. Available at https://www.lshtm.ac.uk/research/centres-projects-groups/csign [Accessed 24 Feb 2025].

2.6 Anthropological exploration of facilitators and barriers to vaccine deployment and administration during diseases outbreaks

Summary

Vaccine hesitancy presents a critical challenge to the effective deployment of vaccines during disease outbreaks. Despite global recognition of its importance, vaccine hesitancy remains insufficiently understood in low- and middle-income countries (LMICs), and is frequently attributed to ignorance, overlooking valid concerns and local contexts.

A £747,000 grant from the UKVN enabled researchers from the London School of Hygiene and Tropical Medicine and project partners to implement the 'AViD' project: an Anthropological exploration of facilitators and barriers to vaccine deployment and administration during diseases outbreaks. AViD investigated the social and cultural dimensions of vaccine hesitancy in six LMICs, employing a multi-case study approach co-designed with local researchers to ensure community engagement.

The AViD project generated evidence on how local beliefs, past experiences with health systems, and wider political or religious factors shape vaccine acceptance. Its findings were applied in real time during the COVID-19 pandemic in Sierra Leone to inform vaccination strategies. Outputs include peer-reviewed publications and training materials, which have informed policy discussions and contributed to capacity building in low- and middle income countries.

The sociopolitical factors of vaccine hesitancy during outbreaks

Infectious diseases pose a major burden on health of individuals worldwide[116], with low- and middle-income countries (LMICs) disproportionately affected due to weak health systems and limited access to sanitation and clean water.[117] In LMICs, outbreaks of highly infectious diseases like Ebola can lead to thousands of deaths and significant health and economic impact on vulnerable communities.[118] During outbreaks, a key challenge in administering vaccines is vaccine hesitancy, which occurs when individuals delay or refuse vaccination due to concerns about safety or necessity.[119] While global attitudes towards vaccines are generally positive[120], the World Health Organization (WHO) identified vaccine hesitancy in 2019 as one of the top ten threats to global health due to its negative impact on immunisation rates.[121]

Vaccine hesitancy is often incorrectly attributed to public ignorance rather than potential legitimate concerns about vaccine safety or efficacy[122]. Consequently, humanitarian responses to disease outbreaks in LMICs may not fully consider the political, religious, social,

[116] Naghavi, Mohsen et al. (2024). Global burden associated with 85 pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Infectious Diseases, Volume 24, Issue 8, 868 - 895

[117] WHO (2018). WHO's work in emergencies: prepare, prevent, detect and respond: annual report 2018. Available at https://iris.who.int/handle/10665/312267 [Accessed 25 February 2025]

[118] UNDP (2016). Socio-Economic Impact of the Ebola Virus Disease in West Africa. Available at https://www.undp.org/africa/publications/socio-economic-impact-ebola-virus-disease-west-africa [Accessed 25 February 2025]

[119] Dubé, E., Laberge, C., Guay, M., Bramadat, P., Roy, R. and Bettinger, J.A., 2013. Vaccine hesitancy: an overview. Human vaccines & immunotherapeutics, 9(8), pp.1763-1773. DOI: https://doi.org/10.4161/hv.24657

[120] Wellcome (2018). Wellcome Global Monitor 2018. Available at https://wellcome.org/reports/wellcome-global-monitor/2018/summary-key-findings#Attitudes [Accessed 25 February 2025]

[121] WHO (2019). Ten threats to global health in 2019. Available at https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 [Accessed 25 February 2025]

[122] Vanderslott, S., Enria, L., Bowmer, A., Kamara, A. and Lees, S., 2022. Attributing public ignorance in vaccination narratives. *Social Science & Medicine*, *307*, p.115152. DOI: https://doi.org/10.1016/j.socscimed.2022.115152

and cultural factors influencing vaccine acceptance.[123] While anthropological research has explored these factors in various contexts[124,125], vaccine hesitancy remains understudied in LMICs[126]. There are significant knowledge gaps in understanding vaccine hesitancy during outbreaks in the context of local health system and community experiences with vaccines. Thus, further research is needed to identify the complex web of factors that facilitate or hinder vaccination during disease outbreaks.

Anthropological insights into vaccine acceptance during health emergencies

The project 'Anthropological exploration of facilitators and barriers to vaccine deployment and administration during diseases outbreaks' (AViD) aimed to investigate the actions that can be taken to optimise vaccine acceptance in LMICs. It was led by the London School of Hygiene and Tropical Medicine (LSHTM) and received approximately £747k in funding from the UK Vaccine Network 1.0 via the NIHR's 'Epidemiology for Vaccinology' funding competition. It ran from April 2018 to March 2022.[127]

The overarching objective of AViD was to explore the political, economic, health system, and community factors influencing vaccine development and deployment, particularly during disease outbreaks. The project team was led by Prof. Shelley Lees and co-applicants from the LSHTM with expertise in anthropology and public health. Alongside the LSHTM, the AViD team included researchers from two research groups (the Humanitarian Crises Centre and the Vaccine Confidence Project), the research company Anthrologica and the University of Oxford. Anthrologica contributed with expertise in applied anthropology for global health and facilitated communication with policymakers and researchers in LMICs. The University of Oxford team, through the Oxford Vaccine Group, contributed with expertise in vaccine hesitancy and offered strategic guidance, serving as the project's steering committee.

Investigating vaccine deployment through multi-country case studies

The AViD project implemented a multiple-case study approach in six LMICs, using interviews, document analysis, participant observation and other social sciences methods. This approach allowed the team to investigate the broader vaccine deployment 'ecosystem' and different factors influencing vaccine acceptance in LMICs. All six case studies were developed in parallel by researchers from the AViD project team, with significant inputs from sub-contracted local researchers in each country. Local researchers co-designed and conducted data collection activities, and provided input to analyses and write-up of findings. Each case study produced specific findings, which are summarised in Table 2 by topic area.

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[123] Bhatt, A., Monk, V., Bhatti, A., Eiden, A.L., Hermany, L., Hansen, N., Connolly, M.P., Baxter, L., Vanderslott, S., Mitrovich, R. and Slater, R., 2024. Identifying factors that can be used to assess a country's readiness to deploy a new vaccine or improve uptake of an underutilised vaccine: a scoping review. *BMJ open*, *14*(5), p.e080370

[124] Stellmach, M. et al (2018). Anthropology in public health emergencies: what is anthropology good for? *BMJ Global Health 2018;3:e000534.*

[125] Wilkinson A, Fairhead J. (2016). Comparison of social resistance to Ebola response in Sierra Leone and Guinea suggests explanations lie in political configurations not culture. *Crit Public Health 1;27(1):14-27. doi: 10.1080/09581596.2016.1252034*.

[126] Simas, C., Larson, H.J. (2021). Overcoming vaccine hesitancy in low-income and middle-income regions. *Nat Rev Dis Primers 7, 41* https://doi.org/10.1038/s41572-021-00279-w

[127] The competition provided Official Development Assistance (ODA) funding for the development of epidemiological models, tools and research to assist with the deployment and clinical trialling of vaccines in outbreak situations in LMICs.

Table 2 Overview of AViD case studies

Case study number, title and country (lead)	Case study high-level findings
Policy-Level and Health System Factors	
1. The Political and Economic Factors Influencing Vaccine Deployment (Sierra Leone) (Led by Dr Luisa Enria)	Identified several factors influencing vaccine development, such as the overemphasis on 'community resistance' while underplaying other challenges (e.g. lack of cold chain infrastructure)
2. Responses of Healthcare Systems to Vaccine Controversies (India) (Led by Dr Sam Vanderslott)	Identified lack of literacy, misinformation and other factors negatively impacting vaccination in India
Local Knowledge and Perspectives of Vaccines	
3. Local knowledge Construction Surrounding Vaccines (Uganda) (Led by Dr Alex Bowmer)	Identified a link between negative experiences with livestock vaccination and hesitancy towards human vaccination
4. Impact of Zika Outbreak in Public Trust, Vaccine Confidence and Hesitancy (Brazil) (Led by Dr Clarissa Simas)	Identified key factors for improving maternal vaccine acceptance, such as use communication campaign and vaccination cards/booklets
Emergency deployment in practice	
5. Anthropological exploration of the roll out of the Ebola Vaccine (DRC) (Led by Anthropologica and Dr Lys Alcayna-Stevens)	Identified correlation between general vaccine hesitancy and hesitancy around the Ebola vaccine deployed during the 2018 outbreak in DRC
6. Ethnography study of the roll out of COVID-19 vaccines (Tanzania) (Led by Prof Shelley Lees and Mark Marchant)	Identified rumours, beliefs and perceptions about the safety and efficacy of COVID-19, such as decreased fertility and other adverse events.

A learning exercise was conducted with AViD project team members by Mark Marchant and Theresa Jones, via internal interviews, to obtain cross-case study insights. This approach provided four key insights on the added value of qualitative methods in vaccine deployment:

- To get beyond dominant narratives, such as blaming low vaccination rates to 'ignorant' communities
- To engage marginalised groups to understand their perspectives
- To adapt new methods to conduct research, such as virtual platforms to conduct interviews and analysis of social media content
- To acknowledge issues of positionality and power in research, and emphasise the importance of enabling inputs from LMICs in the design of research methods

The AViD project resulted in eight peer-reviewed articles, two blogs, one book chapter and one podcast about vaccine attitudes and deployment.[128,129,130]. Due to the COVID-19 pandemic, some research findings are still being published. In addition, the team developed three briefing documents to support healthcare providers, policymakers and industry actors to understand the role of social sciences in emergency settings.[131] Overall, the AViD project helped to move the narrative of vaccine hesitancy away from 'ignorant publics', informing policy makers about the social, political, and economic factors that influence vaccine uptake.

Community engagement as core practice

Community engagement (CE) was embedded throughout AViD case studies as both a methodological and ethical commitment.[132] While strategies were tailored to each case study's context and research aims, all case studies sought to establish reciprocal relationships with participants, local researchers or health actors. CE activities were not limited to dissemination but included collaborative design of research tools, community-led feedback sessions, and capacity building workshops. For example, in Sierra Leone, AViD researchers worked closely with the District Health Management Team to ensure that study goals aligned with their priorities. In Uganda, the AViD team partnered with community-based organisations to co-develop referral pathways and reimbursement strategies that were meaningful in context. In the DRC, the project prioritised returning to communities to share and discuss findings, creating spaces for reflection and dialogue, and learning from this was included in research outputs. Embedding CE across the project also fostered collective reflexivity among researchers, prompting deeper attention to power dynamics, accountability, and ethics to learn from each other how to meaningfully include community members and local actors to shape research findings and interpretation.[133]

Responding to the COVID-19 pandemic

Due to the COVID-19 pandemic, case study 1 was adapted by rapidly incorporating research on vaccine confidence and public trust factors affecting vaccine deployment. This flexible approach enabled collection of data to support COVID-19 response strategies in real-time. Emerging insights from this activity were shared with the Kambia District Health Medical Team in Sierra Leone via telephone calls, as well as presented in meetings.[134]

Case study 6 was developed in response to the COVID-19 pandemic, to examine vaccine hesitancy in Tanzania. Community health workers (CHW) were trained in social science

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[128] Sonar Global (2021). Learning from the social science of vaccine deployment and administration. Available at https://sonar-global.eu/podcast/learning-from-the-social-science-of-vaccine-deployment-and-administration/ [Accessed 25 February 2025].

[129] SSHAP (2021). What can social science research teach us about COVID-19 vaccine deployment? Available at https://www.socialscienceinaction.org/blogs-and-news/what-can-social-science-research-teach-us-about-covid-19-vaccine-deployment/ [Accessed 25 February 2025].

[130] SSHAP (2021). What can we learn from attitudes towards veterinary vaccination in southern Uganda? Available at https://www.socialscienceinaction.org/blogs-and-news/what-can-we-learn-from-attitudes-towards-veterinary-vaccination-in-southern-uganda/ [Accessed 25 February 2025].

[131] SSHAP (2020). Social science research for vaccine deployment in epidemic outbreaks. Available at Social science research for vaccine deployment in epidemic outbreaks - Social Science in Humanitarian Action Platform [Accessed 25 February 2025].

[132] Personal communication, Prof. Shelley Lees. 4 March 2025.

[133] Personal communication, Prof. Shelley Lees. 4 March 2025.

[134] Jones, T., et al. (2022). Changing gear: Experiences of how existing qualitative research can adapt to an unfolding health emergency. *Front Sociol. 2022 Oct 28;7:958861.* doi: 10.3389/fsoc.2022.958861

research methods to collect data on factors contributing to vaccine hesitancy, such as fears about vaccine safety. The AViD team shared key findings, recommendations, and CHW training materials with Tanzania's Ministry of Health Department of Risk Coordination and Community Engagement, to support COVID-19 vaccination policies.

The importance of social sciences in vaccine deployment

Insights from the AViD project contributed to global health discussions and provided evidence to policymakers about the importance of social sciences in vaccine deployment.

The project's rapid adaptation during the COVID-19 pandemic highlighted the critical role of qualitative research in understanding social dynamics during vaccine deployment. In Sierra Leone, data on community perceptions about the COVID-19 vaccine helped to adjust vaccination strategies in real-time. In Tanzania, data on vaccine hesitancy informed the development of the newly established public health structure to respond to the COVID-19 crisis. Although it is not possible to directly attribute improved vaccine uptake to AViD research activities, evidence suggests that incorporating community engagement in vaccine communication campaigns can improve vaccination coverage.[135] Thus, AViD insights on community factors influencing vaccine acceptance during the COVID-19 pandemic may have contributed to increased vaccination rates in both countries.

Findings from case study 3 on the intersection of animal and human vaccines included a study on the acceptability of the ChAdOx1 RVF vaccine for Rift Valley Fever. The study found that 45% of surveyed farmers were unwilling to receive the vaccine due to safety concerns (n = 96). These findings highlight the need for targeted engagement strategies to improve vaccine acceptance. The results were presented to the One Health Commission and Uganda's Ministry of Health to support future One Health vaccination policies.

Strengthening local research capacity for outbreak response

The AViD project contributed to new collaborations and capacity building in LMICs. Local researchers from NGOs, universities and research centres in Brazil, Sierra Leone, Tanzania and Uganda contributed to the study by coordinating and conducting data collection activities. The project team produced training materials for researchers to apply qualitative research methods during vaccine deployment. Training courses and workshops in community listening and vaccine misinformation were conducted to upskill approximately 100 CHWs in Sierra Leone, Tanzania and Uganda.[136] AViD team members also presented to the WHO and the UK's Department for Health and Social Care on the topics of vaccine confidence and communication strategies for global epidemics.[137]

Challenges and lessons learned

Local researchers played a key role in enabling successful data collection activities in Brazil, Sierra Leone, Tanzania and Uganda. Their understanding of local cultures, languages, and ethical considerations helped to build trust with local populations, facilitating the implementation of research activities. This local expertise was embedded in the research design, contributing to the strength of AViD's project findings.

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[135] Ekezie, W., et al (2024). Vaccination Communication Strategies and Uptake in Africa: A Systematic Review. *Vaccines 2024, 12(12), 1333*; https://doi.org/10.3390/vaccines12121333

[136] Personal communication, Prof. Shelley Lees. 4 March 2025.

[137] Project final report

Collaboration across several initiatives was an important enabler of the AViD project, helping to build an extensive knowledge base on vaccination strategy in diverse settings and contexts. For example, AViD team members collaborated with other UKVN funded projects, such as project 'EDK', which provided electronic data collection tools to support research activities in the DRC. AViD researchers were also involved in projects related to epidemic preparedness, such as the multidisciplinary network for epidemics response in sub-Saharan Africa (ALERRT)[138] and the vaccine trial projects to assess novel vaccines against Ebola (EBOVAC).

The primary challenge faced by the project was the COVID-19 pandemic, which caused delays to data collection activities. In Brazil, all interviews had to be conducted online due to lockdown and distancing measures. In addition, the pandemic shifted policy priorities, as researchers and policy focussed on mitigation strategies. These challenges led to delays, which were addressed through a one-year project extension.

The UKVN provided a unique opportunity to investigate the complex factors influencing vaccination uptake during disease outbreaks. In 2018, funding for social science research on vaccine hesitancy during outbreaks was extremely limited, and competition for grants remains high.[139] In addition, the UVKN and its delivery partner, NIHR, facilitated the adaptation of the AViD project, ensuring flexibility to work on the Ebola 2018 outbreak and later providing additional funding and a one-year extension in response to the COVID-19 pandemic.

Conclusion

A deeper and more comprehensive understanding of social factors that impact vaccine uptake in emergency settings supports more effective vaccination strategies. As such, the AViD project findings have the potential to continue to inform policy and contribute to future responses to outbreaks.

Following the completion of the AViD project, the team planned additional research projects using a multiple-case study approach to investigate factors impacting vaccine acceptance in different contexts and locations. However, they were unable to secure further funding for these activities.[140]

[138] EDCTP (2018). Accelerating research in emergency situations. Available at https://publications.edctp.org/international-partnerships-against-infectious-diseases/aleert [Accessed 25 February 2025].

[139] Personal communication, Prof. Shelley Lees. 4 March 2025.

[140] Personal communication, Prof. Shelley Lees. 4 March 2025.

2.7 Vaccine Efficacy Evaluation for Priority Emerging Diseases

Summary

Many emerging diseases still lack licensed vaccines, and the unpredictable nature of outbreaks poses substantial challenges for designing and implementing vaccine trials. The 'Vaccine Efficacy Evaluation for Priority Emerging Diseases' (VEEPED) project addressed this issue by developing mathematical models to support vaccine trial design and inform outbreak response strategies for seven of the UKVN's priority pathogens.

A £1.5 million UKVN grant enabled researchers from the London School of Hygiene and Tropical Medicine and project partners - Imperial College London, University of Warwick and University of Oxford -, to produce data-driven models to simulate disease transmission and evaluate vaccination strategies. These models supported assessment of the rVSV-ZEBOV vaccine, contributing to its eventual licensing as the first approved Ebola vaccine, and informed World Health Organisation policy recommendations for its deployment.

The project highlighted the importance of tailoring vaccination strategies based on disease characteristics and transmission pathways. It showed that One Health approaches – considering both human and animal health – can be particularly effective. For example, in the case of Rift Valley Fever, vaccination livestock was found to reduce transmission more effectively than vaccinating people. For low-prevalence diseases such as MERS-CoV and Marburg virus, the research showed that targeting healthcare workers and other high-risk groups is more efficient than mass vaccination.

VEEPED generated over 30 peer reviewed publications and contributed valuable insights to international efforts during the COVID-19 pandemic.

Modelling epidemics to inform vaccine trials and deployment

Infectious diseases outbreaks pose a significant health and economic burden on low-and middle-income countries (LMICs). The 2014 Ebola outbreak in West Africa resulted in over 11,000 deaths and estimated economic loss exceeding $50bn.[141] Vaccination is crucial to combat infectious diseases, but many pathogens in the UK Vaccine Network (UKVN)'s priority list[142] lack a licensed vaccine. For a vaccine to be licensed, evidence on its effectiveness must be obtained in clinical trials during outbreaks. However, as outbreaks are unpredictable and must be controlled quickly, the design and conduct of vaccine trials is challenging. In addition, effective vaccine deployment during outbreaks relies on epidemiological data. However, collection and interpretation of this data during outbreaks is constrained by inadequate surveillance systems, insufficient laboratory capacity and other infrastructure limitations.

Mathematical models can help to address these challenges. These models simulate disease outbreaks, predict how epidemics might evolve and assess the potential impact of vaccine strategies.[143] This can inform the design of clinical trials, support disease surveillance and inform vaccination programmes. In 2018, there were gaps in mathematical models for UK Vaccine Network (UKVN) priority pathogens. Better statistical methods were needed to understand drivers of outbreaks, such as how diseases spread in different environments and contexts.

[141] Caroline Huber, Lyn Finelli, Warren Stevens (2018). The Economic and Social Burden of the 2014 Ebola Outbreak in West Africa. The Journal of Infectious Diseases, Volume 218, Issue Supplement_5, 15 December 2018, Pages S698–S704

[142] Gov.uk (2025). UK Vaccines Network. Gov.uk. Available at: https://www.gov.uk/government/groups/uk-vaccines-network [Accessed 6 Mar 2025]

[143] A Camacho et al. (2017). Real-time dynamic modelling for the design of a cluster-randomized phase 3 Ebola vaccine trial in Sierra Leone. Vaccine, Volume 35, Issue 4, 544-551.

Addressing these gaps is essential for vaccine development and optimal vaccination strategies.

Developing data-driven mathematical models for UKVN priority pathogens

The 'Vaccine Efficacy Evaluation for Priority Emerging Diseases' (VEEPED) project aimed to develop data-driven mathematical models for seven of the twelve UKVN priority pathogens to inform the design of clinical trials and vaccination strategies during outbreaks. Running from April 2018 to March 2022, the project was led by the London School of Hygiene and Tropical Medicine (LSHTM) and received approximately £1.5m in funding from the UKVN 1.0 via the NIHR's 'Epidemiology for Vaccinology' funding competition.[144] VEEPED was led by Prof. John Edmunds at the LSHTM in partnership with Imperial College London, University of Warwick and University of Oxford. Researchers in the teams included leading UK epidemiologists who were also part of the WHO R&D Blueprint team and the UK Vaccine Network.

VEEPED research partners selected seven pathogens based on availability of epidemiological data. The project developed transmission models for each pathogen and assessed vaccination strategies to mitigate the impact of outbreaks. Each partner university worked on selected pathogens: LSHTM worked on models for Ebola, Marburg, Crimean–Congo Haemorrhagic Fever (CCHF) and Rift Valley Fever; Imperial College London worked on models for MERS-COV and Lassa Fever; and the University of Warwick worked on a model for Plague. The University of Oxford contributed with identification of target product profiles, epidemiology reviews and model integration with regulatory and logistical considerations. In 2019, the Nigeria Centre for Disease Control and Prevention (NCDC) joined VEEPED as a formal partner and contributed to data collection for the Lassa Fever model.

Understanding transmission to inform vaccine trials and vaccination strategies

Initial project activities consisted of reviewing available epidemiological data and assessing potential trial designs. Subsequently, project activities focused on incorporating and simulating the identified epidemiological parameters into new mathematical models for each disease. Parameters included transmission rates and routes, secondary infections, interventions effects and several others. As part of the project, NCDC supported data analysis of geographical drivers and climate-related dynamics of Lassa Fever in Nigeria.

The models developed by VEEPED contributed to new knowledge for responding to future Ebola outbreaks. Identification of high-risk areas using data from the Ebola 2018-20 outbreak in the Democratic Republic of the Congo (DRC) provided insights into the importance of combining expert opinion with mathematical forecasting when responding to outbreaks.[145] Importantly, the VEEPED project contributed to the safety and effectiveness study of the rVSV-ZEBOV Ebola vaccine[146], which later became the first licensed vaccine for Ebola. Other project

[144] The competition provided Official Development Assistance (ODA) funding for the development of epidemiological models, tools and research to assist with the deployment and clinical trialling of vaccines in outbreak situations in LMICs.

[145] Munday, J. D. et al (2024). Forecasting the spatial spread of an Ebola epidemic in real-time: comparing predictions of mathematical models and experts. https://doi.org/10.1101/2024.03.14.24304285

[146] Watson, C.H., et al (2024). rVSV-ZEBOV vaccination in people with pre-existing immunity to Ebolavirus: an open-label safety and immunogenicity study in Guinean communities affected by Ebola virus disease (l'essai proches). BMC Medicine 22(1).

findings included analysis of the risks of vaccinating pregnant women during Ebola outbreaks and analysis of the impact of vaccinating healthcare workers in Sierra Leone against Ebola.[147]

Informing One Health approaches for tackling infectious diseases

A key finding of the VEEPED project was highlighting the value of One Health approaches to tackling infectious diseases, in which human and animal health interventions are coordinated to reduce the transmission of diseases. In the case of Rift Valley Fever, the project demonstrated that livestock vaccination is more likely to control infections than human vaccination[148]. For CCHF, the project demonstrated that targeting high-risk human groups, such as farmers, is likely more effective than focusing on livestock vaccination.[149]

Optimising vaccination for low-prevalence diseases

Certain infectious diseases, such as Marburg virus and MERS-COV, tend to cause outbreaks with relatively few cases. This makes it challenging for public health authorities to decide whether widespread vaccination is necessary or if a more targeted approach for high-risk groups would be more effective. The VEEPED project demonstrated that implementing combined vaccination approaches, including ring and target vaccination of high-risk groups, is more likely to reduce the impact of Marburg virus outbreaks[150]. For MERS-CoV, project findings highlighted the importance of vaccinating healthcare workers during outbreaks.[151]

Understanding the geographical and environmental factors of outbreaks

Predicting disease outbreaks greatly improves the deployment of interventions to stop the spread of infections. However, mathematical models to predict outbreaks rely on understanding the drivers of infectious diseases. Work conducted by the VEEPED project team identified the geographical and climate factors influencing the incidence of Lassa Fever in Nigeria.[152] Similarly, work conducted by the project team identified factors influencing Plague outbreaks in India, such as humidity levels.[153]

Supporting global response to COVID-19

The VEEPED project enabled team members to contribute to international efforts during the COVID-19 pandemic. Statistical methods were adapted and further developed to understand transmissions, vaccine deployment and impact on healthcare systems. For example, methods

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[147] Jendrossek, M., et al (2019). Health care worker vaccination against Ebola: Vaccine acceptance and employment duration in Sierra Leone. Vaccine, 37(8), 1101–1108.

[148] Métras, R et al (2020). Estimation of Rift Valley fever virus spillover to humans during the Mayotte 2018–2019 epidemic. Proceedings of the National Academy of Sciences, 117(39), 24567–24574

[149] Vesga, J.F., et al (2022). Transmission dynamics and vaccination strategies for Crimean-Congo haemorrhagic fever virus in Afghanistan: A modelling study. PLOS Neglected Tropical Diseases, 16(5), pp.e0010454–e0010454.

[150] Qian, G., et al (2022). Modelling Vaccination Strategies for the Control of Marburg Virus Disease Outbreaks. medRxiv

[151] Laydon, D.J., et al (2023). Impact of proactive and reactive vaccination strategies for health-care workers against MERS-CoV: a mathematical modelling study. 11(5), pp.e759–e769.

[152] Redding, D.W., et al (2021). Geographical drivers and climate-linked dynamics of Lassa fever in Nigeria. Nature Communications, [online] 12(1), p.5759.

[153] Tennant, W.S.D., Tildesley, M.J., Spencer, S.E.F. and Keeling, M.J. (2020). Climate drivers of plague epidemiology in British India, 1898–1949. Proceedings of the Royal Society B: Biological Sciences, 287(1928), p.20200538.

for analysing the ring vaccination approach during the Ebola 2018-20 DRC outbreak were further developed into a standalone R package to support COVID-19 contact tracing. Overall, COVID-19 work conducted by the VEEPED project team contributed to over 60 scientific publications.

Disseminating knowledge and supporting other research projects

The findings of the VEEPED project were published in over 30 peer-reviewed articles covering vaccine efficacy, trial design and disease transmission. These publications included the new mathematical models and associated computer code for use by researchers and public health organisations. In addition to publications, the NCDC delivered a two-week intensive data analysis course and a three-day workshop to upskill health professionals in Nigeria involved in Lassa Fever surveillance activities.

The VEEPED project team also supported other research projects. In collaboration with the UKVN-funded project AViD, the VEEPED project team helped to identify factors leading to vaccine hesitancy in Tanzania.[154] Understanding these factors can support the design of more effective vaccination strategies.

Advancing mathematical modelling for epidemic preparedness

The UKVN catalysed research on mathematical models for infectious diseases with epidemic potential. VEEPED was the first project to bring together research expertise from three leading epidemiological modelling groups in the UK (LSHTM, Imperial College London and University of Warwick). Some of the publications stemming from VEEPED have been cited more than 1000 times, indicating broad interest and uptake. The project findings have the potential to inform future vaccination strategies for UKVN priority pathogens, ultimately improving responses to outbreaks.

Before UKVN investments in epidemiology for vaccinology, the funding landscape in this area was very limited. The success of VEEPED contributed to the recognition that mathematical models play an important role in mitigating outbreaks. Recognising this, the Coalition for Epidemic Preparedness Innovations (CEPI) has since started to invest in epidemiology research.[155] In 2024, CEPI awarded $2.4m to University of Oxford to model vaccine trials for Nipah, Chikungunya, Lassa, Rift Valley fever, Ebola and Coronaviruses.[156] This work builds on VEEPED findings to optimise vaccination strategies.

Informing global vaccination policies

VEEPED project findings contributed to better understanding of the dynamics of Ebola outbreaks, vaccine effectiveness and vaccination strategies. The assessment of the rVSV-ZEBOV Ebola vaccine and the identified risks of vaccinating pregnant women during Ebola outbreaks have contributed to the current WHO policy recommendations for Ebola

[154] The AViD project (Anthropological exploration of facilitators and barriers to vaccine deployment and administration during disease outbreaks) was led by LSHTM as part of the NIHR's Epidemiology for Vaccinology competition

[155] CEPI (2023). CEPI-funded project to enhance scientific understanding of deadly Nipah virus strains. CEPI. Available at: https://cepi.net/cepi-funded-project-enhance-scientific-understanding-deadly-nipah-virus-strains [Accessed 6 Mar 2025].

[156] CEPI (2024). University of Oxford pandemic computer simulations to guide future vaccine trials. CEPI. Available at https://cepi.net/university-oxford-pandemic-computer-simulations-guide-future-vaccine-trials [Accessed 6 Mar 2025].

vaccination.[157] These recommendations inform vaccination strategies in the context of outbreaks, suggest preventive actions and vaccine stockpiling.

During the COVID-19 pandemic, the VEEPED project team collaborated closely to support the UK's crisis response, particularly through contributions to the Scientific Pandemic Influenza Group on Modelling, a sub-group of SAGE.[158] This work benefited from the methods developed within the VEEPED project. Findings were disseminated internationally, contributing to WHO policy documents on COVID-19 immunisation.[159,160]

Challenges and lessons learnt

The VEEPED project enabled collaboration between leading UK experts in mathematical models for epidemiology, strengthening the UK's capabilities to support outbreak response. The project benefitted from the informal networks of team members, as well as from their membership in the WHO R&D Blueprint team and other global health organisations. This network helped to bring awareness of VEEPED project findings.

The COVID-19 pandemic posed a substantial challenge for the VEEPED project, as it required team members to prioritise UK and international response to the health emergency. This shift in priorities slowed down research activities and publication of research findings. Knowledge dissemination events, such as a final project meeting with partners, could not be held. In addition to the pandemic, the project was affected by timing constraints due to insufficient time for staff recruitment between award date and project start date. This effectively reduced the project duration from 3 to 2.5 years, adding pressure on teams.

A key barrier to future impact is the lack of sustained research funding opportunities, which are essential for job security, safeguarding knowledge and fostering research progress. While the funding landscape for epidemiology research has improved in recent years, the field remains vulnerable to losing critical capabilities due to lack of sustained funding opportunities.[161]

Conclusion

Since the conclusion of the VEEPED project, researchers have continued to build on project findings by developing mathematical models for other UKVN priority pathogens, including Chikungunya and Nipah Virus. Ongoing studies, supported by SCARDA - a vaccine research consortium funded by the Japanese Agency for Medical Research and Development – are investigating the transmission dynamics of these viruses.[162,163]

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[157] WHO (2024). Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations. WHO. Available at: https://cdn.who.int/media/docs/default-source/immunization/sage/2024/may/sage-ebola-report-final-draft.pdf?sfvrsn=325acc6_1 [Accessed 6 Mar 2025].

[158] https://www.gov.uk/government/organisations/scientific-advisory-group-for-emergencies

[159] WHO (2023). Immunization Analysis and Insights, COVID-19 Vaccine Effectiveness. WHO. Available at: https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/covid-19-vaccine-effectiveness-and-impact [Accessed 6 Mar 2025].

[160] Survey response from project partners.

[161] Personal communication, Prof John Edmunds. 20 February 2025.

[162] Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response

[163] Kang, H., et al (2024). Chikungunya seroprevalence, force of infection, and prevalence of chronic disability after infection in endemic and epidemic settings: a systematic review, meta-analysis, and modelling study. Lancet Infect Dis 24: 488–503

The VEEPED project highlighted the importance of mathematical models in mitigating outbreaks. Project findings contributed to international policy on vaccination for emerging diseases and supported response to the COVID-19 pandemic. Further dissemination of project findings to international and national policymakers will be important to maximise future impact.

2.8 Advanced development of a safe and effective Rift Valley Fever vaccine for livestock

Summary

Rift Valley Fever (RVF) is a viral disease caused by the Rift Valley Fever Virus (RVFV), mainly transmitted to humans and livestock by mosquitoes. RVF leads to high fatality rates (up to 90%) in young livestock and abortion in pregnant animals. Besides economic losses to farmers, outbreaks in animals are linked to the disease spreading to humans

A £2.36 million UKVN grant enabled researchers from the Pirbright Institute, led by Prof George Warimwe, the University of Oxford, and Kenyan partners - the International Livestock Research Institute (ILRI) and the KEMRI-Wellcome Trust Research Programme (KWTRP) -, to advance development of the ChAdOx1-RVF vaccine candidate for use in livestock. Preclinical studies had already demonstrated that a single dose of the ChAdOx1 RVF vaccine candidate provided 100% protection against RVFV in mice, sheep, goats, and cattle.

After producing the vaccine to GMP standards, the team showed that a reduced dose of ChAdOx1-RVF still protected animals from RVF, was safe in pregnant livestock and, in a 700-animal Kenyan field trial, triggered stronger immune responses than the only currently licensed livestock vaccine against RVFV, the Smithburn vaccine.

The project strengthened Kenyan research capacity through training for conducting field trials in compliance with veterinary Good Clinical Practice (vGCP) standards. This catalysed investments in both personnel and infrastructure, enhancing the institute's ability to conduct further livestock vaccine studies in the future. At the same time, ILRI and KWTRP played a key role in the trial delivery, including sourcing trial animals, overseeing daily operations, and trial monitoring. Proactive communication with the local regulator was essential to the study: Because Kenya classified the viral-vector vaccine as a Genetically Modified Organism (GMO) under plant-oriented rules, the vaccine trial was the first to fit into this framework, requiring close coordination between the researchers and national regulators.

The team is currently improving the manufacturing process to bring costs down to veterinary-vaccine levels, and engaging with animal-health companies and Kenyan regulators to secure local licensing.

Rift Valley Fever: a threat to livestock and human health

Rift Valley Fever (RVF) is a viral illness caused by Rift Valley Fever Virus (RVFV), which is transmitted to humans and livestock – primarily sheep, goats and cattle – by various mosquito species. The first outbreak of RVF occurred in the Rift Valley Province of Kenya in 1931[164]. Since then, RVFV has spread across Africa and the Middle East, raising concerns about further disease transmission and outbreaks[165].

RVFV results in high fatality rates (up to 90%) in young livestock and abortion in pregnant animals[166]. The virus typically spreads and amplifies in animals before causing human outbreaks, with transmission occurring through mosquito bites or contact with contaminated

[164] Daubney R, Hudson JR, Garnham PC. Enzootic hepatitis or Rift Valley fever: an undescribed virus disease of sheep, cattle and man from East Africa. Journal of Pathology and Bacteriology. 1931;34:545–579

[165] Linthicum KJ, Britch SC, Anyamba A. Rift Valley Fever: An Emerging Mosquito-Borne Disease. Annu Rev Entomol. 2016;61:395-415. doi:10.1146/annurev-ento-010715-023819

[166] Bird B.H., Ksiazek T.G., Nichol S.T., Maclachlan N.J. Rift Valley fever virus. J. Am. Vet. Med. Assoc. 2009;234:883–893. doi: 10.2460/javma.234.7.883.

tissues and fluids. The clinical manifestation of RVFV in humans can range from mild illness to severe haemorrhagic syndrome, which can have fatality rates of up to 50%[167,168].

The potential impact of a future RVF outbreak on human health and economic production, combined with the lack of effective countermeasures, has led the World Health Organisation (WHO) to classify RVFV as a priority pathogen for vaccine research and development[169]. Currently, there are no licensed vaccines or antiviral drugs available to prevent or treat RVF in humans. Furthermore, existing livestock vaccines are not suitable for large-scale rollout due to multi-dose regimens or limited effectiveness[170].

Prior to receiving a grant from the UK Vaccine Network (UKVN), researchers at the Jenner Institute at the University of Oxford had begun developing a vaccine against RVFV using the ChAdOx1 platform. The ChAdOx1 viral vector delivers genetic material encoding proteins specific to the pathogen, which trigger an immune response without causing disease[171]. The group had already developed several vaccine candidates using this platform, including against malaria, influenza, and tuberculosis[172].

Preclinical studies conducted by the Oxford group demonstrated that a single dose of the ChAdOx1 RVF vaccine candidate provided 100% protection against Rift Valley fever virus (RVFV) challenge in mice, sheep, goats, and cattle[173,174]. The immune response elicited by this vaccine was comparable to that of the Smithburn vaccine – the most widely used RVFV vaccine for livestock in Africa. Notably, ChAdOx1 RVF is compatible with commonly available DIVA (Differentiating Infected from Vaccinated Animals) diagnostic kits, which are essential for effective disease surveillance and control during outbreaks.

Combined with its strong safety profile and ability to induce robust neutralising antibody responses, ChAdOx1 RVF is a promising vaccine to be progressed in livestock trials.

Developing a livestock vaccine for Rift Valley Fever

The project titled 'Advanced development of a safe and effective Rift Valley Fever vaccine for livestock' received £2.3m in funding from the UKVN via NIHR's NETSCC competition for development of vaccine candidates, between 2016 and 2021.[175] The primary objective was to manufacture the ChAdOx1 RVF vaccine candidate according to Good Manufacturing Practice (GMP) standards and assess its safety and efficacy in providing protection against

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[167] World Health Organization. Rift valley fever. World Health Organization. Published December 15, 2022. Available here. (Accessed February 24, 2025)

[168] Madani TA, Al-Mazrou YY, Al-Jeffri MH, et al. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. Clin Infect Dis. 2003;37(8):1084-1092. doi:10.1086/378747

[169] Mehand MS, Al-Shorbaji F, Millett P, et al. The WHO R&D Blueprint: 2018 review of emerging infectious diseases requiring urgent research and development efforts. Antiviral Res 2018; 159:63–7.

[170] Faburay B, LaBeaud AD, McVey DS, Wilson WC, Richt JA. Current Status of Rift Valley Fever Vaccine Development. Vaccines (Basel). 2017;5(3):29. Published 2017 Sep 19. doi:10.3390/vaccines5030029

[171] Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One. 2012;7(7):e40385. doi:10.1371/journal.pone.0040385

[172] Hill A. Development of the ChAdOx vaccine platform. The Jenner Institute. Published February 24, 2025. Available here. (Accessed February 24, 2025)

[173] Warimwe GM, Lorenzo G, Lopez-Gil E, et al. Immunogenicity and efficacy of a chimpanzee adenovirus-vectored Rift Valley fever vaccine in mice. *Virol J*. 2013;10:349. Published 2013 Dec 5. doi:10.1186/1743-422X-10-349

[174] Warimwe GM, Gesharisha J, Carr BV, et al. Chimpanzee Adenovirus Vaccine Provides Multispecies Protection against Rift Valley Fever. Sci Rep. 2016;6:20617. Published 2016 Feb 5. doi:10.1038/srep20617

[175] NETSCC refers to NIHR Evaluation, Trials and Studies Coordinating Centre

RVFV in pregnant sheep, goats, cattle, and camels. This is a critical concern, as many existing vaccines can induce abortions in pregnant animals. Additionally, the project aimed to compare the safety and immunogenicity of the ChAdOx1 RVF vaccine candidate with those of the licensed Smithburn RVF vaccine.

The project was led by Professor George Warimwe at the Pirbright Institute in the UK, with co-principal investigators Professor Bryan Charleston, also from the Pirbright Institute, and Professor Sir Adrian Hill from the Jenner Institute at the University of Oxford. Additionally, the project involved two collaborations with two organisations located in Kenya: the International Livestock Research Institute (ILRI) and the KEMRI-Wellcome Trust Research Programme (KWTRP). Prof Warimwe has seen firsthand the serious impact of RVF in LMICs, including the fear and losses it can cause in affected communities. As he explained:

"There's a strong personal connection to this work for me. I was born and raised in Kenya. Rift Valley Fever (RVF) has always been a disease I grew up hearing about. My grandparents kept animals, so I was always aware of the constant threat it posed. Unlike many other livestock diseases, RVF stood out due the devastating losses it causes. That's why I choose to tackle RVF and it turned out to be one of the priority pathogens listed by the UK Vaccine Network "

Generating robust data through international trials and manufacturing success

The project team at the University of Oxford was successful in manufacturing the ChAdOx1 RVF vaccine, including a clinical GMP batch through a contract with Advaxia Biologics (formerly Advent), Italy. The researchers then conducted a series of trials to assess the safety and efficacy of the vaccine across different species and settings:

- At The Pirbright Institute in the UK, a vaccine dose optimisation study evaluated how reduced doses of the ChAdOx1 RVF vaccine performed in sheep and cattle. The findings confirmed that reduced doses still produced strong immune responses. This has important implications for vaccine production and deployment - using lower doses can reduce manufacturing costs and allow more animals to be vaccinated per batch, enhancing the feasibility and impact of large-scale vaccination efforts.
- In the Netherlands, the research team partnered with a Dr. Jeroen Kortekaas and Dr. Paul Schreur at Wageningen Bioveterinary Research Institute, Lelystad, to assess the safety, immunogenicity, and efficacy of the ChAdOx1 RVF vaccine in pregnant sheep and goats. The vaccine was found to be safe and provided strong protection against RVF disease and foetal loss. The study's findings were published in *NPJ Vaccines*[176].
- In Kenya, a large-scale field trial – the largest of its kind in Africa (around 700 animals) – was conducted at ILRI and evaluated immune responses in sheep, goats, cattle, and camels vaccinated with either the ChAdOx1 RVF or the Smithburn vaccine. Preliminary data indicates that ChAdOx1 RVF is well tolerated across all species tested and elicits an immune response in a larger proportion of animals than the Smithburn vaccine[177].

In parallel, with funding from the International Veterinary Vaccinology Network, the researchers evaluated the stability of the ChAdOx1 RVF vaccine under varying storage conditions. The vaccine remained stable and retained its immunogenic properties for extended periods when stored at standard refrigeration temperatures (2–8 °C). Importantly, it also demonstrated potential to remain stable at elevated ambient temperatures, depending on the dose and

[176] Stedman A, Wright D, Wichgers Schreur PJ, et al. Safety and efficacy of ChAdOx1 RVF vaccine against Rift Valley fever in pregnant sheep and goats. NPJ Vaccines. 2019;4:44. Published 2019 Oct 18. doi:10.1038/s41541-019-0138-0

[177] Project final report

duration of storage – an encouraging finding for vaccine deployment in countries with limited refrigeration infrastructure.

Additionally, as the vaccine is classified as a genetically modified organism (GMO), a critical regulatory requirement was to confirm the absence of residual viral vaccine in animals post-vaccination. The researchers demonstrated that the vaccine was not detectable in the animals' blood or tissues, which will enable regulatory authorities to approve their return to the food chain. The finding also sets a positive precedent for future GMO vaccine trials and will contribute to shaping biosafety protocols in Kenya.

Building local capacity and enabling future livestock vaccine development

The promising safety and immunogenicity data from the ChAdOx1 RVF trials have de-risked its further development and brought the vaccine candidate closer to regulatory approval across multiple livestock species.

In addition, the project contributed to building vaccine research capacity in Kenya. Staff at the ILRI in Nairobi received extensive training on conducting field trials in compliance with veterinary Good Clinical Practice (vGCP) standards. This catalysed investments in both personnel and infrastructure, enhancing the institute's ability to conduct further livestock vaccine studies in the future. Furthermore, the project supported a PhD student from The Pirbright Institute to relocate to ILRI, fostering knowledge exchange and aiding the development of trial protocols.

Challenges and lessons learnt

The success of the project was largely driven by the pivotal roles played by ILRI and KWTRP, which were crucial due to their in-country presence and local expertise. These institutes were in a unique position to implement the trials effectively because of their established connections and deep knowledge of the Kenyan context—something that the Pirbright Institute would not have been able to achieve without their support. ILRI was instrumental in the clinical trial implementation, including sourcing trial animals, overseeing daily operations, and processing samples. KWTRP contributed by leading the monitoring of the trial, managing sample storage, and conducting laboratory assays.

Reliance agreements between ILRI and KWTRP significantly streamlined the ethical and regulatory approval process. The ILRI and KWTRP formally agreed to recognise ILRI's animal care and use committee (IACUC) for the review and oversight of the livestock trial. Additional approval was obtained from the Pirbright Institute's Animal Welfare and Ethical Review Body (AWERB), ensuring compliance with both Kenyan and UK regulatory requirements.

Additionally, proactive science communication and relationship-building with government regulators were essential to securing approval for this first-of-its-kind field trial. The trial team helped build regulatory confidence by clearly explaining the study design, conducting thorough risk assessments, and implementing mitigation strategies (e.g. fitting GPS collars on animals).

The project also encountered challenges:

- *Manufacturing setback*: A critical issue during GMP manufacturing, caused by repeated nucleotide sequences, led to truncated antigens that compromised the vaccine's genetic stability. This required a complete redesign and re-manufacturing, causing significant delays but ultimately leading to improved design practices for future vaccines.

- *Procurement delays*: Delays in securing consumables and reagents, due to customs and permit issues in Kenya, resulted in some items taking over six months to arrive. Collaboration between partner institutes (ILRI, KWTRP) helped prevent last-minute shortages by enabling the sharing of consumables across sites.
- *Trial delays*: Recruitment of camels to the field study in Kenya was hindered by COVID-19 restrictions, making it necessary to split recruitment into two separate periods, which delayed the trial. Despite efforts, it was difficult to secure a sufficient number of camels for the trial.
- *GMO regulatory hurdles*: As a viral-vectored vaccine, ChAdOx1 RVF was classified as a GMO in Kenya. This marked the first veterinary GMO vaccine field trial overseen by the Kenyan National Biosafety Authority (NBA), which had traditionally focussed on plant GMOs. The existing regulatory frameworks were not well-suited to vaccine trials, requiring extensive coordination between the research team, the NBA and the Kenyan Directorate of Veterinary Services (DVS). As part of the approval process, the NBA and the DVS had to accompany vaccine shipments from the airport to the trial site and be present during vaccinations.

Conclusion

The next key step is to secure a commercial partner to support the continued development and deployment of the ChAdOx1 RVF vaccine. The Pirbright Institute and the University of Oxford are currently optimising the vaccine's manufacturing process for veterinary commercialisation. The manufacturing approach used for the UKVN-funded study - originally developed for human applications - lacks the cost-effectiveness and scalability needed for veterinary applications. Optimisation of the process is key to attracting commercial partners and enabling large-scale production.

Regulatory authorities in Kenya, engaged through this project, have expressed strong support for the vaccine's local approval. Looking ahead, future plans include exploring the potential for co-administering ChAdOx1 RVF with other routine livestock vaccines.

2.9 Phase I studies of a novel chimpanzee adenovirus MERS

Summary

Middle East Respiratory Syndrome (MERS) is caused by the MERS coronavirus (MERS-CoV), primarily transmitted to humans through contact with infected camels[178]. MERS can lead to acute respiratory distress and death in the most severe cases. Human cases have been reported across the Middle East, Africa, and South Asia, with 943 deaths from 2021 to 2024[179,180].

A £2.05 million UKVN grant enabled researchers at the University of Oxford, led by Prof Sarah Gilbert, and partners at King Abdullah International Medical Research Centre (KAIMRC), Saudi Arabia, to advance a viral-vectored vaccine against MERS-CoV for human use, ChAdOx1-MERS.

The team manufactured the vaccine candidate to GMP standard and showed that a single dose was safe, well tolerated and immunogenic in Phase I trials in the UK and Saudi Arabia. Given the similarities between the MERS-CoV and SARS-CoV-2 viruses, knowledge gained from this research contributed to the rapid development of the Oxford-AstraZeneca Covid-19 vaccine in 2020. For example, the ChAdOx1 MERS Phase I dose studies informed early dose selection for the ChAdOx1 Covid-19 vaccine, streamlining the path to clinical trials.

Funded by CEPI, the University of Oxford team are currently conducting a Phase I trial of ChAdOx1-MERS, focussing on efficacy of the vaccine in older adults.[181] An additional US$34.8 million were provided by CEPI to conduct a Phase II trial of the vaccine candidate in the Middle East.[182] If the trial results are positive, CEPI will provide further funding to create a reserve of 100,000 doses for rapid deployment in future MERS outbreaks, as well as facilitate technology transfer to a regional manufacturer to supply LMICs.

MERS: a deadly respiratory virus with epidemic potential

Middle East respiratory syndrome (MERS) is a viral illness caused by MERS coronavirus (MERS-CoV), which belongs to the same family as the virus responsible for COVID-19. The World Health Organization (WHO) recognised MERS as an emerging pathogen that could trigger an outbreak and has listed it as a priority infectious disease that requires urgent research for vaccine development.[183]

MERS-CoV is a zoonotic virus primarily transmitted to humans from infected camels. It can also be spread from human to human, particularly in hospital settings.[184] The clinical manifestation of MERS-CoV infection in humans can range from asymptomatic cases to severe infections and death. Since the identification of MERS-CoV in Saudi Arabia in 2012, the virus has become endemic in camels in the region and human cases have occurred in several countries in the

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[178] Killerby ME, Biggs HM, Midgley CM, Gerber SI, Watson JT. Middle East Respiratory Syndrome Coronavirus Transmission. Emerg Infect Dis. 2020;26(2):191-198. doi:10.3201/eid2602.190697

[179] Zaki, A.M., Van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D. and Fouchier, R.A., 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *New England Journal of Medicine*, *367*(19), pp.1814-1820

[180] World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). World Health Organization website. Published December 2019. Available here. (Accessed February 14, 2025)

[181] Oxford Vaccine Group. First vaccine trial in older people launched for Middle East Respiratory Syndrome (MERS). Oxford Vaccine Group. Published November 17, 2021. Available here. (Accessed February 14, 2025).

[182] https://cepi.net/new-partnership-aims-advance-vaccine-against-mers-coronavirus

183 Mehand MS, Al-Shorbaji F, Millett P, et al. The WHO R&D Blueprint: 2018 review of emerging infectious diseases requiring urgent research and development efforts. *Antiviral Res.* 2018;159:63–67.

184 Killerby ME, Biggs HM, Midgley CM, Gerber SI, Watson JT. Middle East Respiratory Syndrome Coronavirus transmission. *Emerg Infect Dis.* 2020;26(2):191–198. doi:10.3201/eid2602.190697.

Middle East, Africa, and South Asia.[185, 186] From 2012 to 2024, a total of 2,613 laboratory-confirmed cases of MERS were reported globally, resulting in 943 deaths and a case-fatality rate (CFR) of 36%.[187] The largest reported MERS outbreak occurred in South Korea in 2015, originating from a single traveller returning from the Middle East. This outbreak led to 186 cases, 38 deaths, and the quarantine of 16,993 individuals for 14 days to control transmission.[188] The outbreak is estimated to have caused a reduction of 2.1m non-citizen visitors, resulting in a loss of $2.6b in tourism revenue for South Korea.[189] Currently, there are no licensed vaccines or antiviral drugs available for prevention or treatment of MERS-CoV in humans or animals.

Prior to receiving a grant from the UK Vaccine Network (UKVN), researchers at the Jenner Institute at the University of Oxford had begun developing a vaccine against MERS-CoV using the ChAdOx1 platform. This platform consists of a viral vector which delivers genetic material encoding proteins specific to the pathogen and triggers an immune response without causing disease.[190] The group had already developed vaccine candidates using the ChAdOx1 platform, including against malaria, influenza, and tuberculosis.[191] In preclinical studies, the ChAdOx1 MERS-CoV vaccine candidate had triggered a strong immune response and protection against lethal viral challenge in animal models, supporting the vaccine candidate's progression into clinical trials.[192,193]

Enabling rapid clinical development of a novel vaccine

The project titled 'Phase I Studies of a Novel Chimpanzee Adenovirus MERS Vaccine' was funded between 2016 and 2021 by a £2.05 million grant from the UKVN via NIHR's NETSCC competition for development of vaccine candidates, with co-funding of $1.1 million from the Coalition for Epidemic Preparedness Innovations (CEPI). The project aimed to manufacture the ChAdOx1 MERS vaccine to Good Manufacturing Practice (GMP) standards and evaluate its safety and immunogenicity, initially in a small Phase I trial in the UK, followed by a Phase I study in the Kingdom of Saudi Arabia (KSA). The UK study was expected to provide clinical data more quickly, facilitating the approval process for the subsequent study in KSA, where MERS is most common. The project was led by Professor Sarah Gilbert from the Jenner Institute at the University of Oxford, with co-principal investigators Professor Adrian Hill (also from the Jenner

185 Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367(19):1814–1820.

186 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). World Health Organization website. Published December 2019. Available at <https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)>. (Accessed February 14, 2025)

187 World Health Organization Regional Office for the Eastern Mediterranean. MERS outbreaks. World Health Organization Regional Office for the Eastern Mediterranean website. Published December 2021. Available here. (Accessed February 14, 2025)

188 Oh MD, Park WB, Park SW, et al. Middle East respiratory syndrome: what we learned from the 2015 outbreak in the Republic of Korea. *Korean J Intern Med.* 2018;33(2):233–246. doi:10.3904/kjim.2018.031.

189 Joo H, Maskery BA, Berro AD, Rotz LD, Lee YK, Brown CM. Economic impact of the 2015 MERS outbreak on the Republic of Korea's tourism-related industries. *Health Secur.* 2019;17(2):100–108. doi:10.1089/hs.2018.0115.

190 Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. *PLoS One.* 2012;7(7):e40385. doi:10.1371/journal.pone.0040385.

191 Hill A. Development of the ChAdOx vaccine platform. The Jenner Institute. Published February 24, 2025. Available here. (Accessed February 24, 2025)

192 Munster VJ, Wells D, Lambe T, et al. Protective efficacy of a novel simian adenovirus vaccine against lethal MERS-CoV challenge in a transgenic human DPP4 mouse model. *NPJ Vaccines.* 2017;2:28. Published 2017 Oct 16. doi:10.1038/s41541-017-0029-1.

193 Alharbi NK, Qasim I, Almasoud A, et al. Humoral immunogenicity and efficacy of a single dose of ChAdOx1 MERS vaccine candidate in dromedary camels. *Sci Rep.* 2019;9(1):16292. Published 2019 Nov 8. doi:10.1038/s41598-019-52730-4.

Institute) and Dr. Giorgio Napolitani (MRC Human Immunology Unit, University of Oxford), in collaboration with the King Abdullah International Medical Research Centre (KAIMRC) in KSA.

First-in-human clinical trial in UK and Saudi Arabia

The research team at Oxford successfully manufactured ChAdOx1 MERS vaccine to GMP standards at the Clinical Biomanufacturing Facility in Oxford using standard methods previously developed for the first ChAdOx1-vectored vaccine.

From March to August 2018, 24 participants were enrolled to a dose-escalation Phase I trial (MERS001) at the Centre for Clinical Vaccinology and Tropical Medicine in Oxford, UK.[194] Participants were given a low, intermediate, or high dose of the vaccine candidate. The ChAdOx1 MERS vaccine was found to be safe and well tolerated at all tested doses, and a single dose was able to elicit immune responses. The results of this first-in-human clinical trial were published in 2020 in the *Lancet Infectious Diseases*.[195]

Following the UK trial, approval was obtained for a Phase Ib dose-escalation trial (MERS002) in Saudi Arabia. Between December 2019 and June 2020, 24 participants were enrolled and given a low, intermediate or high dose of the vaccine candidate.[196] The trial results showed that a single dose of the ChAdOx1 MERS vaccine was well tolerated in all three dose groups, with no serious adverse events reported during the six months of follow-up. [197]

Follow-on funding for third Phase I trial

The strong safety and immunogenicity data from both Phase I trials supported the continued development of ChAdOx1 MERS vaccine.

Older people are at a higher risk of severe illness and death if infected with MERS virus. Funded by £12m from CEPI, the research team is currently conducting a third Phase I clinical trial to evaluate the ChAdOx1 MERS vaccine in older people.[198] The study is led by the University of Oxford's Vaccine Group in collaboration with the Liverpool School of Tropical Medicine and the NIHR Clinical Research Facility at Royal Liverpool University Hospital. It launched in 2023 with the aim of recruiting 84 participants aged 50 to 70, and is now approaching completion. In addition to assessing the safety and immune response, the study also examines if the

194 U.S. National Library of Medicine. A study to evaluate the safety and immunogenicity of MERS-CoV vaccine in healthy adults (NCT03399578). ClinicalTrials.gov. Published December 11, 2017. Updated February 10, 2021. Available at <https://clinicaltrials.gov/study/NCT03399578?cond=MERS&rank=2>. (Accessed February 14, 2025).

195 Folegatti PM, Bittaye M, Flaxman A, et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. *Lancet Infect Dis.* 2020;20(7):816–826. doi:10.1016/S1473-3099(20)30160-2. Published correction appears in *Lancet Infect Dis.* 2020 Jul;20(7):e148. doi:10.1016/S1473-3099(20)30393-5. Published correction appears in *Lancet Infect Dis.* 2020 Jul;20(7):e148. doi:10.1016/S1473-3099(20)30508-9.

196 U.S. National Library of Medicine. A study to evaluate the safety and immunogenicity of MERS-CoV vaccine in healthy adults (NCT04170829). *ClinicalTrials.gov*. Published November 11, 2019. Updated March 1, 2022. Available from: https://clinicaltrials.gov/study/NCT04170829. Accessed February 14, 2025.

197 Bosaeed M, Balkhy HH, Almaziad S, et al. Safety and immunogenicity of ChAdOx1 MERS vaccine candidate in healthy Middle Eastern adults (MERS002): an open-label, non-randomised, dose-escalation, phase 1b trial. *Lancet Microbe*. 2022;3(1):e11–e20. doi:10.1016/S2666-5247(21)00193-2.

198 Oxford Vaccine Group. First vaccine trial in older people launched for Middle East Respiratory Syndrome (MERS). Oxford Vaccine Group. Published November 17, 2021. Available at < https://www.ovg.ox.ac.uk/news/first-vaccine-trial-in-older-people-launched-for-middle-east-respiratory-syndrome-mers#:~:text=The%20trials%20found%20the%20vaccine,two%20doses%20of%20the%20vaccine.>. (Accessed February 14, 2025).

immunogenicity of the MERS vaccine is affected by prior vaccination against COVID-19.[199] The study will provide insights into differences between responses in individuals that had received the mRNA or the ChAdOx1 COVID-19 vaccine, how existing COVID-19 antibodies affect the immune response to the MERS vaccine and how different coronavirus spike antibodies interact. Early results suggest that baseline immune responses to MERS-CoV infection have shifted compared to pre-pandemic responses, likely due to prior coronavirus vaccinations and infections.

'This latest Phase I trial of Oxford's MERS vaccine, developed on the ChAdOx1 platform – one of only a few clinically validated rapid-response platforms globally – is of particular importance as the findings will provide critical guidance on how we can better protect vulnerable communities from the health and socioeconomic impact of this deadly pathogen." (Dr Melanie Saville, Executive Director of Vaccine Research & Development at CEPI)[200]

Strengthening Regulatory Relationships and Capacity Building

The project has enabled the research team at the University of Oxford to build strong relationships with the regulatory authority in the KSA, which will support faster implementation of future clinical studies there. Additionally, the project facilitated capacity building by supporting a post-doctoral researcher from KSA to work at the University of Oxford during the first Phase I study. This experience equipped the researcher with expertise and skills to contribute to the subsequent Phase I study in KSA, with continued support from the research team in Oxford.

Accelerating the development of the Oxford-AstraZeneca COVID vaccine

The project played an important role in underpinning the development of the Oxford-AstraZeneca COVID vaccine which also uses the ChAdOx1 platform. The experience gained from developing the ChAdOx1 MERS vaccine accelerated the development of the ChAdOx1 COVID-19 vaccine, given the similarities between these two viruses. The Phase I dosing studies for the ChAdOx1 MERS vaccine informed early dose selection for the ChAdOx1 nCoV-19 vaccine, streamlining the clinical development path. The Oxford-AstraZeneca COVID-19 vaccine is estimated to have saved over 6 million lives worldwide.[201]

"We had a head-start in our development of the Oxford/AstraZeneca COVID-19 vaccine, thanks to the many years already spent researching a vaccine for another coronavirus, MERS (Professor Dame Sarah Gilbert, Pandemic Sciences Institute, University of Oxford)[202]

Challenges and lessons learnt

The co-location and strong track record of the Jenner Institute research labs, the Clinical Biomanufacturing Facility and the Centre for Clinical Vaccinology and Tropical Medicine at the University of Oxford in vaccine manufacturing, development and clinical trials, along with

199 Personal communication, Professor Sarah Gilbert. 19 February 2025.

200 University of Oxford. Oxford and Liverpool scientists launch new vaccine trial for Middle East Respiratory Syndrome (MERS). Published September 18, 2023.. Available at < https://www.ox.ac.uk/news/2023-09-18-oxford-and-liverpool-scientists-launch-new-vaccine-trial-middle-east-respiratory-1 > (Accessed June 13, 2025).

201 Airfinity. AstraZeneca and Pfizer/BioNTech saved over 12 million lives in the first year of vaccination. Jul 12, 2022. Available at < https://www.airfinity.com/articles/astrazeneca-and-pfizer-biontech-saved-over-12-million-lives-in-the-first> (Accessed February 14, 2025).

202 Coalition for Epidemic Preparedness Innovations (CEPI). New partnership aims to advance vaccine against MERS coronavirus. Published December 21, Available at < https://cepi.net/new-partnership-aims-advance-vaccine-against-mers-coronavirus > (2023. Accessed June 13, 2025)

existing collaborations in KSA, were key enabling factors contributing to the success of this project.

Several barriers were encountered during the project's implementation:

- The COVID-19 pandemic resulted in the two-dose extension study to the UK trial being halted, and only three participants received two doses. Despite the limited data, the study provided preliminary (unpublished) evidence suggesting that a second dose could enhance the immune response.
- The Phase I clinical trial in the KSA was originally planned to include a larger number of participants, without the low dose level being used at all. However, the regulator in KSA mandated that the trial design replicate the UK Phase I design, limiting the trial size.
- The regulatory process for the Phase I clinical trial in KSA took considerable time, as it was the first Phase I clinical trial conducted in the country. While causing challenges, the experience is expected to streamline the approval processes for future clinical trials in KSA.

Conclusion

The UKVN-funded Phase I trials demonstrated that the ChAdOx1 MERS vaccine is safe and triggers immune responses in UK as well as KSA populations. Building on these promising findings, CEPI funded a third Phase I trial which is currently nearing completion, and will feed into decisions to take the vaccine candidate forward into a Phase II trial.

Conducting a traditional Phase III efficacy trial in humans is not feasible due to the small number of MERS cases. The plan is therefore to develop the ChAdOx1 MERS vaccine for emergency use authorisation for conditional use approach, which relies on animal studies to demonstrate effectiveness. To navigate this pathway, the research team has been working closely with the European Medicines Agency (EMA), which has granted the vaccine a priority medicine designation (PRIME) and is providing scientific guidance. Through the engagement, the EMA has endorsed an alternative approval strategy that does not require a Phase III trial. Instead, vaccine efficacy can be established using non-human primate studies, while a pivotal Phase II study will assess safety and immune response in a larger trial population in the Middle East[16].

In late 2023, the University of Oxford established a partnership with Barinthus Biotherapeutics, a clinical-stage biopharmaceutical company in Oxfordshire. Funded by CEPI, this partnership will provide Barinthus Biotherapeutics with up to $34.8m for further clinical development of the ChAdOx1 MERS vaccine in Phase II trials.[203] However, Barinthus has since decided to focus on cancer vaccines using a different technology and is no longer involved in the MERS programme. Instead, the new company, Alazid, will take over their role in the development of the vaccine. Depending on the trial results, CEPI will provide additional funding to establish a reserve of 100,000 doses which can be rapidly deployed in the event of a MERS outbreak. Additionally, CEPI will facilitate technology transfer to an appropriate regional manufacturer to enable supply for low- and middle-income countries, with the vaccine priced at no more than the manufacturing cost plus a 10% margin.

203 Coalition for Epidemic Preparedness Innovations. New partnership aims to advance vaccine against MERS coronavirus. CEPI. Published February 10, 2025. Available at <https://cepi.net/new-partnership-aims-advance-vaccine-against-mers-coronavirus>. (Accessed February 14, 2025)

Once licensed, the vaccine can be stockpiled for future MERS outbreaks and deployed strategically. It may also be used to vaccinate travellers, particularly religious pilgrims to Saudi Arabia, who risk exposure to MERS-CoV-infected camels, ultimately helping to reduce disease transmission.

Additionally, work has also commenced with collaborators in KAIMRC to evaluate the ChAdOx1 MERS vaccine in camels. Early results show promising signs that the vaccine partially protects camels from MERS.[204] If successful, this approach could help to reduce potential transmission, particularly for individuals who work in close proximity with camels. Furthermore, licensing the vaccine for use in camels is expected to be easier than for humans, because Phase III trials in humans require large outbreaks, which are difficult to predict.

204 Alharbi NK, Qasim I, Almasoud A, et al. Humoral immunogenicity and efficacy of a single dose of ChAdOx1 MERS vaccine candidate in dromedary camels. *Sci Rep.* 2019;9(1):16292.

2.10 Phase I studies of a novel chimpanzee adenovirus Rift Valley Fever vaccine

Summary

Rift Valley Fever (RVF) is a viral disease caused by the Rift Valley Fever Virus (RVFV), mainly transmitted to humans and livestock by mosquitoes. In humans, RVF symptoms range from mild illness to severe haemorrhagic syndrome, which can have fatality rates of up to 50%.

A £2.18 million UKVN award enabled a team from the University of Oxford, led by Prof Pontiano Kaleebu, and the MRC/UVRI Uganda Research Unit to advance development of the ChAdOx1-RVF vaccine candidate.

After producing ChAdOx1-RVF to GMP standards, the team conducted Phase I trials in the UK and Uganda. The trial results showed that the vaccine was well tolerated and generated immune responses across all dose levels. This promising finding secured a US$3.7 million grant from CEPI to advance development in a Phase II study in Kenya.

Among the challenges encountered by the research team was the insufficient genetic stability of the first vaccine batch, which had to be addressed and caused a delay to the project. However, the setback provided valuable insights, leading to a revised method for incorporating transgenes into the ChAdOx1 vector platform. This improved approach was subsequently used in the development of other vaccine candidates, including the Oxford/AstraZeneca COVID-19 vaccine, and has played an important role in advancing scalable manufacturing of ChAdOx1-vectored vaccines.

Next, the team will complete the Phase II trial in Kenya and, along with supporting non-human-primate work, pursue emergency use authorisation via the "Animal Rule", a pathway designed for diseases that are too sporadic to undergo conventional Phase III trials.

Rift Valey Fever: a zoonotic threat with no human vaccine

Rift Valley Fever (RVF) is a viral illness caused by Rift Valley Fever Virus (RVFV), which is transmitted to humans and livestock – primarily sheep, goats and cattle – by various mosquito species. The first outbreak of RVF occurred in the Rift Valley Province of Kenya in 1931.[205] Since then, RVFV has spread across Africa and the Middle East, raising concerns about further disease transmission and outbreaks.[206]

RVFV leads to high fatality rates (up to 90%) in young livestock and abortion in pregnant animals.[207] The virus typically spreads and amplifies in animals before causing human outbreaks, with transmission occurring through mosquito bites or contact with contaminated tissues and fluids. The clinical manifestation of RVFV in humans can range from mild illness to severe haemorrhagic syndrome, which can have fatality rates of up to 50%.[208,209]

The potential impact of a future RVF outbreak on human health and economic production, combined with the lack of effective countermeasures, has led the World Health Organisation

205 Daubney R, Hudson JR, Garnham PC. Enzootic hepatitis or Rift Valley fever: an undescribed virus disease of sheep, cattle and man from East Africa. *J Pathol Bacteriol.* 1931;34(4):545–579. Published 1931. doi:10.1002/path.1700340418.

206 Linthicum KJ, Britch SC, Anyamba A. Rift Valley fever: an emerging mosquito-borne disease. *Annu Rev Entomol.* 2016;61:395–415. Published 2016 Jan 7. doi:10.1146/annurev-ento-010715-023819.

207 Bird BH, Ksiazek TG, Nichol ST, Maclachlan NJ. Rift Valley fever virus. *J Am Vet Med Assoc.* 2009;234(7):883–893. Published 2009 Apr 1. doi:10.2460/javma.234.7.883.

208 World Health Organization. Rift Valley fever. *World Health Organization.* Published December 15, 2022. Accessed February 24, 2025. https://www.who.int/news-room/fact-sheets/detail/rift-valley-fever

209 Madani TA, Al-Mazrou YY, Al-Jeffri MH, et al. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. *Clin Infect Dis.* 2003;37(8):1084–1092. Published 2003 Oct 15. doi:10.1086/378747.

(WHO) to classify RVFV as a priority pathogen for vaccine research and development.[210] Currently, there are no licensed vaccines or antiviral drugs available to prevent or treat RVF in humans. Furthermore, existing livestock vaccines are not suitable for large-scale rollout due to multi-dose regimens or limited effectiveness.[211]

Prior to receiving a grant from the UK Vaccine Network (UKVN), researchers at the Jenner Institute at the University of Oxford had begun developing a vaccine against RVFV using the ChAdOx1 platform. The ChAdOx1 viral vector delivers genetic material encoding proteins specific to the pathogen, which trigger an immune response without causing disease.[212] The group had already developed vaccines candidates using this platform, including against malaria, influenza, and tuberculosis.[213]

Preclinical studies conducted by the Oxford group had demonstrated that a single dose of the ChAdOx1 RVF vaccine candidate provided 100% protection against RVFV challenge in mice, sheep, goats and cattle.[214,215] Additionally, the immune response triggered by this vaccine candidate was as strong as the response to the Smithburn vaccine, the most widely used livestock RVFV vaccine in Africa. This supported ChAdOx1 RVF's progression to human clinical trials.

Enabling the first human trials of a Rift Valley Fever vaccines

The project titled 'Phase I studies of a novel chimpanzee adenovirus Rift Valley Fever vaccine' was funded by a £2.18 million grant from UKVN via NIHR's NETSCC competition for development of vaccine candidates between 2016 and 2023. The main aim of the project was to manufacture the ChAdOx1 RVF vaccine candidate according to Good Manufacturing Practice (GMP) standards and to evaluate its safety and immunogenicity in Phase I clinical studies in healthy adult volunteers, in the UK and Uganda. The project was led by Professor Pontiano Kaleebu from the MRC/UVRI Research Unit in Uganda, with co-principal investigators Professor Alison Elliott (also from the MRC/UVRI Uganda Research Unit) and Professor Adrian Hill and Dr George Warimwe from the Jenner Institute, University of Oxford.

Phase 1 clinical trials confirm safety and immune response

The ChAdOx1 RVF vaccine was successfully manufactured to GMP standards at the University of Oxford's Clinical Biomanufacturing Facility. Following this, the research team were granted regulatory and ethical approval to conduct a Phase I clinical trial in healthy individuals in the UK.

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210 Mehand MS, Al-Shorbaji F, Millett P, et al. The WHO R&D Blueprint: 2018 review of emerging infectious diseases requiring urgent research and development efforts. *Antiviral Res.* 2018;159:63–67. Published 2018 Apr. doi:10.1016/j.antiviral.2018.09.009.

211 Faburay B, LaBeaud AD, McVey DS, Wilson WC, Richt JA. Current status of Rift Valley fever vaccine development. *Vaccines (Basel)*. 2017;5(3):29. Published 2017 Sep 19. doi:10.3390/vaccines5030029.

212 Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. *PLoS One*. 2012;7(7):e40385. Published 2012 Jul 20. doi:10.1371/journal.pone.0040385.

213 Hill A. Development of the ChAdOx vaccine platform. *The Jenner Institute*. Published February 24, 2025. Accessed February 24, 2025. https://www.jenner.ac.uk/about/the-oxford-astrazeneca-covid-19-vaccine/ChAdOx-platform

214 Warimwe GM, Lorenzo G, Lopez-Gil E, et al. Immunogenicity and efficacy of a chimpanzee adenovirus-vectored Rift Valley fever vaccine in mice. *Virol J.* 2013;10:349. Published 2013 Dec 5. doi:10.1186/1743-422X-10-349.

215 Warimwe GM, Gesharisha J, Carr BV, et al. Chimpanzee adenovirus vaccine provides multispecies protection against Rift Valley fever. *Sci Rep.* 2016;6:20617. Published 2016 Feb 5. doi:10.1038/srep20617.

Between 11th June 2021 and 13th January 2022, 15 participants were enrolled into an open-label, non-randomised, first-in-human Phase I clinical trial (RVF001) at the Centre for Clinical Vaccinology and Tropical Medicine, Oxford, UK.[216] Participants were divided into low, intermediate, and high-dose groups and monitored over a three-month period. The ChAdOx1 RVF vaccine was found to be safe and well tolerated at all tested doses, with a single low dose able to elicit immune responses. The results of this first-in-human clinical trial were published in the *Lancet*.[217]

The results from the Phase I trial in the UK informed the development of protocols and expedited regulatory approval for a Phase Ib trial in Uganda (RVF002), involving 30 participants. The study showed that a single dose of the ChAdOx1 RVF vaccine was well tolerated in all dose groups and elicited immune responses similar to those observed in the UK trial, with no serious adverse events reported during the three-month follow-up period.[218] A manuscript is currently being prepared to publish the trial results.

Towards Phase II clinical trials with CEPI support

The promising safety and immunogenicity data from the UK and Uganda trials of ChAdOx1 RVF provided strong evidence supporting the continued development of the vaccine candidate. Based on the trial data, Dr George Warimwe, co-PI from the research team at the University of Oxford, secured $3.7m in follow-on funding from the Coalition for Epidemic Preparedness Innovations (CEPI) for a Phase II clinical trial in adults in Kenya.[219] The trial will be conducted in collaboration with the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Institute. The team plans to recruit 240 healthy adult trial participants, pending local regulatory approvals, to further evaluate vaccine safety and immunogenicity.

The project also led to training for early-stage researchers. Through the collaboration, a medical student based at the MRC/UVRI Uganda Research Unit was able to work at the University of Oxford and gain hands-on experience of the methodology. The researcher has since advanced to pursue a PhD at the London School of Hygiene and Tropical Medicine in the UK, bringing expertise gained from the project to further research RVF clinical manifestations, immuno-epidemiology and vaccine development in Uganda.

Challenges and lessons learnt

The success of the project builds on the long-standing collaboration between the MRC/UVRI Uganda Research Unit and the University of Oxford.

- **Sharing of knowledge and infrastructure**: The partnership allowed the researchers to pool knowledge and resources, helping to enhance expertise, increase efficiencies and accelerate vaccine development. The University of Oxford's Clinical Biomanufacturing Facility provided critical infrastructure and expertise, enabling the production of the ChAdOx1 RVF vaccine under GMP conditions. The necessary facilities

216 U.S. National Library of Medicine. Safety and immunogenicity of a candidate RVFV vaccine (RVF001). *ClinicalTrials.gov*. Identifier NCT04754776. Updated February 24, 2025. Accessed February 24, 2025. https://clinicaltrials.gov/study/NCT04754776

217 Jenkin D, Wright D, Folegatti PM, et al. Safety and immunogenicity of a ChAdOx1 vaccine against Rift Valley fever in UK adults: an open-label, non-randomised, first-in-human phase 1 clinical trial. *Lancet Infect Dis.* 2023;23(8):956–964. Published 2023 Aug. doi:10.1016/S1473-3099(23)00068-3.

218 Final project report

219 Coalition for Epidemic Preparedness Innovations. Promising human Rift Valley fever vaccine enters phase II clinical trials in Kenya. *Coalition for Epidemic Preparedness Innovations.* Published February 23, 2025. Accessed February 24, 2025. https://cepi.net/promising-human-rift-valley-fever-vaccine-enter-phase-ii-clinical-trials-kenya.

and capabilities would not have been available in Uganda. Furthermore, the researchers at the University of Oxford had access to specialised facilities for testing the effectiveness of the antibodies produced in response to vaccination against RVFV.

- **Strong links to the local community:** The MRC/UVRI Uganda Research Unit has extensive experience in conducting clinical trials in the local setting, which was a key enabling factor in the recruitment of trial participants. The Unit's local links proved particularly important during the COVID-19 pandemic: Misinformation on the risks of blood clots associated with the AstraZeneca COVID-19 vaccine, which is also based on the ChAdOx1 platform, increased vaccine hesitancy in the community and reduced willingness to participate in the ChAdOx1 RVF trial. In response, the team intensified community engagement to explain the level of risks and benefits of the research. This ultimately supported trial recruitment.

The project also encountered challenges that led to delays:

- **Issues with vaccine production**: The team had to re-manufacture a vaccine batch due to insufficient genetic stability of the first batch. While this setback delayed progress, it provided valuable insights that led to a revised method for incorporating transgenes into the ChAdOx1 vector platform. This new approach was later applied to other vaccine programs at Oxford, including the Oxford/AstraZeneca COVID-19 vaccine, contributing to advancements in the scalable manufacturing of ChAdOx1-vectored vaccines.
- **Delays in ethics and regulatory approvals:** With COVID-19 studies taking priority during the pandemic, approvals for the RVF vaccine Phase I trials were delayed. As a result, the trial protocol had to be amended, including reducing the number of participants and shortening the follow-up period to meet grant timelines.

Conclusion

The Phase I trials showed that the ChAdOx1 RVF vaccine is safe and triggers immune responses in humans. A Phase II trial is planned, and if successful, will provide additional data to advance vaccine development. Since a traditional Phase III trial in humans is not feasible due to the low number of RVF cases, the team plans to pursue emergency use authorisation for the ChAdOx1 RVF vaccine through the Animal Rule approach, which uses animal studies to demonstrate efficacy. To support this approach, the researchers will conduct a Phase II trial in non-human primates, using blood from vaccinated healthy volunteers to determine the optimal dose of neutralising antibodies required to provide protection against RVFV (a strategy that enabled licensure of the world's first chikungunya vaccine).[220]

2.11 Supporting vaccine R&D through serological standards and animal models

Summary

Vaccine development for emerging diseases is costly and complex, requiring high-containment facilities and specialised testing. Serological standards - reference materials for measuring immune responses – can reduce costs and complexity by enabling earlier

220 Food & Drug Administration. FDA approves first vaccine to prevent disease caused by Chikungunya virus. *Food & Drug Administration*. 2023. Accessed February 24, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-prevent-disease-caused-chikungunya-virus.

evaluation of vaccine candidates. In 2016, no World Health Organization (WHO) international serological standards existed for any of the UKVN's twelve priority pathogens.

A £2.5 million UKVN grant enabled researchers at the UK's National Institute for Biological Standards and Control – and partners at Public Health England and at the Defence Science and Technology Laboratory -, to accelerate the development of these standards and assess their protective value using animal challenge models.

The 'Serological Vaccine Standards' project supported the establishment of WHO international standards for eight emerging diseases. Standards for Ebola, Rift Valley fever and Zika were directly attributed to the project, while contributions were made to those for MERS, Lassa, Marburg, Nipah and Q fever.

These standards now underpin global vaccine development efforts by ensuring consistent, comparable immune response data across studies and settings, including in low- and middle-income countries. The project also demonstrated, through animal models, that standards for MERS and Chikungunya confer protective immunity, providing correlate of protection for vaccine development. This work supports faster, more reliable vaccine development and facilitates international collaboration and regulatory approval.

Overcoming barriers in vaccine development for emerging diseases

Vaccine development for emerging diseases such as Ebola virus disease is challenged by high costs and operational complexity. Advancing vaccine candidates from preclinical to Phase IIa stage is estimated to cost $319m to $469m.[221] In the preclinical stage, vaccine developers are required to work in high containment facilities (biosafety level three or four), which are expensive and limited in availability. Vaccine development also requires demonstrating vaccine efficacy in animal challenge models, which can be costly and complex involving multiple animal species.[222] Serological standards and pre-validated animal challenge models can be used to reduce the costs and the complexity associated with vaccine research and development (R&D), thereby accelerating progress.

Serological standards play a crucial role in vaccine R&D by assuring the accuracy, consistency, and comparability of immune response measurements across different studies and laboratories. These standards serve as reference materials to calibrate the measurement of immune response induced by different vaccine candidates. Regulatory agencies often require the use of such standards to confirm vaccine performance. Standards are typically developed by one of three national regulatory institutes – the Medicines Healthcare products Regulatory Agency (MHRA) in the UK, Paul Ehrlich Institute (PEI) Germany and Center for Biologics Evaluation and Research (CBER) USA) - in collaboration with the World Health Organization (WHO). Candidate standards are usually prepared from convalescent serum collected from the blood of recovered patients that contain antibodies against the target pathogen. To achieve international standard recognition, researchers conduct international collaborative studies to replicate experiments in many expert laboratories around the world to verify suitability and accuracy of the candidate. The WHO Expert Committee on Biological Standardization (ECBS) then evaluates the results and, if applicable, establishes the reference material as a WHO International Serum Standard.

221 Gouglas D, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *Lancet Global Health*. 2018;6(12):e1386–e1396. (2018) doi:10.1016/S2214-109X(18)30341-7.

222 Kiros TG, Levast B, Auray G, Strom S, van Kessel J, Gerdts V. The importance of animal models in the development of vaccines. In: Baschieri S, editor. *Innovation in Vaccinology*. Springer; 2012. p. 205-221. doi:10.1007/978-94-007-4543-8_11.

In parallel to serological standards, public sector research organisations use their specialist high bio-containment facilities to develop and characterise animal models for vaccine development. During the earlier phases of vaccine R&D, animal models can be used to better understand disease mechanism. They also allow researchers to evaluate whether vaccine candidates or antibody preparations elicit an immune response and confer protection against infection or disease caused by specific pathogens.

Crucially, validated animal models can be used to evaluate the level of antibodies required for protection and support the establishment of a 'correlate of protection' (CoP) – a measurable immune marker in humans, such as an antibody level, that predicts protection from disease (and is quantified using serological standards). In early development, CoPs help assess vaccine efficacy and reduce reliance on large-scale, costly animal studies. For emerging diseases, CoPs are also crucial in advanced clinical trials (Phase III): where traditional efficacy studies may be unfeasible due to the unpredictability and level of outbreaks, CoPs enable regulatory approval based on immune responses. Validated CoPs can thus streamline regulation and reduce trial size, time, and cost.

In 2016, no WHO established international serological standards were available to support the ongoing development of candidate vaccines for any of the 12 UK Vaccine Network (UKVN) priority pathogens.[223]

Accelerating standards development and pre-clinical testing

Recognising this gap, the UKVN-funded the project 'Serological Vaccine Standards for Emerging Diseases', headed by the National Institute for Biological Standards and Control, the global leader in the development of serological standards (NIBSC, now part of the MHRA).[224,225]

Between 2016 and 2022, NIBSC was awarded £2.5m in funding from the UKVN via two Innovate UK's competitive funding calls, to accelerate the development of serological standards and establish whether and how much convalescent serum standard is required to protect in pre-validated animal models for each of the UKVN priority pathogens.[226] Led by Dr. Neil Almond at NIBSC, the project was conducted in partnership with Public Health England (PHE, now UK Health Security Agency) and the Defence Science and Technology Laboratory (DSTL). The overarching aim of the project was to accelerate the development of serological standards to support vaccine R&D for emerging diseases. To achieve this, the project had two objectives:

1. Prepare new serological standards by supporting the sourcing and collection of serum from recovered patients and conduct *in vitro* testing to identify protective antibodies for UKVN priority pathogens
2. Establish whether these new serological standards contained protective antibody through *in vivo* animal testing in pre-validated animal challenge models for UKVN priority pathogens

223 Chikungunya, Crimean-Congo Haemorrhagic Fever, Ebola, Hantavirus, Lassa, Marburg, Middle East Respiratory Syndrome, Nipah, Plague, Q Fever, Rift Valley Fever and Zika

224 MHRA refers to the UK's Medicines and Healthcare products Regulatory Agency

225 UK Government. NIBSC Ebola reference reagents endorsed as global standards by WHO. *UK Government.* Published November 5, 2015. Accessed May 6, 2025. https://www.gov.uk/government/news/nibsc-ebola-reference-reagents-endorsed-as-global-standards-by-who

226 Innovate UK competition 'Development of candidate vaccines and vaccine platform technologies at the preclinical stage (£25m), Stage 1 and Stage 2'

Researchers at the NIBSC conducted the molecular, pathology, serological analyses and interpretation, and were responsible for project management. DSTL and PHE provided access to high containment facilities and conducted laboratory analyses. They also supported collection of convalescent blood samples to prepare suitable standards for the project.

Collecting samples and testing immune responses for UKVN priority pathogens

Between 2016 and 2017, the project team focused on three UKVN priority pathogens: Ebola, Zika and Middle East Respiratory Syndrome (MERS).[227] From 2018 to 2022, the UKVN provided additional funding to enable research on the nine remaining UKVN priority pathogens.[228] As a result of the COVID-19 pandemic, some funds were reprioritised, and ultimately diverted from research on Nipah, Hantavirus and Plague to support the development of challenge models and antibody reference standards for SARS-CoV-2.[229]

The project team successfully supported the collection of blood samples and other relevant materials for nine UKVN priority pathogens: Crimean-Congo Haemorrhagic Fever (CCHF), Ebola, Lassa, Marburg, MERS, Plague, Q Fever, Rift Valley Fever (RVF) and Zika. In addition to *in vitro* testing, the project team conducted *in vivo* animal testing for seven pathogens: Chikungunya, CCHF, Ebola, Lassa, MERS, RVF and Zika. The findings were published in seven articles in peer-reviewed journals, with three further articles in preparation. Team members also disseminated results at international conferences.[230]

WHO international serological standards for UKVN priority pathogens

The collection of blood serum and in-vitro analyses in this project contributed to the development of WHO international serological standards for eight UKVN priority pathogens. For these eight pathogens, serological standards for Ebola (established in 2018)[231], RVF (2023)[232] and Zika (2018)[233] can be directly attributed to the UKVN-funded project. For the other five standards, the UKVN-funded activities made important contributions:

227 UK Research and Innovation. Serological vaccine standards for Ebola, Zika, and MERS-CoV. Accessed 6 May 2025. https://gtr.ukri.org/projects?ref=971527

228 UK Research and Innovation. Serological vaccine standards for emerging diseases. Accessed 6 May 2025. https://gtr.ukri.org/projects?ref=971613

229 Personal communication, Dr. Neil Almond. 26 February 2025.

230 Project final reports and responses to survey conducted in the UKVN evaluation

231 World Health Organization. WHO collaborative study to assess the suitability of the 1st International Standard and the 1st International Reference Panel for antibodies to Ebola virus. *World Health Organization.* 2017. Accessed May 6, 2025. https://www.who.int/publications/m/item/WHO-BS-2017.2316

232 World Health Organization. WHO Expert Committee on Biological Standardization: seventy-seventh report. *World Health Organization.* 2023. Accessed May 6, 2025. https://iris.who.int/bitstream/handle/10665/373128/9789240078116-eng.pdf?sequence=1

233 World Health Organization. WHO Expert Committee on Biological Standardization: Executive Summary of the 69th Meeting. *World Health Organization.* 2018. Accessed 6 May 2025. Available at: https://cdn.who.int/media/docs/default-source/biologicals/ecbs/ecbs_executive_summary_final_20_nov_2018.ik.pdf?sfvrsn=db0ad2b_1&download=true

- Serological standards for MERS (2020)[234] and Lassa (2021)[235] benefitted from the materials collected in the project, but were established mainly via NIBSC business as usual activities
- Serological standards for Marburg (2024), Nipah (2023) and Q fever (2023) also benefitted from the project's activities but were completed with UKVN 2.0 funding obtained in 2023 (follow-on funding outside the project discussed in this case study).

MHRA is continuing the development of a serological standard for Plague under UKVN 2.0. The serological standard for Chikungunya was developed in 2022 by the Paul Ehrlich Institute.[236]

Animal models for early indicators of vaccine protection

Animal challenge models were developed and used to test candidate or established WHO International standards for seven of the 12 UKVN priority pathogens. The outcomes varied for each reference material tested.[237]

For MERS and Chikungunya virus, animal challenge models demonstrated that the serological standards provide protection against these diseases, enabling identification of a correlate of protection for vaccine development.[238] A further outcome for MERS was the development of a small animal model (mice), which opens the door for further research using smaller and less ethically sensitive animal models.[239]

The outcome of studies in other challenge models were less conclusive. Testing of international standard for Zika in different animal models showed different outcomes in each model, raising questions of whether mouse or non-human primate models better reflect the situation in humans and their response to treatment with convalescent serum.[240] Research on CCHF identified differences in donor samples and their ability to protect against disease.[241] For Ebola, the guinea pig challenge model conferred only partial protection against the disease, while data for Lassa and RVFV were inconclusive.[242]

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234 Mattiuzzo G, et al. Establishment of the 1st WHO International Standard for anti-MERS-CoV antibody. *World Health Organization*. 2020. Available at: https://cdn.who.int/media/docs/default-source/biologicals/ecbs/ecbs_executive_summary_final_20_nov_2018.ik.pdf?sfvrsn=db0ad2b_1&download=true

235 Mattiuzzo G et al. Establishment of the first WHO International Standard and Reference Panel for anti-Lassa fever virus antibody. *World Health Organization*. 2021. Available at: https://cdn.who.int/media/docs/default-source/biologicals/call-for-comments/bs.2021.2406_who-1st-is-lassa-fever-virus-antibody.pdf?download=true&sfvrsn=f6f99f5c_5

236 Baylis SA, et al. Collaborative study to evaluate a candidate World Health Organization International Standard for antibodies to Chikungunya virus. *World Health Organization*. 2022. Available at: https://cdn.who.int/media/docs/default-source/biologicals/ecbs/ecbs_executive_summary_final_20_nov_2018.ik.pdf?sfvrsn=db0ad2b_1&download=true

237 Personal communication, Dr. Neil Almond. 26 February 2025.

238 Personal communication, Dr. Neil Almond. 26 February 2025.

239 New RRC, Moore BD, Butcher W, et al. Antibody-mediated protection against MERS-CoV in the murine model. *Vaccine*. 2019;37(30):4094–4102. (2019) doi:10.1016/j.vaccine.2019.05.074.

240 Graham VA et al. Comparison of Chikungunya virus-induced disease progression and pathogenesis in type-I interferon receptor-deficient mice (A129) and two wild-type (129Sv/Ev and C57BL/6) mouse strains. *Viruses*. 2024;16(10):1534. doi:10.3390/v16101534.

241 Kempster S, Hassall M, Graham V, et al. Convalescent human plasma candidate reference materials protect against Crimean-Congo haemorrhagic fever virus (CCHFV) challenge in an A129 mouse model. *Virus Res*. 2024;346:199409. doi:10.1016/j.virusres.2024.199409.

242 Dowall SD, Kempster S, Findlay-Wilson S, et al. Towards quantification of protective antibody responses by passive transfer of the 1st WHO International Standard for Ebola virus antibody in a guinea pig model. *Vaccine*. 2020;38(2):345–349. doi:10.1016/j.vaccine.2019.10.009.

Advancing global vaccine development and reducing preclinical barriers

The establishment of the first WHO international serological standards for eight emerging infectious diseases represents a major advancement for vaccine development worldwide. In 2024, MHRA sold 44,030 units of reference materials for serological standards, highlighting the global demand and impact of these materials on vaccine development.[243] These standards enable researchers to identify promising vaccine candidates earlier, reducing reliance on costly high containment facilities. In addition, once a vaccine is licensed, serological standards provide data on antibody levels, informing booster vaccination strategies and safety of vaccine production.

WHO international serological standards play a key role in supporting multi-centre clinical trials, including those conducted in LMICs. They allow immunogenicity data from different studies to be compared without highly specialised centralised laboratories, which are often limiting in LMICs. This facilitates international comparison of vaccine responses, supporting the development of new vaccines.[244] These standards also streamline regulatory approval processes by aligning vaccines produced in LMIC with internationally accepted benchmarks.

The development and validation of animal challenge models also provide significant benefits for vaccine R&D. Many vaccine candidates fail during human trials despite showing promise in animal studies.[245] By improving the reliability of preclinical testing, these validated models help researcher to assess a vaccine's potential effectiveness, reducing early-stage development costs and increasing likelihood of success in human trials.

Conclusion

The UKVN provided crucial funding to accelerate the development of serological standards and animal challenge models to support vaccine R&D for emerging diseases.

MHRA was awarded £3.5m in funding through the UKVN 2.0 to further advance serological standards and animal models for Marburg, Nipah, Plague, and Q fever.[246] This follow-on work will continue to drive forward the development of serological standards and animal challenge models, supporting vaccine R&D for emerging diseases.

243 Medicines and Healthcare products Regulatory Agency. Medicines and Healthcare products Regulatory Agency Annual Report and Accounts 2023–2024. *UK Government.* 2024. Available at: https://assets.publishing.service.gov.uk/media/66a8ed880808eaf43b50d9df/MHRA_Annual_Report_2024_low_res.pdf

Note that the 44,030 units are described as 'WHO International Standards, Reference reagents and Reference Panels, page 49

244 Page M, Wilkinson DE, Mattiuzzo G, Efstathiou S, Minor P. Developing biological standards for vaccine evaluation. *Future Virol.* 2017;12(8):431–437. doi:10.2217/fvl-2017-0003.

245 MacPherson A, Hutchinson N, Schneider O, et al. Probability of success and timelines for the development of vaccines for emerging and reemerged viral infectious diseases. *Ann Intern Med.* 2021;174(3):416–427. doi:10.7326/M20-5350.

246 Serological Correlates of Vaccine Protection – Marburg/Nipah/Plague/Q-Fever. Reference number: 10086774.

2.12 Assessment of persistence of immunity in multiple viral-vector Ebola vaccines, and response to a booster dose of Ad26.ZEBOV

Summary

The project "Evaluating the Long-Term Immunogenicity of Ebola Virus Vaccines Ad26-ZEBOV and MVA-BN-Filo" was funded by the UKVN 1.0 through a £1.2m Innovate UK award (2017-2022). The project partners - the University of Oxford, Imperial College London, and The Institute for Research, Epidemiological surveillance and Training (IRESSEF) in Dakar, Senegal - had previously conducted six clinical trials investigating various combinations of four different viral vector-based vaccines during the 2014/15 Ebola virus outbreak.

As part of the UKVN-funded project, the team re-contacted participants of the earlier trials for follow-up, to determine the long-term immune response to different Ebola vaccine schedules and to investigate the effect of a delayed booster vaccination (Ad26.ZEBOV, provided by industry partner Janssen) on the immune response.

Results showed that all Ebola virus vaccine schedules studied generated persistent antibody and T cell responses three years after initial vaccination. A late Ad26.ZEBOV booster dose reactivated strong immune responses, confirming the potential for rapid re-immunisation in outbreak scenarios. These results provide evidence for proactive immunisation of high-risk populations, with the potential to inform policy in countries affected by Ebola virus.

The project was supported by the long-term involvement of collaborators, starting with the 2014/15 trials, and by centralised lab analysis, enabling high data comparability. However, challenges included navigating data protection and coordinating follow-up across studies, negotiating industry agreements, and technical issues with sample preparation in Senegal. In addition, the COVID-19 pandemic caused a substantial delay, e.g. in sample shipments. While findings have been presented at international conferences, shifting research priorities and staff turn-over, affected by COVID-19, have so far hindered publication of the project results.

Ebola virus outbreaks and the need for effective vaccination strategies

Ebola virus was identified in 1976 during simultaneous outbreaks in Sudan and the Democratic Republic of the Congo (DRC).[247] The disease spreads through direct contact with infected bodily fluids, contaminated surfaces, or infected animals like fruit bats. Even after recovery, survivors can transmit the virus via semen for several months, and super-spreader events may occur during unsafe burials or healthcare interactions.[248] The average Ebola case fatality rate is approximately 50%, ranging from 25–90% in past outbreaks.[249] The 2014-2016 West African epidemic was the largest outbreak since its identification in 1976, and resulted in 28,646 cases and 11,323 deaths across 10 countries.[250] The impact of this epidemic and its potential for global spread was a wake-up call to the threat of epidemic diseases more generally and contributed to the establishment of multiple vaccine development efforts, such as the WHO

[247] WHO, Ebola virus disease fact sheet. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease

[248] CDC, How Ebola Disease Spreads. https://www.cdc.gov/ebola/causes/index.html

[249] Izudi, J & Bajunirwe, F (2024) Case fatality rate for Ebola disease, 1976–2022: A meta-analysis of global data, Journal of Infection and Public Health, 17(1) https://doi.org/10.1016/j.jiph.2023.10.020

[250] Nanclares, C *et al* (2016). Ebola virus disease, Democratic Republic of the Congo, 2014. Emerging infectious diseases, 22(9), 1579. https://doi.org/10.3201/eid2209.160354

R&D Blueprint[251] (2015), the UK Vaccine Network[252] (UKVN) (2016) and the Coalition for Epidemic Preparedness Innovations[253] (CEPI) (2017).

A review of clinical trials and approved products identified a total of 15 Ebola virus vaccine candidates in development, with four vaccines against Zaire Ebola virus (EBOV) reaching regulatory approval. The latter includes Merck's rVSV-ZEBOV (Ervebo[254]) vaccine and a two-dose regimen of Janssen's Ad26.ZEBOV and MVA-BN-Filo (Zabdeno[255] and Mvabea[256]), which are prequalified for global deployment by the World Health Organisation (WHO). In addition to EBOV, MVA-BN-Filo contains multiple antigens targeting related species Sudan Ebola virus, Marburg virus, and Taï Forest virus. All of the prequalified Ebola vaccines use a viral vector-platform to deliver Ebola virus proteins into the vaccinated individual, which elicits immune responses that confer protection against the disease.

To develop optimal vaccination strategies, researchers need a clear understanding of how long immune responses last following vaccination, i.e., whether vaccines should be deployed reactively (in response to outbreaks) or – in case of long-lasting immune memory - can be provided proactively through prophylactic immunisation. Since the 2014-2016 Ebola outbreak, knowledge and use of viral vector platforms for vaccines has expanded, with recent applications including the University of Oxford's ChAdOx1 COVID-19 vaccine (Vaxzevria[257]). However, at the start of UKVN 1.0, in 2016, immune responses to viral vector vaccines against Ebola virus disease had been demonstrated for a 12-month period only; data on the long-term durability of immunity in different populations or under field conditions, was not available.[258,259]

Understanding long-term immunity to guide future outbreak response

The UKVN 1.0 provided an award (£1.2m, Aug 17-Mar 22[260]) via Innovate UK's Small Business Research Initiative to determine the duration of immune responses induced by different Ebola vaccine schedules up to five years after initial immunisation and following an optional booster dose. Led by the University of Oxford, the project conducted three follow-on studies, REVOLVE,[261] RESOLVE,[262] and PRISM[263] as part of this award, involving participants of completed

[251] WHO, WHO R&D Blueprint for Epidemics, https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics

[252] Noad, R *et al* (2021) Scoping report for the UK Vaccine Network: Options for investment in vaccines and vaccine technology for infectious diseases with epidemic potential. Project Report. London School of Hygiene and Tropical Medicine. https://doi.org/10.17037/PUBS.04665413

[253] CEPI, The creation of CEPI. https://cepi.net/why-we-exist

[254] EMA, Ervebo authorisation details. https://www.ema.europa.eu/en/medicines/human/EPAR/ervebo

[255] EMA, Zabdeno authorisation details. https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno

[256] EMA, Mvabea authorisation details. https://www.ema.europa.eu/en/medicines/human/EPAR/mvabea

[257] EMA, Vaxzevria authorisation details. https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria

[258] https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/persistence-of-the-immune-response-after-ebola-vaccine-immunisation/

[259] Huttner A et al (2018) Determinants of antibody persistence across doses and continents after single-dose rVSV-ZEBOV vaccination for Ebola virus disease: an observational cohort study. The Lancet Infectious Diseases 18 (7) 738 – 748. DOI: 10.1016/S1473-3099(18)30165-8

[260] UKRI, Ebola vaccines: persistence of immunity & response to booster dose of MVA-EBO Z. £1,209,206, 01/08/2017 to 01/03/2022 https://gtr.ukri.org/projects?ref=971553

[261] ISRCTN, Re-evaluating Optimal Vaccine Schedules Against Ebola (REVOLVE). https://doi.org/10.1186/ISRCTN10481319

[262] ISRCTN, Re-evaluating optimal vaccine schedules against Ebola in Senegal (RESOLVE). https://doi.org/10.1186/ISRCTN15434137

[263] NIH, ClinicalTrials.gov, Persistence of the Immune Response After Immunisation With Ebola Virus Vaccines (PRISM). https://clinicaltrials.gov/study/NCT03140774

phase I/II studies conducted in 2014/2015 (five in the UK and one in Senegal). These original trials had been implemented by the Oxford Vaccine Group and the Jenner Institute (University of Oxford), Imperial College London, and The Institute for Research, Epidemiological Surveillance and Training (IRESSEF) in Dakar (Senegal), all of whom collaborated to deliver the UKVN-funded follow-on studies.

REVOLVE, RESOLVE, and PRISM examined the persistence of the immune response two to three years after vaccination with different combinations of four Ebola vaccines (ChAdOx3.ZEBOV and MVA-EBO-Z, GlaxoSmithKline; Ad26.ZEBOV and MVA-BN-Filo, Janssen), delivered in five different vaccination schedules. In addition, some study participants were given an optional booster dose of Ad26.ZEBOV, provided by industry collaborator Janssen, to evaluate the response to a late booster. Blood samples taken from participants were analysed to determine the level and neutralising activity of Ebola-specific antibodies, as well as the level of T cells ('cellular immunity') that actively target Ebola virus.

In addition to follow-up on the original participants, the PRISM study also included blood samples from healthcare workers in Glasgow who were immunised in 2015 with a single dose of rVSV.ZEBOV, the vaccine later licensed as Ervebo[264] (Merck). This complementary activity contributed valuable comparative data.

The project also contributed to capacity building by facilitating the training of local laboratory scientists at IRESSEF in Senegal in preparation of blood immediately after sample collection, recognising the benefits of encouraging more challenging, ambitious laboratory work to be conducted in low resource settings. Prior to the project, in-person visits and a two-week training programme were conducted at IRESSEF in Senegal to align experienced local staff with Oxford's analysis processes and to implement laboratory assays, including blood sample processing, and flow cytometry.

Sustained immune responses after vaccination, enhanced by late booster

The project found that all Ebola vaccine schedules investigated produced long-lasting immune responses, beyond the previously tested 12-month period, but that there may be some differences between vaccine regimens:

Three years after immunisation with either rVSV-ZEBOV or Ad26.ZEBOV/MVA-BN-Filo, antibodies against the EBOV glycoprotein were detectable in over 66% of recipients, irrespective of the vaccine regimen received.[265] The data also demonstrated stable levels of IgG antibody and T cell responses between two and four years after the primary vaccination courses with Ad26.ZEBOV/MVA-BN-Filo ZV. In contrast to the highly persistent antibody response, T cells were more evident after immunisation with Ad26.ZEBOV/MVA-BN-Filo than rVSV-ZEBOV.

The researchers also showed that a late booster dose of Ad26.ZEBOV, given four years after initial prime-boost vaccination, led to a rapid, sustained increase in antibodies against EBOV. This confirms that the immune system activated by the initial two-dose regimen still "remembered" and can respond quickly when boosted, offering an important strategy for renewing protection during Ebola outbreaks.

The project findings were presented to the American Society for Tropical Medicine and Hygiene, and study data related to AD26.ZEBOV was shared with the industry partner. The results however have not yet been published.

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[264] EMA, Ervebo Ebola Zaire Vaccine, authorisation details https://www.ema.europa.eu/en/medicines/human/EPAR/ervebo#authorisation-details

[265] Personal communication, Prof Matthew Snape, 17 July 2025

Evidence strengthens policy, supporting routine vaccination and booster use

The findings support the use of prime-boost Ebola vaccine regimens in outbreak preparedness, showing that both vaccine schedules recommended by WHO[266] provide long-lasting protection and can be rapidly reactivated with a booster dose years later.

These results offer a practical strategy for maintaining immunity in at-risk populations, for example those living in endemic areas or rapid-response health care workers, and enabling rapid responses during future outbreaks. Ebola vaccination strategies have so far relied on *reactive* strategies, delivering vaccines to people who are most likely to be infected once an outbreak has been identified (ring vaccination). However, outbreaks have occurred frequently in the last ten years, with seven outbreaks in the Democratic Republic of Congo alone since 2017, most recently in 2022 despite the availability of two licensed vaccine schedules. To help limit Ebola transmission (and outbreaks), experts have recommended a shift toward *proactive* routine immunisation of at-risk groups, such as healthcare workers, traditional healers, and transport workers.[267] This strategy could reduce hospital-based spread and ease the logistical challenges of ring vaccination during outbreaks, but its success depends on vaccines that provide long-lasting protection. The UKVN-funded project has provided evidence that prime-boost strategies of viral vector vaccines confer lasting immunity which can be boosted years after vaccination, supporting this approach.

The project findings also point to potential benefits of viral-vector vaccine boosters more generally. As the Ad26.ZEBOV booster was effective even in individuals who had received vaccines based on different vectors four years earlier indicates that cross-platform boosting can work well for these vaccines. This could be applied to vaccine schedules against other diseases, e.g. two licensed COVID-19 vaccines based on ChAdOx and Ad26 (AstraZeneca, Janssen).

Enablers and barriers

Key enablers of the project were the long-term involvement of the collaborating partners, and harmonised sample analysis:

Continuity: The project team was uniquely positioned to investigate and compare the long-term immune responses to different vector-based vaccines and vaccine regimens: The Oxford Vaccine Group and the Jenner Institute (University of Oxford) had conducted the original clinical trials for four of the five Ebola virus vaccine candidates tested in this project, and had responsibility for the pooled data from the various trials. The team hence brought deep knowledge and experience to this project. All members of the project team had collaborated previously, in the Ebola vaccine trials and other research, providing a strong foundation for effective partnership. At the same time, integrating data from multiple studies, and harmonising/navigating sensitivities related to data sharing, participant recontact, and data protection across research groups proved more complex than anticipated.

Comparability: A key enabler of this project was that blood samples obtained from recipients of multiple different vaccines were analysed within the same laboratories. This ensured direct and reliable comparison of immune responses to different vaccines and vaccination schedules, lending strong confidence in the project's findings and conclusions.

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[266] This includes a single dose of rVSV.ZEBOV, or a two-dose schedule of Ad26.ZEBOV followed by MVA-BN-Filo. See WHO, Ebola virus disease: Vaccines, Questions and answers. (2020) https://www.who.int/news-room/questions-and-answers/item/ebola-vaccines

[267] Bausch DG (2021) The need for a new strategy for Ebola vaccination. Nat Med. 27(4):580-581. https://doi.org/10.1038/s41591-021-01313-w

On the other hand, the project encountered a range of challenges during implementation:

COVID-19: All study participants had been immunised by the end of 2019; however, the COVID-19 pandemic delayed the shipping of samples from Senegal to the UK by more than one year, as well as delays occurred with sample processing and analysis. The COVID-19 pandemic also shifted vaccine researchers' priorities (including those of the project team) to focus on coronavirus research.

Industry agreements: While the team had originally planned to test the response to a booster of MVA-EBO-Z, the manufacturer of that vaccine did not agree to its use for the project. Instead, the team set up an academic-industry collaboration agreement with Janssen for use of Ad26.ZEBOV.[268] Contractual negotiations between the University of Oxford and Janssen had to overcome several challenges: As the vaccine candidate was unlicenced at the time of the project, Janssen, as the manufacturer, was responsible for aspects of the study, including safety reporting, ensuring the vaccine was shipped correctly at correct cold chain temperature, and training of staff. The collaborators were successful in finding a mutually acceptable division of tasks, which however required Janssen to entrust academic partners with processes for which it continued to hold responsibility. As Prof Snape explained: *"To actually get provision of an unlicensed vaccine for use by an independent academic group in an independent study - that was, I think, quite an achievement, to be able to look for its use as a late booster dose both in the UK and in Senegal."*

On the positive side, the collaboration with industry helped the project's academic partners to better understand requirements when working with a manufacturer supplying an unlicensed vaccine for clinical research – an experience the team will be able to draw on for future studies.

Trial recruitment challenges: The team faced a recruitment challenge in one of the UK cohorts, with a shortage of follow-up participants in a particularly important group - those who received the Ad26.ZEBOV prime and were due for a booster. This limited the ability to collect sufficient data for meaningful comparisons to the other regimens. However, the overall recruitment rate of 50% of eligible participants was considered positive – as Prof Snape described: *"The rate is really quite impressive, especially as some of [the study] was happening during a pandemic."*

Sample preparation in Senegal: Preparing blood samples for cellular immunity testing in the laboratory in Senegal proved challenging, including the need for extensive training of staff in the multi-step, time-sensitive process. This resulted in variation in the quality of samples, reflecting the challenges of working in a resource-limited setting.

2.13 Development of a new vaccine against plague

Summary

Plague remains a persistent threat to global health, requiring rapid and effective countermeasures to contain outbreaks and save lives. From 2016 to 2024, three consecutive UKVN 1.0/Innovate UK awards totalling £3.9 million advanced the development of a viral vector-based plague vaccine, ChAdOx1 Plague. Led by Prof Andrew Pollard, University of Oxford, the team inserted two antigens from the plague-causing bacterium Yersinia pestis into the ChAdOx1 viral vector, and showed that it provided complete protection against the pathogen in a mouse model. Subsequent clinical trials in the UK and Uganda demonstrated that the vaccine candidate was safe and triggered immune responses in both populations. The team also successfully developed plague-specific laboratory assays and established international collaborations. The ChAdOx1 Plague candidate is now ready to be trialled in future outbreaks, and the team are discussing the manufacture of a stockpile with industry.

[268] Final Report, 2022.

The team has since shifted focus to an RNA-based platform, supported by a £2 million Innovate UK SBRI award (2023–2025). RNA vaccines offer similar rapid deployment advantages without fewer safety concerns compared to adenoviral vectors, which improves their acceptability in high-income markets and for global use outside of major outbreaks. The RNA vaccine R&D draws heavily on development of the ChAdOx-based candidate, including antigen design, assay development, collaboration network, and trial experiences in Uganda.

A key enabler of the project was the successful collaboration between University of Oxford scientists, UK and US high-containment labs, and Ugandan trial partners, combining vaccine know-how, ready animal models, and local community support. On the other hand, project progress was slowed by several challenges, including a lack of validated immunological assays, correlates of protection, and convalescent samples.

Plague: An enduring threat and the case for vaccine innovation

Plague, caused by the bacterium *Yersinia pestis*, remains a persistent threat to global health security. Classified by the World Health Organization (WHO) as a re-emerging infectious disease, plague continues to affect over 25 countries, primarily in Africa, but also Asia and the Americas, with approximately 2,000 cases reported to WHO each year.[269],[270],[271] The disease is transmitted to humans through flea bites or contact with infected animals, with rodents serving as the primary reservoir. Of particular concern is the pneumonic form of plague, which is highly contagious and fatal without prompt treatment, requiring administration of antibiotics within 24 hours of symptom onset. However, as initial symptoms are often non-specific, early detection can be difficult, heightening the risk of rapid transmission during outbreaks. This was illustrated by the 2017 pneumonic plague outbreak in Madagascar, which affected urban areas and – despite relatively fast access to antibiotic treatment once diagnosed – resulted in 209 deaths among 2,417 confirmed cases.[272],[273],[274]

In addition to its ongoing natural circulation in animal reservoirs, the US Centers for Disease Control and Prevention (CDC) classifies *Y. pestis* as a Category A bioterrorism agent due to its high virulence, potential for aerosol transmission, and the emergence of antibiotic-resistant strains.[275],[276] These factors support an urgent need for effective countermeasures. A vaccine capable of eliciting a rapid, protective immune response could reduce transmission, particularly in settings where early diagnosis and treatment are challenging.

There is hence demand for plague vaccines from both low- and middle-income countries (LMICs), where plague remains endemic, and from high-income countries (HICs) concerned about bioterrorism threats and protecting military staff deployed to high-risk areas. A safe and

[269] WHO (2021) Plague. https://www.who.int/news-room/fact-sheets/detail/plague

[270] CDC (2025) Plague. https://www.cdc.gov/plague/maps-statistics/index.html

[271] Sun W (2016) Plague Vaccines: Status and Future. Adv Exp Med Biol. 918:313-360. doi: 10.1007/978-94-024-0890-4_12

[272] WHO (2017) Plague – Madagascar. https://www.who.int/emergencies/disease-outbreak-news/item/15-november-2017-plague-madagascar-en

[273] Nguyen, VK; Parra-Rojas, C; Hernandez-Vargas, EA (2018) The 2017 plague outbreak in Madagascar: Data descriptions and epidemic modelling. Epidemic 25: 20-25. https://doi.org/10.1016/j.epidem.2018.05.001

[274] Williamson ED, Kilgore PB, et al (2024) Progress on the research and development of plague vaccines with a call to action. NPJ Vaccines 7;9(1):162. doi: 10.1038/s41541-024-00958-1

[275] CDC, available at: https://www.selectagents.gov/sat/list.htm

[276] Feodorova,VA & Motin VL (2012) Plague vaccines: current developments and future perspectives. Emerging Microbes & Infections 1: 1-5. https://doi.org/10.1038/emi.2012.34

effective vaccine could enable a sustainable commercial model, with predictable demand from HICs, creating incentives for industry to invest in development, including funding expensive phase III trials. In turn, this investment would allow LMICs facing outbreaks to access the vaccine.

Historically, plague vaccine strategies focussed on inactivated whole-cell and live attenuated vaccines, which provided partial protection but were limited by safety concerns and reduced efficacy against pneumonic plague.[277] Recent efforts have included subunit vaccines targeting *Y. pestis* antigens, showing some promise in animal models. However, they typically induce only antibody responses, with limited cellular immunity, and require multiple injections for effectiveness. Prior to the start of the UKVN, only four plague vaccine candidates had been tested in clinical trials registered in one of the main clinical trials registries. The most advanced among them, a recombinant subunit vaccine developed by the US Army Medical Research Institute of Infectious Diseases (USAMRIID), completed Phase II trials and is poised to enter further clinical and manufacturing development.

A novel approach in this landscape is the development of viral vector vaccines. These vectors offer the advantage that they require only one or two doses for protection, can be engineered to express multiple antigens, and often elicit robust immune responses as their delivery mimics natural infection.[278] Additionally, the rapid onset of immunity, and the vaccine's low cost - estimated at around US$1 per dose, make viral vectors especially suited for outbreak response and use in LMICs.[279]

UKVN-supported development of a plague vaccine – from preclinical research to clinical trials

From 2016 to 2023, UKVN1.0 funded three consecutive Innovate UK awards, each building on the progress of the last, to develop a plague vaccine based on a viral vector platform, the ChAdOx1 platform which had been developed at the Jenner Institute, University of Oxford, in the early 2010s.[280] The projects were led by Professor Andrew Pollard (University of Oxford) and involved a collaboration between researchers from the University of Oxford, the University of Surrey, the UK Health Security Agency (UKHSA), the University of Texas Medical Branch (UTMB), and clinical trial teams in the UK and Uganda, including at the Medical Research Council/Uganda Virus Research Institute and the London School of Hygiene and Tropical Medicine (MRC/UVRI and LSHTM) Research Unit.

The initial award (Oct 2016-Sep 2017, £360k, Innovate UK/UKVN) supported the rapid development and preclinical testing of plague vaccine candidates. Using the ChAdOx1 platform, the researchers inserted two antigens from *Y. pestis* known to be important for the bacterium's ability to cause illness and to trigger a protective immune response in the host. The constructs were evaluated at UKHSA's high-containment facilities by exposing mice to inhaled bacteria – an experimental model mimicking the more fatal pneumonic form of plague.

The ChAdOx1 Plague constructs showed an unprecedented level of protection in mice, surprising even seasoned plague researchers. As Prof Pollard explained: "*What was*

[277] Williamson ED, Kilgore PB, et al (2024) Progress on the research and development of plague vaccines with a call to action. NPJ Vaccines 7;9(1):162. doi: 10.1038/s41541-024-00958-1

[278] Williamson ED, Kilgore PB, et al (2024) Progress on the research and development of plague vaccines with a call to action. NPJ Vaccines 7;9(1):162. doi: 10.1038/s41541-024-00958-1

[279] Gouglas D, Thanh Le T, et al. (2021) Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimization study. The Lancet Global Health 9(5): e576–e584

[280] Dicks MD, Spencer AJ, et al (2012) A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One 7(7):e40385. doi: 10.1371/journal.pone.0040385.

extraordinary was that when we did the challenge studies, there was complete protection. These [the studies] were done at the UKHSA and they were astonished, they'd never seen anything like this before [having tested many plague vaccines]." In addition, the research showed that a single ChAdOx vector encoding two viral antigens induced antibody responses comparable to those triggered by a combination of vectors expressing one antigen each (a single vector approach is preferable to keep the vaccine cost as low as possible).

Building on these positive results, a ChAdOx1 Plague vaccine candidate moved into clinical development with support from a second UKVN award, aiming to assess its safety and ability to trigger an immune response in humans (Sep 2017-Feb 2023, £3.1m, Innovate UK).[281] The team developed protocols and manufactured the vaccine under Good Manufacturing Practice (GMP) conditions, after which researchers at UTMB confirmed its safety in a non-human primate model. The team then successfully recruited the target number of 45 healthy volunteers in Oxfordshire, who each received two doses of the ChAdOx1 Plague vaccine.

Subsequently, a Phase Ib trial in Uganda, the PlaVac trial, was launched using the clinical-grade vaccine batch remaining from the UK trial. Supported by a third UKVN grant (Apr 2022-Mar 2024, £500k, Innovate UK), the trial was conducted in collaboration with the MRC/UVRI and LSHTM Uganda Research Unit, and successfully recruited the target number of 36 volunteers.

Evidence of safety and immunogenicity of the ChAdOx1 Plague vaccine in humans

Both trials showed that the vaccine was safe and that it triggered immune responses in trial participants, including in people who live in areas where plague is most common such as Uganda.

Simple vaccination schedules, ideally requiring only a single dose, are important for successful deployment in LMICs. Laboratory assays in Oxford, using serum samples from trial participants, showed that vaccination induced antibodies against the *Y. pestis* antigens, with a stronger response after two doses. However, it is still unknown whether the immune response from a single dose would be sufficient to protect against plague, as this required testing the vaccine during an actual outbreak.[282] In addition, it remains unclear if the vaccine triggers both antibody and T-cell responses – important for long-lasting protection – as the assays to measure T-cell responses were less robust than expected due to technical challenges.

The UKVN-funded research was hence successful in developing a novel viral-vector vaccine against the plague, which triggers an immune response to the *Y. pestis* antigens in individuals from the UK and Uganda. The research results have been presented at conferences and a publication is accepted by the journal Science Translational Medicine. In addition, the group is preparing a patent application for the ChAdOx1 Plague vaccine, which will be submitted once the clinical data has been fully analysed and incorporated.

Outcomes: Rapid response potential and accelerated development of an RNA-based vaccine

The safety and immunogenicity data support further testing of the ChAdOx1 Plague vaccine. To this end, the research team is in discussions with a manufacturer to produce a stockpile of ChAdOx1 Plague, ready for deployment in larger trials as soon as an outbreak occurs. As Prof Pollard explained: "*At this moment, if there were a pandemic, we can move very rapidly forward with the ChAdOx Plague vaccine, with the data that we already have*."

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[281] https://www.ox.ac.uk/news/2021-07-26-phase-i-trial-begins-new-vaccine-against-plague

[282] A single dose would be much preferable to facilitate vaccination programmes in resource-poor settings.

However, while the ChAdOx vaccine platform is highly scalable and cost-effective – making it well-suited for rapid deployment during a pandemic - it is linked to a rare side effect associated with adenovirus vectors, e.g. as observed with the AstraZeneca and Johnson & Johnson COVID-19 vaccines. This safety concern reduces its acceptability outside of major outbreaks when risk from the disease is low, and discourages industry from investing in its further development. As a result, Prof Pollard and his team have shifted their current development efforts towards RNA-based platforms, which offer similar flexibility but are more likely to be accepted by high-income markets due to the absence of known serious side effects. The team successfully secured an Innovate UK SBRI award (£2m, Sep 2023-Sep 2025) to support this work.

While the team are no longer actively progressing the ChAdOx1 Plague vaccine, its development provided crucial outputs which can now be transferred to other platforms such as RNA-based vaccines. This includes:

- Data on the suitability of the *Y. pestis* antigens, including the concept of using two types of protein in a single vaccine construct
- Plague laboratory assays developed as part of the UKVN-funded projects, which will enable future plague vaccine trial work
- A new collaboration with UTMB, who have the necessary infrastructure and expertise to conduct plague animal challenge studies, including in a key non-human primate model (for which there is no established expertise in the UK)
- Strengthened partnership with colleagues working at the MRC/UVRI and LSHTM Unit in Uganda, and experience implementing a plague vaccine trial in an LMIC, which will underpin future trials
- A first benchmark for comparing the level of immune response triggered by different vaccine constructs and vaccine types

The projects also helped to strengthen the team's capabilities in bacterial vaccine development. Prof Pollard considers the UKVN distinctive in this way, as it includes two bacterial pathogens on its priority list - *Y. pestis* and *Coxiella burnetii* (Q Fever). In contrast, priority pathogen lists of other organisations, such as the WHO, focus exclusively on viruses, leading many countries to invest primarily in virology, where vaccine development is often less complex. However, bacterial threats could arise naturally or from military action, and the UKVN-funded research has contributed to broadening the UK's capacity in this area.

Enablers and challenges

Key enablers of the plague vaccine development project were collaboration and complementary expertise:

- The Oxford team brought extensive expertise in viral vector technology and vaccine development, having developed the ChAdOx platform and vaccine candidates for a range of pathogens
- This expertise was complemented by capabilities in high-containment animal studies at the UK Health Security Agency (UKHSA) and at UTMB, Texas. For example, access to UTMB's established non-human primate model for plague research reduced time and costs - having to set up similar models in the UK would have been expensive and time-consuming.
- A strong collaboration with the MRC/UVRI and LSHTM Unit in Uganda enabled delivery of the PlaVac trial, supported by the Unit's local connections and community engagement activities. For example, the team organised a public meeting to raise awareness of vaccine research, gain community acceptance, explore knowledge and awareness of plague, receive feedback including concerns and questions, and address any misconceptions

about vaccines more generally. This was key for generating interest and recruiting volunteers to the trial.

The project also faced several scientific and logistical challenges. A key barrier was the lack of standard tools to assess immune responses. There is no validated commercial platform for plague antigens, no international serological standard, and no established correlate of protection, making it difficult to evaluate whether the immune response triggered by the vaccine would prevent disease. In addition, assays have not been validated across labs, and limited access to convalescent human samples (to understand natural immunity) further hampered assay development. Several challenges also led to delays to the project timelines, including:

- Longer than expected process to access the pathogen strain from the US
- Difficulties during GMP production of the vaccine due to limited prior process development. Although this was eventually resolved, it impacted timelines.
- Disruption due to the COVID-19 pandemic, including high demand for non-human primates (which meant the team had to use an alternative species not routinely employed in vaccine studies) and regulatory and logistical challenges related to the pandemic

Conclusion

The UKVN-supported projects successfully delivered a novel plague vaccine candidate, based on a viral vector platform, and created critical tools and partnerships that will accelerate further vaccine development for the plague, e.g. using RNA technology.

2.14 A phase I study of recombinant poxvirus Zika vaccines

Summary

Zika virus, a mosquito-borne flavivirus, emerged as a global health concern during the 2015-16 outbreaks in South America, when it was linked to severe birth defects and neurological complications. In response, the WHO designated Zika a priority to disease to accelerate vaccine development.

A £4.3 million UKVN grant via Innovate UK Small Business Research Initiative (SBRI) competition in 2017 enabled a team led by the University of Liverpool to progress a novel Zika vaccine based on the MVA viral vector platform through pre-clinical testing in a mouse model, manufacturing to GMP standard, and a Phase 1 clinical trial.

Despite several project implementation challenges, including an unstable initial vector construct, manufacturing setbacks, and delay due to the COVID-19 pandemic, the team successfully developed a stable candidate, MVAZIKAB, completed preclinical studies and produced vaccine vials for a Phase 1 trial. While delays meant the project concluded before clinical testing, the team was able to begin a Phase 1 trial in 2023. Early trial data suggest the vaccine is safe and elicits immune responses. The project also generated a patent application (pending).

This was the first time the project team advanced a candidate from preclinical to clinical stage, establishing key capabilities for future vaccine R&D at the University of Liverpool and its NHS partner facility. The team is now applying for further funding to progress the MVAZIKB candidate and adapt the MVA platform for other pathogens. The proposed projects include a MVAZIKB Phase II trial in Brazil, and a collaboration with researchers in Malawi to co-develop MVA-based vaccines.

Targeting Zika: a serious public health threat

Zika virus is a flavivirus, belonging to the same family as Dengue, Yellow Fever, Japanese Encephalitis, and West Nile viruses, all of which are mosquito-borne pathogens known to cause significant human disease.[283] Since its discovery in 1947, sporadic human infections with Zika virus have been detected. Initially confined to Africa and Asia, the virus spread to the Pacific and the Americas, where outbreaks have been recorded since 2007.[284]

Zika gained global attention during the 2015-16 outbreaks in South America (with an estimated 1.5 million people infected in Brazil alone) after being linked to congenital Zika syndrome which includes birth defects such as microcephaly (smaller than normal head size) and other neurological complications.[285,286] An estimated 5–15% of infants born to women infected with Zika virus during pregnancy showed signs of Zika-related complications. In adults, the virus can cause Guillain-Barré Syndrome, a rare neurological disorder characterised by muscle weakness and paralysis and can lead to death or long-term disability.

The 2015-16 outbreaks highlighted Zika virus as a public health threat, especially given the lack of effective treatments and/or vaccines. In response, the WHO added Zika virus disease to its

283 European Centre for Disease Prevention and Control. Factsheet about Zika virus disease. *European Centre for Disease Prevention and Control.* 2021. Available at: https://www.ecdc.europa.eu/en/zika-virus-infection/facts/factsheet

284 World Health Organization. Zika virus. *World Health Organization.* 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/zika-virus

285 Wellcome Trust. World prepared for future Zika virus outbreaks. *Wellcome Trust.* 2024. Available at: https://wellcome.org/news/world-prepared-future-zika-virus-outbreaks

286 World Health Organization. Zika virus. *World Health Organization.* 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/zika-virus

list of priority diseases in 2016 to fast-track R&D.[287,288] Since then, efforts targeting Zika virus have markedly increased, with 15 vaccine candidates advancing to clinical trials (see evaluation final report.

However, Zika vaccine development requires overcoming several challenges to ensure both effectiveness and safety:

- The vaccine must be safe for pregnant women, since Zika can cause severe birth defects.
- The vaccine needs to trigger a strong immune response that provides long-lasting protection, as people in Zika-affected areas may have been exposed to similar viruses like dengue, which can interfere with immunity. Hence, an effective Zika vaccine must induce both robust antibody and T-cell responses to confer durable immunity.
- The vaccine must avoid antibody-dependent enhancement (ADE), a phenomenon where pre-existing antibodies from a prior flavivirus infection or vaccination inadvertently enhance Zika virus infection rather than protect against it. Hence, the vaccine needs to be designed carefully so that it triggers protection against Zika virus while avoiding ADE.

The Modified Vaccinia Ankara (MVA) vector offers several key advantages for a Zika vaccine: it has a strong safety record, does not replicate in human cells (making it safer for use in pregnancy as well as in immunocompromised individuals), can stimulate both antibody and T-cell responses for broader and more durable immunity, and can accommodate large genomic inserts with the potential to vaccinate against more than one disease.[289,290] Additionally, MVA's lack of intellectual property restrictions would allow for more cost-effective vaccine production.[291]

Progressing a novel Zika vaccine from lab to trial

The project entitled "A phase I study of recombinant poxvirus Zika vaccines" received £4.3m in funding through a UKVN-funded Innovate UK Small Business Research Initiative (SBRI) competition in 2017.[292] The aim of the project was to develop two Zika virus vaccine candidates based on MVA and fowl pox (both derived from pox viruses). Unlike other Zika vaccines under development at the time, these candidates would be designed to trigger both antibody and T-cell responses targeting non-structural proteins, conferring durable immunity while avoiding cross-reactivity to other flaviviruses. The research team had nearly completed construction of the vectors; the SBRI funding was to progress the vaccine candidates and:

287 World Health Organization. WHO R&D Blueprint – Zika virus. *World Health Organization*. 2019. Available at: https://www.who.int/teams/blueprint/zika

288 Pérez P, Marín Q, Lázaro-Frías A, et al. A vaccine based on a modified vaccinia virus Ankara vector expressing Zika virus structural proteins controls Zika virus replication in mice. *Sci Rep*. 2018;8:17385. doi:10.1038/s41598-018-35724-6.

289 Pérez P, Marín Q, Lázaro-Frías A, et al. A vaccine based on a modified vaccinia virus Ankara vector expressing Zika virus structural proteins controls Zika virus replication in mice. *Sci Rep*. 2018;8:17385. doi:10.1038/s41598-018-35724-6.

290 UK Research and Innovation. Phase I study of recombinant poxvirus Zika vaccines. Accessed 6 May 2025. Available at: https://gtr.ukri.org/projects?ref=971554

291 End-of-project report

292 UK Research and Innovation. Phase I study of recombinant poxvirus Zika vaccines. Accessed 6 May 2025. Available at: https://gtr.ukri.org/projects?ref=971554

- Demonstrate efficacy in mice by testing whether the vaccine candidates protect against Zika virus infection (a stop/go decision point)
- Produce the vaccines under Good Manufacturing Practice (GMP) standards to meet regulatory requirements for human use.
- Conduct a Phase I clinical trial to assess vaccine safety and immune responses in humans

The project was led by Professor Neil French, University of Liverpool, in collaboration with colleagues and the Health Protection Agency Salisbury. In addition, three specialised contract research and manufacturing organisations were subcontracted, ABL Europe (Good Manufacturing Practice, GMP manufacture), Labcorp® (toxicology), and PCI Pharma services (product labelling).

The Liverpool team had a strong foundation in vaccine research, particularly in bacterial vaccines and flavivirus immunology (e.g., Japanese encephalitis).[293] Although the researchers had not previously taken a human vaccine from preclinical stages to Phase 1 trials, they had deep knowledge of immune response design, especially in the context of flaviviruses and challenges like ADE. In addition, team members included experts who had prior experience in developing and applying the MVA vector platform.

The team used the Clinical Trials Unit (CTU) at the University of Liverpool and the Clinical Research Facility (CRF) at the Liverpool University Hospitals NHS Foundation Trust's for implementation of the phase 1 trial.

Overcoming setbacks to deliver a stable vaccine candidate and trial design

Prior to the project, the team had constructed an MVA-Zika product to progress into clinical studies. However, during preparation for scale-up of manufacturing, they found that the initial version was not sufficiently stable. After several modifications, a stable version – named MVAZIKAB – was generated. Attempts to insert Zika elements into the fowl pox vector were unsuccessful, and this approach was abandoned.

The team tested MVAZIKAB in mice, demonstrating that it had strong immunogenicity and protected against live Zika virus challenge. The vaccine was manufactured under GMP conditions by ABL Europe (Strasbourg France). The other subcontracted companies conducted toxicology tests and labelled the drug product.

The project faced major delays due to the COVID-19 pandemic, and additional setbacks occurred when the early versions of the vector proved unstable and had to be redesigned. Resource reallocation in the clinical trial facilities during the peak of COVID19 research shifted the administrative burden of the trial to the NHS Foundation Trust's CRF. This slowed down the application process for MHRA approval. The CRF had not previously conducted a Phase I human vaccine trial, requiring the research team and CRF staff to learn 'on the job' and develop new governance processes, regulatory understanding, and technical capacity. Ultimately, the three-year contract was extended by an additional one and a half years, moving the end date from August 2020 to March 2022.

At the conclusion of the SBRI contract in March 2022, vials of MVAZIKAB had been manufactured ready for testing. The team had completed the design of a Phase I study to

293 Prof Neil French, personal communication, 27 Feb 2025

evaluate safety and immunogenicity at Liverpool University Hospitals Foundation Trust and was awaiting ethical and MHRA approval to move forward with the first in person study.

A publication on the pre-clinical development of MVAZIKAB is currently under review in the journal Vaccine. In addition, the study submitted a patent application in the UK in December 2023 which is pending approval.[294]

Trial completion and foundation for future work

Shortly after the project ended, the MHRA approved the trial protocol and the Phase I trial was implemented. Participants received the first dose of MVAZIKAB in April 2023.[295,296] The trial has now completed data collection, showing no safety concerns and demonstrating that the vaccine triggered a T-cell immune response in participants.[297] Assays to assess whether the vaccine stimulated antibody production and virus neutralisation are still in progress.

The project generated a collection of clinical trial samples, which the team is currently using to strengthen the immunological data to support follow-on funding applications. In addition, the project resulted in GCP-compliant assays to assess immune responses to MVAZIKAB. These assays can now be adapted for MVA-vectored vaccines targeting other diseases and provide a strong foundation for future vaccine research.

The project has also built the necessary experience and capacity in Liverpool to continue and broaden their involvement in vaccine development. As Professor French commented: "*We set out to make a product [the Zika vaccine] because we hadn't made one in Liverpool before. We were a bit naive about the processes, but we've actually done it now, the science has helped us to develop capacity here. And given that the University of Liverpool has a long history of work in LMICs and global health settings, I think the skill set will be of benefit to the global health community.*"

The experience also resulted in new clinical trial capabilities at the Liverpool University Hospitals NHS Foundation Trust's CRF. This has since enabled the CRF to take on further early-phase studies, including several Phase I trials, e.g. for vaccines against CCHF and Onchocerciasis (river blindness)[298], and the effect of the ChAdOx1-MERS vaccine in older people (see MERS case study). As Professor French commented: "*[This expertise] is a legacy of all of the mistakes made and learning from the Zika project.*"

Challenges and lessons learnt

This project marked the research team's first attempt to integrate vaccine discovery, manufacturing, and human clinical trials within a single project. Previous efforts had focused on individual elements, making this an ambitious but important step forward. As Professor French commented: "*We decided this [the SBRI competition] would be a useful one to go*

294 Patent application number: GB2318495.5. Further information available at the UK Patent register: https://www.search-for-intellectual-property.service.gov.uk/GB2318495.5

295 University of Liverpool. ZIKAVAC: A first-in-person trial of a novel vaccine to prevent Zika virus disease. *ISRCTN Registry*. 2022. Available at: https://www.isrctn.com/ISRCTN13726895

296 University of Liverpool. Liverpool begins first human trial of new Zika vaccine. *University of Liverpool.* 2023. Available at: https://news.liverpool.ac.uk/2023/04/26/liverpool-begins-first-human-trial-of-new-zika-vaccine/

297 Prof Neil French, personal communication, 27 Feb 2025

298 Personal communication, Prof Neil French, 27 Feb 2025

after, to move ourselves forward into product development in a bigger way than we'd previously been involved."

The project encountered a range of challenges which caused lengthy delays. The COVID-19 pandemic resulted in a suspension of laboratory work in 2020 and significantly disrupted vaccine manufacturing capacity. The research team also identified other challenges and valuable learning points:

- Starting with a single vaccine construct proved risky. The initial version was unstable, and the lack of alternative candidates delayed progress. Running multiple options in parallel would have reduced risk and minimised downstream delays, despite the added early complexity and cost.
- Manufacturing arrangements were made too late. Although some early engagement occurred, quotes were only requested after vaccine stability was confirmed. This led to scheduling difficulties and increased cost, exacerbated by pandemic-related demand. Earlier booking of slots, even before stability is confirmed, may carry some risk but offers more flexibility and faster timelines.
- Better planning and anticipation of common issues during manufacturing could have helped prevent delays. Protocol deviations required additional quality checks to meet GMP standards.
- Clinical trial site staffing shortages caused delays and extra burdens on the research team. While trial support was assumed to be in place, actual capacity was insufficient, causing substantial delays. The experience highlighted the need for earlier staffing decisions, ideally with competitive remuneration to attract and retain skilled personnel - especially amid broader sector shortages due to COVID-19 demands.
- Assay development faced setbacks, despite seeking early GCP advice. Greater involvement of experienced, GCP-trained technical staff at the outset would have improved efficiency and reduced errors in assay validation.

The team also noted key enabling factors:

- The inclusion of a Qualified Person (QP) in the project from the beginning. A QP (an expert in the manufacture of medicinal products) ensures compliance, guides documentation, and ultimately signs off on each batch of the vaccine for use. As Professor French commented: "*I would never do this [moving to GMP vaccine production] again without actually starting with a QP in the project proposal. It was such an important person to have involved, who could lead us through the regulatory processes and the requirements of GMP manufacture*."
- Another enabling factor was the Innovate UK SBRI programme, which included appointment of an experienced independent advisor who helped the team avoid errors and was vital in steering the project in the right direction.

Conclusion

Going forward, the team are planning to draw on the knowledge and capacity gained through the MVAZIKAB project and have submitted or are preparing several funding applications. This includes:

- A proposal to the MRC's Developmental Pathway Funding Scheme for a Phase II trial in collaboration with partners in Brazil, along with discussions with a local manufacturer to produce the Zika vaccine (planned)

- A proposal to CEPI to improve the MVA vector platform more broadly, with the aim making the process of constructing vectors against different targets faster and more efficient (submitted)
- A funding application to Wellcome includes the development of MVA-based vaccines in an LMIC. Drawing on the University of Liverpool's longstanding collaboration with Malawi, the team proposes to build local capacity in developing MVA-based vaccines, starting with monkeypox and eventually using MVA as a broader vaccine platform. As Professor French commented: "*I think the Zika vaccine study has given us more of the skills and confidence to move on to do that*." (submitted)

The MVAZIKAB project marked an important opportunity for the University of Liverpool team to build their capacity for taking a vaccine candidate from early development through to a Phase I clinical trial. Despite delays and challenges, the project delivered a promising vaccine candidate and built sustainable capacity. This laid the groundwork for future research and partnerships, to progress not only the Zika vaccine but also vaccines targeting other diseases.

2.15 Vaccine against mosquito-borne diseases

Summary

Mosquito-borne diseases like Zika, Chikungunya and Rift Valley Fever, affect over 700 million people globally each year. While vaccine development typically targets individual pathogens, UKVN-funded projected let by Imutex Limited (part of the SEEK Group) took a novel approach to develop a vaccine that targets mosquito saliva to disrupt disease transmission at the source.

A £3.6m million UKVN award supported clinical development of AGS-v PLUS, a multivalent vaccine designed to trigger immune responses against salivary proteins injected by mosquitos during feeding. The team, in collaboration with the University of Maryland and support from the US National Institute of Allergy and Infectious Diseases, completed a Phase 1 trial assessing safety and immunogenicity. Results showed the vaccine was well tolerated and generated immune response.

The trial also found that vaccinated participants' blood reduced mosquito fertility and lowered in vitro Zika virus infectivity, providing early proof of principle for this transmission-blocking approach. Findings were published in a peer-reviewed journal and presented at international conferences.

SEEK established ConserV Bioscience Limited to lead further development. The team has secured additional funding from UKVN 2.0 and the US Department of Defence to advance AGS-v Plus, including combination studies with malaria, Zika and Chikungunya vaccine candidates.

Targeting mosquito saliva to fight multiple vector-borne diseases

Mosquito-borne diseases are estimated to infect up to 700 million people and kill over one million people each year worldwide.[299] Mosquitos thrive in tropical and sub-tropical climates, leading to a high prevalence of mosquito-borne diseases in many low- and middle-income countries (LMICs) in Africa, Asia and South America.[300] Many LMICs have underdeveloped health systems and limited services to detect, treat and prevent mosquito-borne diseases. As a result, the negative impact on health and economic costs are more pronounced in these regions.[301]

Recent outbreaks of mosquito-borne diseases such as Zika virus in South America led to the declaration of a Public Health Emergency of International Concern by the World Health Organisation (WHO) in 2016.[302] Since these diseases may be asymptomatic, number of infections can be difficult to determine, however modelling suggests that approximately 132.3

299 World Mosquito Program. Explainer: How climate change is amplifying mosquito-borne diseases. *World Mosquito Program.* 2022. Available at: https://www.worldmosquitoprogram.org/en/news-stories/stories/explainer-how-climate-change-amplifying-mosquito-borne-diseases

300 Leta S et al. Global risk mapping for major diseases transmitted by *Aedes aegypti* and *Aedes albopictus*. *Int J Infect Dis.* 2018;67:25–35. doi:10.1016/j.ijid.2017.11.026.

301 Chilakam R et al. Economic burden of mosquito-borne diseases in low- and middle-income countries: Protocol for a systematic review. *JMIR Res Protoc.* 2023;12:e50985. doi:10.2196/50985.

302 World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. *World Health Organization.* 2016. Available at: https://www.who.int/en/news-room/detail/01-02-2016-who-statement-on-the-first-meeting-of-the-international-health-regulations-(2005)-(ihr-2005)-emergency-committee-on-zika-virus-and-observed-increase-in-neurological-disorders-and-neonatal-malformations

million people were infected with Zika virus alone across the Americas by the end of 2018.[303] Zika infection is associated with rare but serious neurological disorders such as congenital Zika syndrome in newborns and Guillan-Barré syndrome.[304]

Typically, vaccine development targets specific mosquito-borne diseases, such as those from the UK Vaccine Network (UKVN) priority pathogen family list which includes Zika virus, chikungunya virus and Rift Valley fever (RVF). However, rather than targeting individual diseases, some vaccines focus on the animal vector, aiming to prevent transmission to humans.[305] Clinical assessment of vector-focussed vaccine candidates is challenging for multiple reasons, such as the need for specific expertise and for infrastructure that can maintain the animal vectors under laboratory conditions. Additionally, the novelty of the technology creates challenges and uncertainty for developers seeking funding, particularly in the definition of the regulatory pathway from clinical development to market approval and authorisation.[306]

Mosquito saliva plays a crucial role favouring transmission of pathogens, as it helps pathogens evade the host's immune system and creates a hospitable environment for pathogen replication at the bite site. A vaccine candidate (AGS-v PLUS) currently being developed by ConserV Bioscience Ltd was designed to disrupt this process. AGS-v PLUS is composed of mosquito salivary peptides that upon vaccination, re-train the immune system to respond to mosquito saliva by activating immune cells to secrete cytokines and chemokines that will create an environment that makes viral replication at the bite site harder. In addition, the composition of mosquito saliva has evolved to facilitate blood feeding by impeding coagulation and controlling blood flow. The immune response to the salivary components in AGS-v PLUS has the potential to modify mosquito feeding as well. When the female mosquito ingests blood, antibodies against salivary proteins may bind to proteins present in the mosquito salivary glands, inducing inflammation that will reduce mosquito feeding. If female mosquitoes don't feed sufficient blood after mating with a male, their diet will not include sufficient protein to lay fertile eggs which will develop into viable larvae. Thus, over time, the mosquito population will be reduced in areas where a large percentage of humans are vaccinated. Prior to this UKVN project, the vaccine candidate and underlying peptides have already been patented in multiple countries by the SEEK group and there were no other comparative active clinical trials evaluating a vector saliva vaccine.[307]

Supporting first-in-human trials for a novel multivalent vaccine

The project 'Vaccine against mosquito-borne diseases' aimed to support clinical development of a multivalent vaccine candidate, that protects against multiple pathogens. The project received £3.6m in funding from the UKVN via Innovate UK competition for clinical stage vaccine development.

303 Moore SM et al. Leveraging multiple data types to estimate the size of the Zika epidemic in the Americas. *PLoS Negl Trop Dis*. 2020;14(9):e0008640. doi:10.1371/journal.pntd.0008640.

304 Broutet N et al. Zika Virus as a Cause of Neurologic Disorders. *NEJM*. 2016;374(16):1506–1509. doi:10.1056/NEJMp1602708.

305 Londono-Renteria B, Troupin A, Colpitts TM. Arbovirosis and potential transmission blocking vaccines. *Parasites Vectors*. 2016;9:516. doi:10.1186/s13071-016-1802-0.

306 Nunes et al. Development of a transmission-blocking malaria vaccine: Progress, challenges, and the path forward. *Vaccine*. 2014. 32(43):5531–9. https://doi.org/10.1016/j.vaccine.2014.07.030

307 For example, the vaccine candidate AGS-v PLUS is patented in the US (USRE47222E1) and in the EU (EP2783694B1)

The project was led by Imutex Limited (UK), a member of the SEEK group. Following a reorganisation, SEEK's new subsidiary ConserV Bioscience Limited (UK) will lead the further development of the AGS-V PLUS vaccine candidate. The company collaborated with the Centre for Vaccine Development and Global Health at the University of Maryland (USA) who conducted the clinical study. The centre is also one of the few trial sites worldwide with capabilities to run mosquito-bite challenge studies for this type of vaccine, and this capability is not available in UK. The National Institute of Allergy and Infectious Disease (NIAID, USA) sponsored the trial, supporting regulatory, data and medical monitoring, pharmacovigilance activities and statistical analysis of data. A number of subcontractors in Europe, United States, Australia, and the United Kingdom were also involved and responsible for GMP manufacturing, toxicology, pre-clinical animal studies and clinical trial data management.

Phase 1 trial demonstrates vaccine safety and immune response

The project team designed and delivered a Phase I clinical trial (NCT04009824) to test the safety and immunogenicity (ability to generate an immune response) of the vaccine candidate in healthy volunteers at the University of Maryland.[308] The trial concluded in February 2021, with results showing that the vaccine was safe to use and generated immunogenicity in the vaccinated group. The trial also tested the effect of including two different adjuvants to improve the immune response, finding a conclusively stronger response with one of these.

The clinical trial was successful in its aims, demonstrating that the candidate was safe and well-tolerated by trial participants. Compared with the placebo group all vaccinated groups had a greater immune response, reflected by the significantly greater fold change in AGS-v PLUS-induced antibodies and cellular responses.

Alongside the primary and secondary endpoints of the trial, the following exploratory endpoints were also evaluated:

- Laboratory reared clean female mosquitoes from two different mosquito species (*Aedes aegypti* and *Aedes albopictus*) were allowed to feed from vaccinated subjects. The mosquitoes were taken to the insectary and monitored for survival and fertility. The results showed that the vaccine reduced the number of viable eggs and eggs laid by *Aedes albopictus*, resulting in fewer offspring.
- An *in vitro* Zika virus infectivity assay was developed to mimic the environment at an infectious bite site. The assay aimed to investigate the effect that serum and cellular components have in Zika virus infectivity by exposing blood (cells and serum) from study participants to a sample of Zika virus coated in mosquito saliva. After a short incubation, the virus was laid on cells to determine infectivity. The study found that average infectivity was reduced in blood from participants who received a dose of the adjuvanted AGS-v PLUS candidate, indicating that the vaccination-triggered immune response recognised the mosquito saliva and created a hostile environment for the Zika virus.

The results of all the clinical trial activities were published in a peer-reviewed article and were disseminated through a conference presentation at the annual international meeting of the

308 National Institute of Allergy and Infectious Diseases. Evaluating the Safety and Immunogenicity of AGS-v PLUS, a Universal Mosquito-Borne Disease and Mosquito Control Vaccine. *ClinicalTrials.gov*. 2022. Identifier: NCT04009824. Available at: https://clinicaltrials.gov/study/NCT04009824?term=NCT04009824&rank=1.

American Society of Tropical Medicine and Hygiene in 2021.[309,310] News articles were published about the research in by New Scientist and Spanish newspaper La Vanguardia. [311,312]
As well as the successful outcome of the phase I clinical trial, the project helped to establish the vaccine candidate's proof of principle. It demonstrated that vaccinating humans with mosquito salivary peptides can impair reproduction in female mosquitoes, and that immune responses against mosquito saliva prompted by the candidate can reduce infectivity of Zika virus. Future efficacy studies will confirm if the *in vitro* effects on Zika Virus translate into human protection from infection.

Towards next-generation vector-targeted vaccines

The success of the project has led to an increase in companies and researchers working in this area of mosquito saliva vaccine research. Two current follow-on projects conducted by ConserV Bioscience are testing mosquito salivary protein antigens in combination with pathogen specific vaccine candidates; for malaria with the Walter Reed Army Institute in the USA funded by the US Department of Defence, and for Zika and chikungunya viruses as part of UKVN 2.0 funding through Innovate UK.[313,314] Due to the novelty of the technology, such a combinatorial approach aims to reduce reluctance of investment in later-stage commercialisation and eventual uptake of the vaccine by pairing it with an established technology. These two projects aim to provide efficacy data in mice with human versions of pathogens infecting mice. As part of the malaria combination vaccine project, the team are also aiming to determine if the best approach is by delivering the antigens as synthetic peptides or encoded in mRNA, to inform the direction of future vaccine development.

The project also enabled ConserV Bioscience to forge a new strategically beneficial collaborative relationship with the University of Maryland, for any future potential work where mosquito challenge studies may be required. Project team members are also actively participating in the EU consortium 'Development and Characterisation of a Pan-Flavivirus Vaccine Candidate' (FLAVIVACCINE).[315] Through the consortium, they provide consultation and advice to help academic researchers with preclinical and clinical development of flavivirus vaccines and regulatory submissions guidance.

Challenges and lessons learnt

309 Friedman-Klabanoff D et al. Safety and immunogenicity of AGS-v PLUS, a mosquito saliva peptide vaccine against arboviral diseases: A randomized, double-blind, placebo-controlled Phase 1 trial. *eBioMedicine*. 2022;86:104375. https://doi.org/10.1016/j.ebiom.2022.104375

310 American Society of Tropical Medicine and Hygiene. Abstract #0929. In: ASTMH 2021 Annual Meeting Abstract Book. Arlington, VA: American Society of Tropical Medicine and Hygiene; November 2021. Available from: https://www.astmh.org/getmedia/59a95de8-1a06-49ca-9fd0-286454cc241a/ASTMH-2021-Annual-Meeting-Abstract-Book.pdf

311 Le Page, M. A single vaccine could protect against many mosquito-borne diseases. *New Scientist*. November 29, 2021. Available at: https://www.newscientist.com/article/2299128-a-single-vaccine-could-protect-against-many-mosquito-borne-diseases/.

312 Rius, M. La vacuna contra las picaduras de mosquito, en marcha. *La Vanguardia*. December 1, 2021. Available from: https://www.lavanguardia.com/vida/20211201/7899008/vacuna-picaduras-mosquito-marcha.html.

313 https://conservbio.com/news/conserv-bioscience-in-collaboration-with-walter-reed-army-institute-of-research-awarded-a-grant-by-cdmrp-to-evaluate-a-novel-malaria-vaccine-candidate/

314 Further information on project 10083718 can be found at: https://gtr.ukri.org/projects?ref=10083718

315 Institut de recherche pour le développement (IRD). FLAVIVACCINE: Project to improve global flavivirus defence kicks off. *Institut de Recherche pour le Développement*. February 2024. Available at: https://en.ird.fr/flavivaccine-project-improve-global-flavivirus-defence-kicks.

ConserV Bioscience had previously collaborated with most of the project's subcontracted organisations where they had built trusted relationships that ensured efficient delivery of work, despite many activities being carried out by multiple organisations across different continents. The COVID-19 pandemic posed substantial challenges to the project, limiting access to laboratories and increasing administrative burden. The number of trial participants taking part in the mosquito challenge study was reduced due to social distance restrictions. Difficulties in obtaining access to laboratories due to COVID-19 restrictions further delayed analysis of samples collected. As a lesson learned from this experience, future risk mitigation strategies will include protocols for conducting trials in challenging settings when in-person attendance is limited (e.g. during a pandemic). Furthermore, adopting a more conservative approach to forecasting project timelines will enable better project management and planning.

Conclusion

AGS-v PLUS is the first mosquito saliva vaccine ever to reach Phase I trials, and successful applications for follow-on work in preparation for Phase II trials are a positive signal. The vaccine has the potential to revolutionise vaccine approaches to mosquito-borne diseases, protecting against a multitude of diseases with a single vaccine. Reduction in the high rates of infection, illness and mortality from mosquito-borne diseases will greatly improve human wellbeing and reduce burden to health systems in LMICs.

The approach taken by this technology could be extended to develop vaccines protecting against diseases transmitted by other blood-feeding insects such as sandflies (vector for Leishmania) and ticks (vectors for Lyme disease). Publicly available data on protein sequences of ticks and sandflies can facilitate antigen identification in an approach used by ConserV Bioscience's antigenic peptide prediction model that supported development of the AGS-v PLUS vaccine.

2.16 Rapid, accessible, globally distributed RNA vaccine manufacture on demand

Summary

Access to vaccine manufacturing remains limited in many low- and middle-income countries (LMICs), where infrastructure and cold chain capabilities are often insufficient. To address this, a UKVN-funded project led by the UK based BiologIC Technologies Limited aimed to develop a compact, modular mRNA manufacturing platform that supports decentralised vaccine production in low-resource settings.

With £475,000 funding from the UKVN, BiologIC developed and validated a prototype of an automated system that can produce RNA vaccines without using living cells. Working with the Centre for Process Innovation, the team benchmarked the system against current industry standards and initiated development of a quality management system to support future clinical and regulatory use. The project also supported regulatory landscape mapping and IP strategy development.

Designed for use in challenging environments, the system requires minimal infrastructure, uses less energy, and reduces reliance on cold chain logistics or highly specialised personnel, making it well-suited for LMICs aiming to build local vaccine production capacity.

These achievements enabled BiologIC to secure £2.62 million in follow-on funding from Innovate UK and CEPI. Additionally, CEPI are providing $4.7m of funding for a consortium including BiologIC to implement the system as part of CEPI's 100 days mission. As the technology has matured, BiologIC has entered into new partnerships with commercial partners to apply the platform in related therapeutic areas, including cell and gene therapies and space biomanufacturing.

Supporting vaccine manufacturing in LMICs

Low- and middle-income countries (LMICs) face significant challenges in manufacturing vaccines, often lacking the necessary infrastructure and expertise to manufacture vaccines locally. In addition, some vaccines require complex supply chain capabilities, such as cold chain storage and distribution. For this reason, the development and production of vaccines are largely concentrated in high-income countries, affecting the affordability and speed of vaccine deployment during outbreaks in LMICs.

The World Health Organisation (WHO) and the Coalition for Epidemic Preparedness Innovations (CEPI) have highlighted that achieving global vaccine equity requires expanding local manufacturing in LMICs.[316] The African Union has set a goal to produce 60% of all vaccines used in Africa by 2040.[317] To address these challenges, funders emphasise the need to support technological development for vaccine manufacturing in low resource settings.[318]

RNA (ribonucleic acid) vaccine technologies (such as messenger, mRNA) have successfully been established as an alternative to conventional vaccine manufacture and were the platform of choice for many companies in combatting the COVID-19 pandemic. The mRNA vaccine platform is highly flexible and enables a faster infectious disease outbreak response

316 World Health Organization. Global Vaccine Market Report 2022. *World Health Organization*; 2022. Available at: https://www.who.int/publications/i/item/9789240062726.

317 GAVI, the Vaccine Alliance. Expanding Sustainable Vaccine Manufacturing in Africa: Priorities for Support. November 2022. Available at: https://www.gavi.org/sites/default/files/document/2022/Gavi-Expanding-Sustainable-Vaccine-Manufacturing-in-Africa-2022.pdf.

318 Hayman B et al. Sustainable vaccine manufacturing in low- and middle-income countries. *Vaccine*. 2022;40(46):6605–6608. Available at: https://doi.org/10.1016/j.vaccine.2022.10.044.

compared with traditional vaccine production methods that rely on cell cultures. This characteristic makes RNA vaccines an ideal candidate for rapid vaccine responses at the location of outbreaks in epidemic responses.[319] Classical mRNA manufacturing starts with creating the mRNA through in vitro reactions, followed by several steps of cleaning including breaking down unwanted DNA, separating out waste using chemical reactions and filtering out any impurities. A delivery system such as use of Lipid Nanoparticles (LNPs) are used in final vaccine products.[320]

RNA vaccine manufacturing is an expensive process that requires specialised equipment and technical expertise. Furthermore, a central challenge lies in designing a thermostable vaccine dosage form that can be stored, shipped, and distributed independently of an expensive cold chain, which remote areas in LMICs often lack. The WHO mRNA vaccine technology transfer hub is an example of an initiative that aims to build capacity for enable LMICs to produce mRNA vaccines. [321]

Building a prototype for decentralised, automated RNA vaccine production

The project 'Rapid, accessible, globally distributed RNA vaccine manufacture on demand' received £475,000 funding from the UKVN via Innovate UK to support the development of a prototype mRNA vaccine manufacturing platform.[322] The platform aims to provide an avenue for democratising rapid mRNA vaccine manufacturing capacity in LMICs without substantial infrastructure investments, improving vaccine equity and rapid response time to infectious disease outbreaks.

The project was led by UK-based company BiologIC Technologies Limited. The Centre for Process Innovation (CPI) in the UK were subcontracted to provide expertise in mRNA manufacturing workflow development and provide benchmarking data to compare the performance of the integrated modular system against industry standards. Across BiologIC and CPI, the project team included expertise in RNA biochemistry, biomanufacturing process engineering, biophysics, software development and commercial operations.

The project advanced the development and established proof-of-concept of BiologIC's prototype continuous RNA biomanufacturing system and associated software. Specifically, the project validated the *in vitro* bioprocessor system, which enables the synthesis of biological materials without the use of living cells. Complementing these technical developments, BiologIC conducted landscape mapping to inform the company's regulatory and intellectual property (IP) strategies for the technology. Insights from this exercise highlighted that future clients will require the system to meet international quality standards (e.g. ISO9001) and to be sufficiently robust for use in tightly regulated environments, such as those governed by Good Manufacturing Practice (GMP). To address this, BiologIC began developing a Quality Management System (QMS) as part of the UKVN-funded project. Ultimately, this will support

319 Sousa Rosa S, Prazeres DMF, Azevedo AM, Marques MPC. mRNA vaccines manufacturing: Challenges and bottlenecks. *Vaccine*. 2021;39(16):2190-2200. doi:10.1016/j.vaccine.2021.03.038.

320 Lokras AG, Bobak TR, Baghel SS, Sebastiani F, Foged C. Advances in the design and delivery of RNA vaccines for infectious diseases. *Advanced Drug Delivery Reviews*. 2024;213:115419. doi:10.1016/j.addr.2024.115419.

321 World Health Organization. Moving forward on goal to boost local production, WHO establishes global manufacturing training hub in Republic of Korea. 2022. Available at: https://www.who.int/news/item/23-02-2022-moving-forward-on-goal-to-boost-local-pharmaceutical-production-who-establishes-global-biomanufacturing-training-hub-in-republic-of-korea#:~:text=The%20World%20Health%20Organization%20(WHO,monoclonal%20antibodies%20and%20cancer%20treatments.

322 UK Research and Innovation. Rapid, accessible, globally distributed RNA vaccine manufacture on demand (March 2022 – March 2023). Available at: https://gtr.ukri.org/projects?ref=10025959.

users of their technology in regulatory submissions for clinical trials and product marketing. BiologIC has presented their technology at multiple conferences.[323,324]

Platform development and new R&D partnerships

UKVN funding provided critical resources for the development of the prototype. The project catalysed BiologIC to further develop the technology, and the company successfully obtained follow-on funding, including:

- £2.3m awarded via Innovate UK between 2021 and 2024 to further develop the platform technology software and continuous manufacturing capability
- £18,000 funding from the Analysis for Innovators (A4I) funding programme in 2023 to support validation studies[325]
- $320,000 funding from CEPI in 2024 to further develop proof-of-concept in the AI-enabled modular system for fully automated continuous processing[326]

Additional work commencing in 2025 is supported by $4.7m in funding from CEPI to create a development pipeline that greatly reduces bottlenecks in DNA template design and manufacturing, shortening the production timeline from approximately a month to two days. To achieve this, BiologIC is partnering with DNA Script (a French SME) and the Future Vaccines Manufacturing Research (FVMR) EPSRC Hub at Imperial College London.[327] This work aims to integrate the rapid manufacturing system with DNA Script's process for rapid DNA template design and production, using saRNA vaccine technology designed at FVMR.

UKVN funding also contributed to BiologIC developing their capabilities in adjacent therapeutic areas on similar platforms to the mRNA manufacturing system. BiologIC have progressed commercial relationships, with more partners accessing the platform to manufacture other applications including in the area of cell and gene therapies, monoclonal antibodies, antibody drug conjugates and stem cells. Additionally, BiologIC have entered the space biomanufacturing ecosystem, receiving funding from the UK Space Agency.[328] These activities provide a strategic long-term opportunity for BiologIC, which would not have been possible without the initial UKVN award.

Conclusion

323 LinkedIn. BiologIC Technologies Nordic Life Science Days conference presentation. 2023. Available at: https://www.linkedin.com/posts/richard-vellacott-373b8611_sustainability-nlsdays-cellandgenetherapy-activity-6981245169815674880-hNIZ?utm_source=share&utm_medium=member_desktop&rcm=ACoAAC67ZAUBKmCPdhLsTaG0A6p_UnB3S-obbjc.

324 LinkedIn, BiologIC Technologies Engineering Design Show conference presentation. 2022. https://www.linkedin.com/posts/biologic-technologies_the-engineering-design-show-exhibition-activity-6846457204590149632-J0LI?utm_source=share&utm_medium=member_desktop&rcm=ACoAAC67ZAUBKmCPdhLsTaG0A6p_UnB3S-obbjc

325 UK Research and Innovation. Enabling sustainable biomanufacturing by reducing the use of single-use plastics in biopharma with the biocomputer platform (June 2023–March 2024). Available at: https://gtr.ukri.org/projects?ref=10073572.

326 Coalition for Epidemic Preparedness Innovations. Project to explore speed up of mRNA vaccine production deployable for local outbreaks (July 2024). Available at: https://cepi.net/project-explore-speed-mrna-vaccine-production-deployable-local-outbreaks.

327 Coalition for Epidemic Preparedness Innovations. Pushing mRNA vaccine development timelines to new speeds (February 2025). Available at: https://cepi.net/pushing-mrna-vaccine-development-timelines-new-speeds.

328 BiologIC Technologies. UK Space Agency partnership (July 2024). Available at: http://biologic-tech.com/uk-space-agency-partnership/.

The longer-term vision for BiologIC's technology is to democratise rapid mRNA manufacturing capacity in LMICs. CEPI's CEO recognised that BiologIC's technology closely supports CEPI's 100 days vaccine mission, emphasising the value of speed and decentralised vaccine manufacturing in overcoming issues of vaccine equity in LMICs and supporting effective responses to outbreaks.[329] A key enabler for future impact is the integration and automation of high-quality manufacturing practices as part of the instrument's design, reducing the level of technical expertise required to operate the system. In addition, the system has been designed to include built-in quality control processes, integrated at the point of system manufacture, reducing the need for extensive compliance checks at each vaccine production site. These factors aim to greatly reduce the need for individuals highly skilled in mRNA manufacturing and quality assurance.

The platform's small footprint design enables localised manufacturing in low resource settings in multiple ways. The platform fits inside a standardised computer chassis and requires less extensive or specialised infrastructure to house and operate it. Through process intensification strategies including continuous manufacturing and modular integration, output per unit of space is increased. The platform requires lower energy consumption compared with classical mRNA manufacturing, also improving its appropriateness in low-resource settings. These characteristics aim to improve the affordability, flexibility and sustainability of vaccine manufacturing.

Cold chain requirements and logistical challenges for transporting mRNA vaccines and their input materials are a key challenge for delivery and use in low resource settings in LMICs. These challenges contribute to global inequity in supply of vaccines and other health products, as seen during the COVID-19 pandemic.[330] With the platform's smaller footprint, fewer input materials are required and supply chains at point of need are much simpler compared to that of classical mRNA manufacturing. By providing an option for decentralised manufacture, this enables LMICs to avoid the highly complex and globalised supply chains for mRNA vaccine manufacture.

The system also supports accelerated turnaround for production of vaccines compared with classical manufacture, which has significant implications for responding to future outbreaks. The ability to progress from pathogen detection to a synthesised vaccine *de novo*, fully formulated, in a very short period of time, will enable rapid and local containment of an infectious disease outbreak at source. Local, rapid manufacturing is considered a key part of these aims, and CEPI follow-on funding for BiologIC starting in 2025 aims to explore this possibility.

329 Coalition for Epidemic Preparedness Innovations (CEPI). Project to explore speed up of mRNA vaccine production deployable for local outbreaks. (July 2024). Available at: https://cepi.net/project-explore-speed-mrna-vaccine-production-deployable-local-outbreaks.

330 Talbot A, de Koning-Ward TF, Layton D. Left out in the cold - inequity in infectious disease control due to cold chain disparity. *Vaccine*. 2025;45:126648. doi:10.1016/j.vaccine.2024.126648.

2.17 Development of an economically viable CCHF virus vaccine

Summary

Crimean-Congo haemorrhagic fever (CCHF) is the most widespread tick-borne viral disease affecting humans, with case fatality rates reaching 40%. Despite its public health impact, no globally approved human vaccine exists. A UKVN-funded project led by Oxford Expression Technologies Ltd (OET) is addressing this gap by developing a novel protein subunit vaccine using its baculovirus-insect cell expression platform, flashBAC™.

With £2.76 million funding from the UKVN, the project team developed vaccine candidates based on CCHF virus glycoproteins. The project established a new insect cell, enabling safe, clinical-grade protein production. Preclinical studies in mice demonstrated immune responses, and the vaccine formulation was optimised to remove the need for ultra-cold supply chain. This makes the candidate well suited to manufacture and deployment in LMICs, where cold chain infrastructure is limited.

With UKVN 2.0 support, the project is advancing towards GMP-scale production and a planned Phase 1 trial. The project has strengthened OET's capabilities and contributed to commercial success of the cell line, having enabled OET to grow substantially and expand their work through new global partnerships with multiple vaccine development companies and consortia.

Addressing the global gap in CCHF vaccine development

Crimean-Congo haemorrhagic fever (CCHF) is the world's most prevalent tick-borne viral disease affecting humans. The disease has a high case fatality rate, up to 40%, with survivors experiencing long-term health issues such as malaise and fatigue that have additional socioeconomic impacts.[331] CCHF is listed on the WHO's priority list for Research and Development, as well as the US National Institute of Allergy and Infectious Diseases (NIAID) priority A List.[332,333] As well as through tick bites, the virus (CCHFV) can be transmitted to people via livestock animals; human-to-human transmission occurs through close contact with blood and other bodily secretions of infected persons. CCHFV is endemic in regions where the principal tick vector, *Hyalomma* genus, particularly *Hyalomma marginatum*, is prevalent, including Africa, the Balkans, the Middle East and Asia.

CCHF vaccine development faces a number of substantial challenges, including the high rate of CCHFV genome mutations, and a requirement for high-containment level facilities (e.g. CL-4).[334] Only one CCHFV vaccine, developed by the Bulgarian National Centre for Infectious and Parasitic Diseases, has seen limited use in Eastern Europe.[335] However, this vaccine is not approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA). As a result, there is no globally approved CCHFV vaccine for humans or

331 World Health Organization. Crimean-Congo haemorrhagic fever fact sheet. 2025. Available at: https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever.

332 World Health Organization. WHO list of pathogens with epidemic and PHEIC potential. 2024. Available at: https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts.

333 National Institute of Allergy and Infectious Diseases. Biodefense pathogens. 2024. Available at: https://www.niaid.nih.gov/research/niaid-biodefense-pathogens#i.

334 Kraus AA, Mirazimi A. Molecular biology and pathogenesis of Crimean–Congo hemorrhagic fever virus. *Future Virology*. 2010;5(4). doi:10.2217/fvl.10.23.

335 Papa A, Papadimitriou E, Christova I. The Bulgarian vaccine Crimean-Congo haemorrhagic fever virus strain. *Scandinavian Journal of Infectious Diseases*. 2010;43(3). doi:10.3109/00365548.2010.540036.

animals at present, although four vaccine candidates are currently in clinical development (see Rapid Evidence Review).[336]

Oxford Expression Technologies Limited Ltd (OET) is a biotechnology company specialising in protein expression, using *flash*BAC™ a baculovirus-insect cell expression system (see also case study 3). The company is developing a CCHF vaccine based on CCHFV surface glycoproteins that can simulate a protective immune response. These proteins are produced by cloning CCHFV gene regions into baculovirus, infecting insect cells, and purifying the CCHFV protein from the cell culture.[337] Several vaccines produced in insect cell cultures are currently in use, such as those against Influenza (Flublok®, Protein Sciences Corporation/Sanofi[338]), Human Papilloma Virus (HPV) (CERVARIX®, GlaxoSmithKline[339]), and COVID-19 (Nuvaxovid JN.1, NovaVax[340]).

OET's *flash*BAC™-insect cell expression system is suited to vaccine manufacturing and rollout in low- and middle-income countries (LMICs). As the system produces a CCHFV protein subunit, rather than dealing with the whole virus, the vaccine can be produced in lower-containment environments, thereby eliminating the need for high-biosafety containment facilities. Furthermore, protein-based vaccines are stable at higher storage temperatures (4˚C) compared with other platform technologies. For example, mRNA vaccines require storage at -80˚C, making complex cold-storage chains a major challenge in low-resource settings.[341]

Engineering a protein-based CCHF vaccine using insect cell expression

Three UKVN1.0 grants supported OET's pre-clinical development of the CCHF vaccine candidate.

Under the initial grant (09/2016 - 09/2017, £217,428), OET identified candidate vaccine targets by synthesising DNA sequences encoding CCHFV proteins (Gc and Gn), inserting these into baculovirus vectors using OET's proprietary flashBAC™ system, and expressing the protein variants in an insect cell line.[342] Out of 65 initial protein constructs, the team identified those that produced the highest levels of soluble, easily purifiable protein - an essential factor for ensuring the candidate's suitability for vaccine development and large-scale manufacturing. The project also included preliminary immunogenicity studies, which demonstrated that the vaccine candidates could elicit antibody responses in mice.

To support this work, the OET team decided to create their own novel insect cell line (SfC1B5), building new internal capabilities instead of relying on commercially available, but costly, alternatives. A key advantage of OET's SfC1B5 cell line is the absence of insect rhabdovirus, which is commonly found in comparable insect cell lines and precludes their use for clinical

336 Ahata B, Akçapınar GB. CCHFV vaccine development, current challenges, limitations, and future directions. *Front Immunol*. 2023;14(1). doi:10.3389/fimmu.2023.1238882.

337 Cox MJ. Recombinant protein vaccines produced in insect cells. *Vaccine*. 2012;30(10):1777-1786. doi:10.1016/j.vaccine.2012.01.016.

338 U.S. Food and Drug Administration. Flublok. Available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/flublok. Accessed 6 May 2025.

339 European Medicines Agency. Cervarix. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/cervarix. Accessed 6 May 2025.

340 U.S. Food and Drug Administration. NovaVax COVID-19 Vaccine. Available at: https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/novavax-covid-19-vaccine-adjuvanted. Accessed 6 May 2025.

341 Kim D., et al. Resource allocation for different types of vaccines against COVID-19: Tradeoffs and synergies between efficacy and reach. *Vaccine*. 2021;39(47):6931-6939. doi:10.1016/j.vaccine.2021.10.025.

342 Oxford Expression Technologies. The home of *flash*Bac™ technology. Available at: https://www.oetltd.com/flashbactm-and-starter-kits. Accessed 6 May 2025.

products (i.e. cannot be used for in-human studies). The SfC1B5 cell line underwent rigorous external analysis which demonstrated that it attained the standards required for manufacturing under Good Manufacturing Practice (GMP) conditions, i.e. it is suitable for manufacturing clinical-grade material. The cells are currently stored in a master cell bank at Bioreliance (Scotland) and are available commercially under a material transfer agreement from OET.[343]

The second grant (02/2018 – 01/2022, £2.173m) built on these findings by carrying out a more detailed preclinical evaluation and characterisation of the candidate vaccine. The team conducted further mice challenge studies to examine the effect of different adjuvants and the candidate's potential to elicit cell-mediated responses (e.g. T-cell responses). Through this work, the team identified a protein-adjuvant combination that produced a high survival rate and full recovery in challenged mice. The project also included the development of protocols for expression and purification of Gc/Gn proteins from insect cell cultures, optimising vaccine yield, purity and potency.

The diverse technical demands of the project led OET to establish a research consortium for the second grant. This included the UK Health Security Agency (UKHSA) (Formerly Public Health England), who provided expertise in handling CCHFV and links to countries where the virus is endemic, the University of Oxford's Jenner Institute with expertise in immunology studies and clinical trial design, and scientists from Oxford Brookes University with expertise in experimental design and data analysis. Additionally, Sue Marlow of Marlow Associates acted as Qualified Person supporting clinical development of this vaccine candidate.

The third UKVN 1.0 grant (04/2022 – 03/2023, £377,408) provided one year of additional funding to resume progress following disruption caused by the COVID-19 pandemic. The project advanced development of the vaccine candidate in preparation for GMP manufacture and to support a phase I clinical trial application. As part of this project, OET further optimised vaccine stability during storage at 4˚C and designed a Phase I clinical trial in preparation for future funding applications. UKHSA developed a test to replace live-virus challenge in mouse models, called a pseudo-neutralisation assay, which will enable researchers to test vaccine efficacy in future clinical trials at a lower containment level (CL2 rather than CL4). Additionally, the study team collaborated with UKHSA to finalise the immunisation regime of the vaccine through further animal studies. For this work, the team leveraged knowledge gained from complementary COVID-19 vaccine research to define the role of initial and booster doses in providing protection.

In parallel to progressing the vaccine candidate, the project team collaborated with UKHSA to develop a diagnostic assay for CCHFV. The findings were published in the Journal of Immunological Methods, with the assay currently undergoing further testing, funded by UKVN 2.0 and a Medical Research Council Confidence-in-Concept award (£47,789.97).[344,345]

OET's CCHFV vaccine progress has been presented at multiple European conferences, including the 7th and 8th European Congress of Virology (2019, 2023), The World Vaccine Congress Europe (2019), and the International Molecular Biology and Genetics Symposium (2021). However, work on the vaccine candidate itself has not yet led to a publication, whilst the OET team have been considering patent options.

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343 OET. SfC1B5 Insect cells. Available at: https://www.oetltd.com/product-page/sfc1b5-insect-cells-under-mta. Accessed 6 May 2025.

344 Dowall SD, et al. Development of humanised antibodies for Crimean-Congo Haemorrhagic fever virus: Comparison of hybridoma-based versus phage library techniques. *J Immunol Methods*. 2023;512:113405. doi:10.1016/j.jim.2022.113405.

345 LSTM. Generation of a source of positive antibody controls for development of an ELISA diagnostic test for Crimean-Congo Haemorrhagic Fever virus. 2016-17. Available at: https://rcdd.lstmed.ac.uk/mrc-confidence-in-concept/cdd-tropical-infectious-disease-consortium-mrc-cic-%E2%80%93-mini-portfolio. Accessed 6 May 2025.

Scaling vaccine manufacturing towards clinical trials

UKVN2.0 continues to support OET's CCHFV vaccine development through an additional £1.4m in funding (2024-2026).[346] The project aims to finalise the conditions for manufacture of the vaccine candidate at scale. As part of this grant, a manufacturing facility in the United States (Expression Systems LLC) will produce 25 L engineering-run batches of the vaccine candidate, which will inform future clinical trials. In addition, UKHSA will test the CCHFV diagnostic assay with international partners, including in Turkey, Bulgaria, Kazakhstan and Tajikistan.

If OET's application for funding for a phase I clinical study is successful, the company expects to start the trial in 2028. Planning further ahead, OET and UKHSA are also currently discussing options for a Phase II clinical trial with a potential partner hospital in Turkey - a country with a relatively high prevalence of CCHFV.

Challenges and lessons learnt

OET's longstanding relationships with researchers from each partner organisation - some spanning over 30 years - played a key role in enabling effective collaboration. While there were no LMIC partnerships at this early stage of vaccine development, the diagnostic assay work in the current funding is working with a number of LMIC partners and has helped identify potential LMIC sites for future Phase II clinical trials.

The COVID-19 pandemic spanned the timeline of the second grant, causing supply chains challenges and disruption to laboratory schedules. Additionally, resources were redirected toward COVID-19 vaccine development, necessitating an additional (third) grant to continue progress on the CCHFV candidate. Project leads also noted that limited funding and short grant timelines are common challenges in vaccine development, including the UKVN grants, which often results in gaps between funding rounds and contributes to staff turnover.

Conclusion

The UKVN-funded projects have allowed OET to expand its vaccine research and development (R&D) capabilities, including expertise in immunological assays and analysis (with the Oxford Jenner Institute and UKHSA), GMP-scale vaccine production (Expression Systems LLC), and clinical translation (with Qualified Person Sue Marlow). These capacity gains have created new business opportunities for OET that would not have been possible without UKVN support, and enabled OET's continued growth – including partnering with a number of global organisations to develop candidate vaccines for use in LMIC countries and a planned move to larger, purpose-built facilities at Oxford Technology Park in 2025.

OET is using the baculovirus expression system, insect cell line and manufacturing processes developed in the UKVN-funded projects to develop vaccine targeting other diseases. For example, the SfC1B5 cell line was used in a SARS-CoV-2 vaccine project funded by Innovate UK (73370).[347] Insights from this project strengthened OET's flashBAC™ expression system, which

346 OET. OET Receives £1.4M UK Contract to Develop Vaccine for Crimean-Congo Haemorrhagic Fever Virus. 2023. Available at: https://www.oetltd.com/post/oet-receives-1-4m-uk-contract-to-develop-vaccine-for-crimean-congo-haemorrhagic-fever-virus. Accessed 6 May 2025.

347 UK Research and Innovation. Covid-19: A rapidly scalable SARS-CoV-2 vaccine platform based on recombinant spoke protein manufactured in insect cells using flashBAC to maximise yield and quality. Available at: https://gtr.ukri.org/projects?ref=73370. Accessed 6 May 2025.

underpins NovaVax's successful development of a COVID-19 vaccine.[348] The NovaVax vaccine is now licenced in the UK and available as a booster vaccine. It is manufactured in India by the Serum Institute, and is widely used in LMICs. The large-scale rollout of this vaccine, with no significant reported safety concerns, has provided real-world safety data and demonstrated that the vaccine is stable under conditions encountered in LMICs. The evidence hence supports development of other vaccines using the flashBAC™ platform.

In addition, OET's SfC1B5 cell line is available at a much lower cost than other insect cell lines, making it a cost-effective option for developing vaccines targeting less commercially viable diseases, including those on the UKVN priority list. The cell line has gained strong traction with other vaccine developers in the UK and abroad, with multiple material transfer and licence agreements signed globally. It has also helped to establish OET as a recognised player and key partner in baculovirus vaccine platform development.

Reflecting on the benefits the UKVN funding provided for OET, project leads Professor Robert Possee and Professor Linda King summarised: *"For us it has been transformational to be part of this programme. […] We've made really good progress towards the end goal [CCHF vaccine development], which is good, but there have also been lots of other benefits. We have learned a huge amount from working with the Jenner Institute in Oxford and from UKHSA about what makes an effective vaccine. We have then been able to use that knowledge and transfer it into our core business […]. That has enabled us to take on projects for other companies that I don't think we could have done five years ago. The same technology will be used to make dozens of vaccines, not just against CCHF."*

348 U.S. Food and Drug Administration. Novavax COVID-19 Vaccine, Adjuvanted (2024). Available at: https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/novavax-covid-19-vaccine-adjuvanted. Accessed 6 May 2025.

2.18 Novel multivalent vaccines against haemorrhagic fevers

Summary

Viral haemorrhagic fevers (VHFs), including those caused by Ebola, Marburg, and Lassa viruses, pose a major threat to public health in low- and middle-income countries (LMICs). Where vaccines exist, they target a single virus, which limits their suitability for immunisation in high-risk populations. The project "Novel multivalent vaccines against haemorrhagic fevers" funded by UKVN/Innovate UK (£3.6 million, 2017–2023) aimed to develop single-dose multivalent vaccines using viral vector platforms.

The team, led by Prof Teresa Lambe at the University of Oxford, successfully developed and tested several multivalent vaccine candidates in animal models. Two bivalent vaccines, ChAdOx1 EBOZ & SUDV (later named biEBOV) and ChAdOx1 MARV & LASV, were prioritised for further development. The biEBOV vaccine demonstrated safety and strong immune responses in Phase I trials in the UK and progressed to Phase Ib trials in Tanzania. While ChAdOx1 MARV & LASV did not proceed to clinical trials due to challenges with combining the MARV and LASV antigens, it informed the development of a monovalent Marburg vaccine, ChAdOx1-MARV.

A major achievement of the project was the WHO's recommendation of the biEBOV and ChAdOx1-MARV vaccines in response to outbreaks in 2022, 2023 and 2024 . The team rapidly transferred vaccine production to the Serum Institute of India, enabling timely manufacture and shipment to support outbreak control in Uganda and Tanzania. Additionally, training and local engagement ensured trial readiness and strengthened local capabilities for future outbreak responses, e.g. at the Ifakara Health Institute in Tanzania.

However, non-human primate studies completed after the conclusion of the project suggested limited protection from the bivalent biEBOV vaccine, likely due to antigenic competition (where the presence of one antigen reduces the immune response to another). As a result, the team paused biEBOV's development and shifted focus toward development of a monovalent SUDV vaccine candidate while the multivalent approach is being re-assessed. The UKVN 2.0 is providing support for development of both, a monovalent SUDV vaccine and clinical development of the ChAdOx1-MARV candidate.

Viral haemorrhagic fevers – the need for multivalent vaccines

Outbreaks of viral haemorrhagic fevers (VHFs) pose a major threat to public health systems in low- and middle-income countries (LMICs). While many VHFs present moderate symptoms, others, such as those caused by Filoviruses (e.g., Ebola and Marburg viruses) and Arenaviruses (e.g., Lassa virus), can lead to severe symptoms and high fatality rates.[349] Ebola outbreaks in West Africa (2014-16, and 2018-20) resulted in over 14,000 deaths and increased poverty rates

[349] Hewson, R (2024) Understanding Viral Haemorrhagic Fevers: Virus Diversity, Vector Ecology, and Public Health Strategies. Pathogens 13, no. 10: 909. https://doi.org/10.3390/pathogens13100909

in the region.[350,351,352,353] Lassa fever is endemic in West Africa, with an estimated 300,000 infections and 5,000 deaths annually.[354]

Vaccination is critical to reducing the impact of VHFs. Historically, vaccine development has focussed on formulations targeting a single pathogen (monovalent formulations). While such vaccines are essential for outbreak response, they are less suitable for preventative immunisation of high-risk groups, such as healthcare workers, due to the high development costs and long development timelines for each vaccine, and the large number of VHF-causing viruses. For example, Ebola comprises six species, such as Zaire ebolavirus (EBOV) and Sudan ebolavirus (SUDV), each requiring a separate vaccine.

Recognising this challenge, the 2016 World Health Organization (WHO) guidance on Filovirus vaccines recommends the development of multivalent vaccines for prophylactic purposes, i.e. vaccines protect against multiple strains or species in a single shot. Multivalent vaccines simplify immunisation schedules, offer broader protection to priority groups, and thus improve outbreak preparedness and response.[355]

In 2017, most vaccines in development targeting VHFs were monovalent, with the exception of MVA-BN-Filo, a multivalent vaccine targeting Ebola and Marburg viruses. However, its multi-dose regimen and reliance on booster doses for certain high-risk groups limited its suitability for outbreak preparedness, in particular in LMICs where vaccine deployment can be challenging.[356,357] Thus, there was a clear need for novel multivalent vaccines capable of targeting several VHF-causing viruses within a single-dose regimen.

Novel multivalent vaccine candidates against viral haemorrhagic fevers

The project "Novel multivalent vaccines against haemorrhagic fevers" aimed to develop viral vector-based vaccines against VHFs, focussing on filoviruses (Ebola and Marburg viruses) and Lassa virus. It was funded via four UKVN/Innovate UK grants with £3.6 million (2017-2023) and led by Prof Teresa Lambe, University of Oxford, with project partners Public Health England (now UK Health Security Agency), the University of Sussex, the US National Institute of Health Rocky Mountain Laboratories, the University of Oxford Clinical BioManufacturing Facility and the Ifakara Health Institute in Tanzania.

Between 2017 and 2018, the project team generated and tested novel multivalent vaccines for VHFs, using two viral platforms: Chimpanzee adenoviral vectors (ChAdOx1) and Modified vaccinia Virus Ankara (MVA).[358] Starting materials for four vaccines were produced using different combinations of vaccine platforms and target viruses:

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[350] Obeng-Kusi M et al (2024) The economic burden of Ebola virus disease: a review and recommendations for analysis. J Med Economics 27: 309-323. https://doi.org/10.1080/13696998.2024.2313358
[351] Cenciarelli, O. et al. (2015). Ebola virus disease 2013-2014 outbreak in West Africa: An analysis of the epidemic spread and response. Int. J. Microbiol. 2015(1), 769121. https://doi.org/10.1155/2015/769121
[352] Gov.uk (2023). Ebola: Overview, history, origins, and transmission. Gov.uk. Available at: https://www.gov.uk/government/publications/ebola-origins-reservoirs-transmission-and-guidelines/ebola-overview-history-origins-and-transmission [Accessed 24 Feb 2025].
[353] United Nations Development Programme (2016). Socio-economic impact of the Ebola virus disease in West Africa. UNDP. Available at: https://www.undp.org/africa/publications/socio-economic-impact-ebola-virus-disease-west-africa [Accessed 24 Feb 2025].
[354] https://cdn.who.int/media/docs/default-source/documents/emergencies/health-topics---lassa-fever/lassa-fever-introduction.pdf
[355] https://cdn.who.int/media/docs/default-source/blue-print/who_multivalent_filovirus_tpp_nov-2016.pdf
[356] Nave L et al (2023) Immunogenicity and Safety of Modified Vaccinia Ankara (MVA) Vaccine-A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Vaccines (Basel) 11(9):1410. doi: 10.3390/vaccines11091410
[357] https://www.who.int/news-room/questions-and-answers/item/ebola-vaccines
[358] Supported by the first project grant, 971510. https://gtr.ukri.org/projects?ref=971510

- Two bivalent vaccines: 'ChAdOx1 EBOZ & SUDV' (Zaire ebolavirus and Sudan ebolavirus) and 'ChAdOx1 MARV & LASV' (Marburg virus and Lassa Virus)
- One trivalent vaccine: 'ChAdOx1 EBOZ, SUDV & MARV'.
- One tetravalent vaccine: 'MVA EBOZ, SUDV, MARV & LASV'

The vaccines were then evaluated in animal models, where they demonstrated strong immunogenicity, e.g. a single shot of the bivalent ChAdOx1 EBOZ & SUDV vaccine offered full protection against both Ebola viruses in animal challenge models.[359],[360] This data, combined with an analysis of manufacturing feasibility, led to the selection of two bivalent vaccine candidates for progression to manufacturing and clinical trials: ChAdOx1 EBOZ & SUDV and ChAdOx1 MARV & LASV.

One of the key achievements of the project was the successful integration of multiple disease antigens into different regions of the ChAdOx1 vector, with each antigen expressing effectively. By allowing multiple antigens to be delivered through a single vector, this approach consolidates protection against several viruses into one formulation, thus simplifying vaccine administration and potentially reducing manufacturing costs.[361,362]

Progressing novel candidates for VHFs towards clinical trials

From 2018, the project team targeted the development of manufacturing protocols compliant with good manufacturing practices (GMP) and to conduct Phase I clinical trials of the two ChAdOx1 bivalent vaccines.[363] However, the COVID-19 pandemic caused delays to the team's progress as its resources and efforts were redirected to contribute to the design of Oxford-AstraZeneca COVID-19 vaccine candidates (which are also built on the ChAdOx1 platform).

- ChAdOx1 EBOZ & SUDV, renamed biEBOV

From 2021 to 2023, the researchers conducted a Phase I clinical trial of the biEBOV vaccine in the UK. The trial demonstrated that a single dose of vaccine was safe and triggered immune responses against both Ebola viruses in healthy volunteers.[364,365,366] This vaccine is being evaluated in a Phase Ib trial in Tanzania to test its safety and immunogenicity in a population more likely to be affected by the viruses.[367] The data are currently being analysed and prepared for publication.

- ChAdOx1 MARV & LASV

Due to challenges associated with combining the MARV and LASV antigens, the bivalent ChAdOx1 MARV & LASV vaccine did not advance to clinical trials. Nevertheless, knowledge gained during its development underpinned the development of a monovalent Marburg vaccine, ChAdOx1-MARV.[368] Between 2022 and 2023, the project team successfully

[359] Efficacy studies were co-funded by the European Commission/ERINHA.
[360] Personal communication, Prof Teresa Lambe. 14 March 2025.
[361] Flaxman, A et al (2024) Potent immunogenicity and protective efficacy of a multi-pathogen vaccination targeting Ebola, Sudan, Marburg and Lassa viruses. PLOS Pathog 20(6): e1012262 https://doi.org/10.1371/journal.ppat.1012262
[362] Personal communication, Prof Teresa Lambe. 14 March 2025.
[363] Supported by the second project grant, 971615. https://gtr.ukri.org/projects?ref=971615
[364] Jenkin D et al (2025) Safety and immunogenicity of a bivalent Ebola virus and Sudan virus ChAdOx1 vectored vaccine in adults in the UK: an open-label, non-randomised, first-in-human, phase 1 clinical trial. Lancet Microbe 6: 101022
[365] https://clinicaltrials.gov/study/NCT05079750
[366] Supported by the third project grant, 10025997. https://gtr.ukri.org/projects?ref=10025997
[367] https://clinicaltrials.gov/study/NCT05301504
[368] Personal communication, Prof Teresa Lambe. 14 March 2025.

manufactured ChAdOx1-MARV under GMP conditions, and validated protocols and materials ready to produce the vaccine when an outbreak occurs.[369]

Supporting fast outbreak responses

In September 2022, the WHO declared an outbreak of SUDV in Uganda and recommended the deployment of several vaccines, including the biEBOV vaccine. [370,371] The project team swiftly coordinated the export of materials for manufacture of the vaccine to the Serum Institute of India (SII). SII rapidly scaled up production, and within only 79 days of the outbreak being declared, the first batch of the vaccine had been produced, shipped, and delivered to health authorities in Uganda to support outbreak control measures.[372,373]

Similarly, the WHO recommended initiating a Phase I trial of the ChAdOx1-MARV vaccine following MARV outbreaks in Equatorial Guinea and Tanzania in 2023, and in Rwanda in 2024.[374] In response to the recommendation, the project team exported the vaccines' starting materials to SII, where multiple doses were produced and shipped to health authorities in Tanzania.[375] The trial is currently on hold as the outbreak is contained.

Conclusion and next steps

A key outcome of the project, enabled by UKVN funding, was the WHO's recommendation of both vaccines and their successful manufacturing and shipment to Ebola and Marburg outbreak regions in Africa. The team facilitated transfer of the vaccine technology to a manufacturer in India, the SII, and, in parallel, engaged with trial sites in Tanzania to provide training in immunological assay techniques. These efforts ensured trial readiness and strengthened local capabilities for future outbreak responses.

After the project concluded, the bivalent ChAdOx1 biEBOV vaccine was evaluated in a non-human primate study, with results suggesting that the vaccine offered poor protection against SUDV challenge in these animals despite the detection of an immune response.[376] This is likely due to antigenic competition, where the presence of one antigen reduces the immune response to another, although further clarification is required. As a result, development of ChAdOx1 biEBOV has been paused while the underlying immune interactions are being investigated and the multivalent approach is being re-assessed. The project team has instead shifted focus toward developing a monovalent vaccine targeting SUDV, supported by funding from the UKVN 2.0.[377] In addition, the project team was awarded UKVN 2.0 funding to advance the monovalent ChAdOx1-MARV vaccine into clinical trials. A Phase I trial started in the UK in 2024, with participant recruitment largely complete (March 2025).[378,379]

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[369] Supported by the fourth project grant, 10025020. https://gtr.ukri.org/projects?ref=10025020
[370] https://www.who.int/emergencies/situations/ebola-uganda-2022
[371] https://www.who.int/news/item/03-11-2022-global-health-agencies-outline-plan-to-support-ugandan-government-led-response-to-outbreak-of-ebola-virus-disease
[372] https://www.ox.ac.uk/news/2022-12-15-oxford-ebola-vaccine-manufactured-and-shipped-record-time-sii-0
[373] https://www.who.int/news/item/09-12-2022-ebola-trial-candidate-vaccines-arrive-in-uganda-in-record-79-days-after-outbreak-declared
[374] https://cdn.who.int/media/docs/default-source/blue-print/who-tag-cvp-report-marburg-trial-for-tag-cvp-review.pdf
[375] Personal communication, Prof Teresa Lambe. 14 March 2025.
[376] https://academic.oup.com/jid/article/230/5/1083/7629702
[377] Personal communication, Prof Teresa Lambe. 14 March 2025.
[378] https://www.ovg.ox.ac.uk/news/oxford-scientists-launch-first-in-human-vaccine-trial-for-deadly-marburg-virus
[379] Personal communication, Prof Teresa Lambe. 14 March 2025.

3 Cross case study analysis

We have used case study examples to illustrate outputs, outcomes and impacts, challenges, and learning across the UKVN 1.0 project portfolio. Here we present a cross-case study analysis of 18 case studies, followed by a qualitative comparative analysis (QCA) of six cases to identify 'recipes' of conditions that determine whether projects achieved an outcome.

Cross-case study analysis: Outcomes and impacts

The cross-case study analysis provides an overview of the types of outcomes and impacts achieved by the 18 case studies, as well as the enablers and barriers to success as highlighted by the case study informants in interviews.

Following completion, all case study projects achieved or progressed towards their intended outcomes (Table 3). Eight projects have already contributed to outbreak response (Ebola, Covid), and nine projects have developed outbreak-ready protocols and processes, with some tools already in use. Most vaccine R&D projects have made progress towards but not yet achieved impacts, reflecting the fact that these candidates are still in pre-clinical or early clinical stages. The UKVN has built capacity, with projects having developed key skills to support future public health emergencies

Table 3 Outcomes and impact of case study projects

	Case study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Project type	TDP	TDP	TDP	TDP	TDP	TDP	TDP	Man	Man	Man	R&D	R&D	R&D	R&D	R&D	R&D	R&D	R&D
OUTCOMES	Protocols and processes for effectively using/trialling vaccines are outbreak ready																		
	Licensed or unlicensed (phase II ready) vaccines ready for use or trialling when an outbreak occurs																		
	New technologies accelerate vaccine response to an unknown pathogen																		
	Improved infrastructure and products to deliver and support emergency vaccine deployment in LMICs																		
	**UK R&D Community is ready and able to support future Public Health Emergencies																		
IMPACT	Prevention and reduction of likelihood of public health emergencies such as outbreaks and AMR																		
	Rapid effective response, building on robust preparedness																		
	Application of technology/expertise in real-world outbreak (Ebola, COVID-19)				Y	Y	Y	Y	Y				Y					Y	Y

TDP = Tool/Data/process; Man = Manufacture; R&D = Vaccine R&D. Scoring reflects the extent to which the case study project contributed to the outputs, outcomes, and impacts defined in the UKVN 1.0 Theory of Change, rather than those originally outlined in the project's proposal.

Dark green: Outcome / impact demonstrated
Tool/data/process available and in use to support outcome / impact
** UKVN-funded experts have demonstrated ability to support public health emergencies

Medium green: Evidence of progress; clear pathway to achieving outcome / impact
Tool/data/process ready to support outcome(s) / impact but not yet in use / unknown if in use
Outcome / impact potentially achieved but not evidenced, e.g. policy influence
** UKVN-funded experts gained key skills to directly support future public health emergencies

Light green: Progress towards outcome / impact, clear potential in the long term
Tool/data: progress made, not yet ready for use
**UKVN-funded experts developed some skills to support future Public health emergencies

White:
Not relevant to case study project; project did not address/target the outcome / impact

Vaccine R&D – multi-step, multi-award development paths

Vaccine R&D projects generally followed a structured development pathway, progressing from pre-clinical development through GMP manufacturing, Phase I first-in-human trials in the UK, and subsequently to Phase Ib trials in endemic regions. Among the case studies, seven candidates entered Phase I trials, and three advanced to Phase Ib trials in endemic regions. Some projects received three to four successive grants to support their candidate's continued development along the R&D pathway, e.g. the ChAdOx plague vaccine and the multivalent haemorrhagic fever vaccine.

13 of 18 case study projects secured additional investment, from UKVN 2.0 (6 case study projects), CEPI (4), BBSRC and Wellcome (2 each), and Innovate UK, MRC, Japan's SCARDA and US DoD (1 each). This indicates that the research is deemed of high quality, is internationally 'competitive' and carries potential for impact. For example, the UK SME BiologIC secured £2.3 million from Innovate UK to continue development of its mRNA manufacture device and is part of a US$5 million consortium funded by CEPI.

Platform development as part of vaccine R&D projects has already supported outbreak responses. For example, work on the MERS virus accelerated the development of the AstraZeneca/Oxford COVID-19 vaccine; and an insect cell line and manufacturing developed through the UKVN-funded projected underpinned the technology used for the Novavax Sars-CoV-19 vaccine.

Capacity building in LMICs

Eleven of the 18 case study projects included collaboration with LMIC researchers, institutes and policy makers. Clinical trials or field work were implemented working with local universities, e.g. Ugandan sites for plague, a livestock trial in Kenya for RVF. Other projects involved sample collection and tests (e.g. immunological assays at Redeemer's University, Nigeria for Lassa). These activities transferred laboratory and trial-governance skills.

In addition, some projects worked with government and policy makers, e.g. Kenya's first GMO veterinary vaccine field trial which ran through ILRI/KEMRI partnership, building regulator confidence and capacity.

Policy impact - rapid redeployment to live emergencies

Four projects pivoted from their original objectives to contribute to outbreak responses. For example, Oxford's ChAdOx1 biEBOV vaccine was manufactured at the Serum Institute India and deployed to Uganda 79 days after outbreak declaration; LSHTM's Electronic Data-Capture team used their toolset in both the 2018–2020 DRC Ebola epidemic and the UK's COVID-19 response.

Two candidates and one platform received WHO outbreak or fast-track endorsement: ChAdOx biEBOV & ChAdOx-MARV included in WHO "ring vaccination" lists and shipped during Sudan-Ebola and Marburg outbreaks. Case study projects also informed WHO policies, e.g. models developed by VEEPED shaped WHO guidance on Ebola vaccination and pregnant-women risk management.

Enablers and barriers

Several enablers were identified by case study informants, mainly relating to access to expertise and advice. Most commonly mentioned were:

- Strong collaborations with HIC researchers and organisations (12 cases)
- Strong collaborations with LMIC researchers and organisations (8)
- Community engagement in LMICs (for project elements in LMICs) (5)

Other success factors included engagement with key global organisations (3), regulators (1), and GMP manufacturing expert and advisor through the SBRI scheme (1 each).

Among barriers mentioned by case study informants, COVID-19 related challenges dominated, such as limited access to people and laboratories (11), disrupted logistics and supply chains (8), and –the top barrier – a shift in staff and policy priorities (13). Other barriers were varied and often project-specific, including technical issues (instability of vector) (4), collaboration issues (3), lack of sustained funding (2), and capacity gaps (lack of experience with laboratory technique/sample analysis; little prior experience with vaccine development, 2 each).

Qualitative Comparative Analysis of UKVN 1.0 cases

A Qualitative Comparative Analysis (QCA) examines which combinations of factors (conditions) are associated with a particular outcome and identifies elements of causal pathways - how, why and under what conditions/in what context do outcomes happen. The methodology allows evaluators to draw higher-level insights on enablers and barriers from across sets of case studies in a structured way. QCA does not provide definitive proof of causal effects or effect size, but results in an evidenced logical line of reasoning which gives some level of confidence of a condition's contribution.

Case selection

QCA requires cases to be broadly comparable yet have sufficient variation in context and outcomes to identify contributing factors.

Six of the 18 case studies describe projects that meet two commonality filters:

- Strategic goal: Development of vaccine candidates for UKVN priority pathogens, for human use
- Stages/progress: proposal text explicitly included GMP manufacture and a Phase I (or Ib) safety trial

Two further projects (OVEL, Bunyavirus consortium) resulted in vaccine candidate development, but this occurred as the outcome of the UKVN award selected for the case study, rather than as an intended objective within the award. These cases were hence excluded from the sample.

The case selection for QCA is presented in Table 4.

Table 4 Case selection for QCA

Case code	Pathogen focus	Core technology	Lead organisation	Candidate
C1	Ebola & Sudan Ebola	ChAdOx1 vector	U of Oxford	ChAdOx biEBOV
C2	MERS-CoV	ChAdOx1 vector	U of Oxford	ChAdOx MERS
C3	RVF	ChAdOx1 vector	U of Oxford & MRC/UVRI	ChAdOx RVF
C4	Plague	ChAdOx1 vector	ChAdOx Plague	ChAdOx Plague
C5	Zika	MVA vector	U of Liverpool	MVA-ZIKA
C6	Mosquito-borne diseases	Peptide/adjuvant	ConserV Bioscience	AGS-v PLUS

Outcome selection

A good outcome to query with QCA has to be a) an intended outcome for all projects in the selection, sufficiently discriminating between the cases, i.e. it must divide the sample into at least some successes and some non-successes, and b) relevant, i.e. plausibly predictive of later public-health impact.

The outcomes (primary and secondary) selected for QCA are presented in Table 5.

Table 5 Outcome selected for QCA

Primary outcome	**Definition (projects score 0–1)**	**Source of information**	**Strengths**	**Caveats**
Phase I trial completed	1 = Phase I completed 0 = Anything short of this outcome	Triangulation possible: Project end report and interview; scientific literature, trials database	Links to probability of reaching Phase II	
Secondary outcomes				
Follow-on funding secured	1 = Substantial budget secured, budget for continued development available 0 = Anything short of this outcome	Triangulation possible: Project end report and interview; targeted online search	External indicator that candidate promising Applies even if Phase I trial has not yet completed	Information may not be available for SMEs/industry as commercially sensitive
Endorsement by policy / regulators; deployment in outbreak situation	1 = Vaccine candidate has entered a regulatory fast-track or procurement mechanism, or been employed during an outbreak 0 = Anything short of this outcome	Triangulation possible: Project end report and interview; targeted online search	Strong predictor of continued development and future stockpile purchase	Affected by time since primary outcome completion and by outbreak situation; sample may be sparse

Explanatory conditions

We considered a range of explanatory conditions based on a tally of factors that emerged as enablers or barriers/challenges across cases. Ultimately, a set of five conditions was selected (Table 6).

Table 6 Explanatory conditions selected for QCA

Code	**Description**	**Scoring**
PLAT-MAT	Mature platform	Technology had candidates in clinical development previously
LMIC-INV	LMIC trial/manufacturing partner engaged early	Named LMIC institution involved before first GMP batch
CONT-FUN	Continuous funding pathway	No gap of more than 12 months between UKVN 1.0 end and next award

IND-ALLY	Consortium includes an industrial developer	Active role beyond paid service
COLLAB-STR	Strength of collaboration	Researcher emphasised collaboration strength in case study and/or evidence of multiple projects with same collaborator(s)

Methodology

We applied crisp-set QCA in R/QCA v3.4. After coding six vaccine projects and five binary conditions, a truth table was built (case-frequency ≥ 1) (Table 7) and minimised using a consistency threshold of 1.00 to obtain parsimonious sufficient paths; necessary-condition analysis applied the standard 0.90 cut-off[380]. Robustness was checked by alternative outcome codings and leave-one-out tests, which left the core solution unchanged[381]. We listed each unique mix of project features in a "truth table," marked whether the projects sharing that mix succeeded.

Table 7 Truth table for summarising 'recipe' for successful primary outcome

Case code	Candidate	Outcome: Candidate advanced into Phase I trial	PLAT-MAT	LMIC-INV	CONT-FUN	IND-ALLY	COLLAB-STR
C1	ChAdOx biEBOV	1	1	1	0	1	1
C2	ChAdOx MERS	1	1	1	1	1	1
C3	ChAdOx RVF	1	1	1	0	0	1
C4	ChAdOx Plague	1	1	1	1	0	1
C5	MVA-ZIKA	0	1	0	1	0	0
C6	AGS-v PLUS	1	0	0	1	1	1

For secondary outcomes, we found that all projects secured substantial follow-on funding, so this variable does not discriminate in the present sample. Only C1 and C2 have achieved external policy/regulatory endorsement to date (sparse sample).

Analysis

[380] Consistency threshold = 1.00 for sufficiency: we only treated a feature-combination as a "recipe for success" when every project that displayed it succeeded and no project displaying it failed; this leads to the shortest, most reliable set of success combinations ("parsimonious paths").

Necessary-condition cut-off = 0.90: to judge a single feature as indispensable we required it to be present in at least 90% of the successful projects.

[381] Two alternative ways of defining "success" were tested and the full QCA re-run both times:

a) Regulatory-gate definition: a project counted as successful if it had cleared a national regulator dosed at least one volunteer, even if the Phase I read-out was not yet available.

b) Manufacturing-gate definition: success was defined as completion of toxicology and release of a GMP clinical batch with the next-stage trial already funded

To make sure the findings were not an artefact of one odd case or one way of scoring the outcome, we removed one project at a time

We then used simple Boolean logic to identify the smallest combinations of features that always coincide with success. The analysis showed two distinct "recipes" that always led to Phase-I completion:

- Mature platform + embedded LMIC partner + strong collaboration – present in the four Oxford-led vector projects (C1–C4).
- Novel platform + industrial lead + strong collaboration – the configuration that explains the success of AGS-v PLUS (C6).

No project lacking strong collaboration succeeded, and every successful project possessed it, making this factor necessary (consistency = 1.00; it is present in 5 of the 6 successes, giving 83% coverage).

Interpretation

The strength of interpretation of the results of this QCA is strongly limited by the small number of cases and low variation in the primary outcome, with a risk of over-interpreting patterns from a sparse dataset. Hence, the analysis should be viewed as illustrative or exploratory, rather than providing robust causal generalisations.

The QCA indicates the importance of strong collaboration and consortium architecture in advancing vaccine candidates from pre-clinical phases into clinical development. LMIC integration accelerated progress: in the four ChAdOx-based projects, the presence of an LMIC trial or manufacturing partner from the start co-occurred with on-time Phase I completion, which was not achieved in C5 (MVA-Zika) which missed its Phase I target. The LMIC partner secured ethics approvals and local recruitment networks, shortening the path between GMP release and first dosing. After sense-checking the QCA conclusion, the key condition may be better explained by a weaker collaboration network - particularly the absence of critical expertise in C5 - rather than the partner's LMIC location.

For another platform, C6: AGS-v PLUS, an industrial lead substituted for platform maturity, provided the collaboration is equally strong. Other insights included that industrial partners were multipliers, but not prerequisites: They were valuable when present, but progression of academia-led projects hinged more on LMIC engagement / LMIC expertise.

Summary

The QCA indicated that strong collaboration and consortium design are important for moving vaccine candidates from pre-clinical to clinical phases. Early integration of LMIC partners accelerated progress: all four ChAdOx projects with LMIC involvement met Phase I timelines, with LMIC partners expediting ethics approvals, recruitment, and manufacturing readiness.

In contrast, case C5 (MVA-Zika) lacked LMIC partners and missed its target. C5's delays may also reflect a weaker consortium and missing expertise.

C6 (AGS-v PLUS) showed that a strong industrial lead can offset limited platform maturity, if collaboration is robust. Industrial partners boosted progress but weren't essential; LMIC engagement proved more critical for academia-led projects.

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