Institution: University of Oxford

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Vaccines against Ebola virus disease contain outbreaks and limit loss of life

Period when the underpinning research was undertaken: 2013 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Matthew Snape	Consultant (Category C, OUH NHS) Associate Professor in Paediatrics and Vaccinology	2009 – Oct 2019 Oct 2019 - Present
Andrew Pollard	Professor of Paediatric Infection and Immunity	2001 – Present
Philip Bejon	Professor of Tropical Medicine, Director of the Wellcome-KEMRI-Oxford Collaborative Research Programme, Kenya	2012 – Present
Patricia Njuguna	Head of Clinical Research/Clinical Trials Facility, KEMRI, Kenya (Category C, KEMRI)	2014 – 2016

Period when the claimed impact occurred: April 2015 – November 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Ebola outbreaks cause devastating loss of life (fatality 25-90%). University of Oxford researchers rapidly tested two vaccinations against Ebola during the 2013-2015 West Africa Ebola pandemic at a time when there were no vaccines or anti-Ebola treatments in use. Through a series of clinical trials, the teams proved the safety and immunogenicity of both vaccines, which provided the evidence required for trials of their efficacy, use in outbreaks and ultimately licencing. The rVSV-ZEBOV-GP vaccine was approved by the European Medicines Agency in November 2019 and then nine other countries; the Ad26.ZEBOV/MVA-BN-Filo vaccine was given European Medicines Agency licensure in July 2020. The rVSV-ZEBOV-GP vaccine was deployed under “compassionate use” to 16,000 people in Guinea in 2015, saving lives and controlling infections that helped to end the pandemic. In the 2018 - 2020 and 2020 outbreaks in the Democratic Republic of Congo, vaccine was quickly deployed leading to outbreaks being rapidly contained limiting the loss of lives and livelihoods.

2. Underpinning research

Despite decades of research on Ebola virus vaccines, when the 2013-2015 West African Ebola virus epidemic broke, there were no licenced vaccines. The infrastructure and experience within Wellcome-KEMRI-Oxford Collaborative Research Programme and the University of Oxford enabled these two teams to move rapidly and with the confidence of in-country partners in trialling potential vaccines. A remarkable success of the subsequent trials was how rapidly they were planned, approved, and implemented. Under the pressure of the outbreak, the timelines for scientific and ethics approval, along with protocol development, were compressed.

rVSV-ZEBOV-GP

The safety and immunogenicity of the candidate Ebola virus vaccine rVSV-ZEBOV-GP (also known as rVSVΔG-ZEBOV-GP, or rVSV-ZEBOV) was evaluated in a Phase I clinical trial carried out by the Wellcome-KEMRI-Oxford Programme (in Kenya) [1], in harmony with three other concurrent trials in Switzerland, Germany and Gabon. The KEMRI-Wellcome Trust Research Programme is a partnership between the Kenya Medical Research Institute (KEMRI) (host institution), the Wellcome Trust (funder) and the University of Oxford (scientific partner). Bejon and Njuguna, from the Wellcome-KEMRI-Oxford Programme, led as Executive Director and Head of Clinical Trials, respectively, and were Principal Investigators in Kenya. Forty volunteers were vaccinated in Kenya, half receiving a low dose and half a higher dose of the rVSV-ZEBOV-GP vaccine. The vaccine had an acceptable safety profile (no serious adverse events), albeit with a high incidence of arthritis in European volunteers, specifically in Switzerland, and with fever in 30% of the Kenyan vaccinees. The candidate vaccine raised antibody responses that neutralized Ebola-like virus particles in the laboratory, which were sustained to 180 days [1]. An additional study involving Bejon and Njuguna on different regimens of vaccination [2] determined antibody persistence following a single dose of rVSV-ZEBOV-GP was sustained across dose ranges and settings. By showing that a single dose gives long lasting protection, these data confirmed that second doses were not a priority question for WHO or others to consider.

Ad26.ZEBOV/MVA-BN-Filo

A second Ebola vaccine development programme studied two different vaccines given in a prime boost vaccine schedule (Ad26.ZEBOV and MVA-BN-Filo). The prime boost approach is a two-step vaccination protocol in which participants are first given a dose of Ad26.ZEBOV vaccine to prime their immune system and then a dose of MVA-BN-Filo at a later point to further enhance the immune response and achieve long-lasting protection. Two studies of this combination vaccine have been conducted by the University of Oxford, designed to obtain information about the safety and immune response in healthy adults. An expedited Phase I clinical trial (conducted 2014-2015, Snape), evaluated the safety and immunogenicity of novel Ebola vaccines (Ad26.ZEBOV and MVA-BN-Filo) given in a prime boost combination [3]. This study demonstrated exceptional speed of delivery, progressing from initiating the project in October 2014, though ethical approval and rapidly recruiting 87 participants in 2 months for a Phase I clinical trial (final enrolment in February 2015) and demonstrated that these vaccines were well tolerated and generated humoral and cellular immune responses to the Ebola glycoprotein. All participants had specific IgG detectable at 21 days after the boost vaccine as well as at the 8-month follow-up. Importantly, immunization with Ad26.ZEBOV or MVA-BN-Filo did not result in any vaccine-related serious adverse events.

The subsequent Phase II study (initiated in 2015, Pollard), allowed a more detailed evaluation of the immune response to the Ad26.ZEBOV and MVA-BN-Filo immunisation schedules [4, 5]. This study demonstrated the safety and immunogenicity of the two component Ad26.ZEBOV and MVA-BN-Filo regimen, in 423 participants, with intervals of 28, 56, and 84 days between doses. Results demonstrated the absence of Ad26.ZEBOV shedding in the week following vaccination, an important safety check for a live viral vector. Robust antibody and T cell responses were induced, with antibodies persisting at 1 year after vaccination. At the time these were the longest duration follow-up for any two-component prime boost Ebola vaccine schedule. The results of this European Phase II study supported the safety and immunogenicity profiles and the intended prophylactic indication for the vaccine regimen.

3. References to the research (University of Oxford researchers in bold)

1. **Agnandji ST**, Huttner A, Zinser ME, ...**Njuguna P**…**Bejon P**…et al. (Total 58 authors of which 5 were University of Oxford) (2016) Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe. *N Engl J Med*. 374(17):1647–1660. DOI:10.1056/NEJMoa1502924
207 citations (on 22/10/2020 as stated by NEJM webpage (CrossRef)).

2. Huttner A, **Agnandji ST**, Combescure C, Fernandes JF, **Bache EB**, **Kabwende L**, Ndungu FM, **Brosnahan J**, Monath TP, Lemaître B, Grillet S, Botto M, Engler O, Portmann J, Siegrist D, **Bejon P**, Silvera P, **Kremsner P**, Siegrist CA; VEBCON; VSV-EBOVAC; VSV-EBOPLUS

Consortia. (July 2018) Determinants of antibody persistence across doses and continents after single-dose rVSV-ZEBOV vaccination for Ebola virus disease: an observational cohort study. *Lancet Infect Dis.* 18(7):738-748. DOI: 10.1016/S1473-3099(18)30165-8

3. **Milligan ID**, **Gibani MM**, …, **Ewer K**, **Angus B**, **Pollard AJ**, **Snape MD**. (Total 31 authors of which 13 were University of Oxford) (2016) Safety and immunogenicity of Novel Adenovirus Type 26 and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. *JAMA*. 315:1610-1623. DOI:10.1001/jama.2016.4218

4. **Winslow RL**, **Milligan ID**, **Voysey M**, Luhn K, Shukarev G, Douoguih M, **Snape MD**. (2017) Immune responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored Ebola Vaccines at 1 year. *JAMA*. 317:1075–1077. DOI: 10.1001/jama.2016.20644

5. **Pollard AJ**, Launay O, Lelievre JD, Lacabaratz C, Grande S, Goldstein N, Robinson C, Gaddah A, Bockstal V, Wiedemann A, Leyssen M, Luhn K, Richert L, Bétard C, **Gibani MM**, **Clutterbuck EA, Snape MD**, Levy Y, Douoguih M, Thiebaut R; EBOVAC2 EBL2001 study group. (17 Nov 2020) Safety and immunogenicity of a two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis*. S1473-3099(20)30476-X. DOI: 10.1016/S1473-3099(20)30476-X

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4. Details of the impact

The fatality rate for Ebola is 25-90%. The 2013 - 2015 West Africa Ebola virus outbreak was unprecedented in scale, with 28,639 reported cases and 11,316 reported deaths. The outbreak cost the economies of Guinea, Liberia, and Sierra Leone USD2,200,000,000 and impacted their healthcare systems through loss of health care workers (Liberia lost 8% of its doctors, nurses, and midwives to Ebola – a total of 513 deaths). Furthermore, the outbreak set back the treatment and control of other diseases (an estimated additional 10,600 lives were lost to HIV, tuberculosis and malaria during the epidemic), greatly affected children (17,300 lost one or both parents, 33-39 weeks schooling lost, gaps in vaccination schedules) and restricted travel [A].

West Africa Ebola outbreak, 2014

The rVSV-ZEBOV-GP vaccine (also known as rVSVΔG-ZEBOV-GP, or rVSV-ZEBOV) progressed from the first in human Phase I study in 2014 [1] to being tested in Guinea in the continuing West African outbreak in 2014/15 in a vaccination trial. In 2015, 7,651 vaccinees in Guinea (along with tens of thousands of potential contacts of these vaccinees), benefitted from protection against Ebola, estimated at nearing 100% [B]. Ultimately this vaccine was used under "expanded access" or what is also known as "compassionate use" for 16,000 people in Guinea in 2015. As a result of the University of Oxford led trials and successful use during the outbreak, the European Medicines Agency announced conditional authorisation of the rVSV-ZEBOV-GP vaccine in October 2019 [C] and WHO announced pre-qualification approval in November 2019 [D]. The regional representative for Africa for Epicentre, the research arm of Médecins Sans Frontières (MSF), who was in charge of Laboratory Coordination for the MSF/Epicentre Phase 3 trial for the rVSV-ZEBOV-GP vaccine in Guinea during this outbreak, described the importance of the vaccine: "*The Ebola vaccine appeared as a game changer*" and he highlighted "*its positive impact on limiting the transmission of the disease or reducing the number of deaths*" [E].

Democratic Republic of Congo (DRC) Ebola outbreak, August 2018 - June 2020

The 10th Ebola outbreak in the North Kivu and Ituri provinces of the DRC was the second largest in the world with 3,481 cases and 2,299 deaths. In examining the evidence required to make a recommendation for use of a vaccine in Ebola outbreaks, the October 2018 background paper

for the WHO Strategic Advisory Group of Experts (SAGE) deliberations [F] referred to the University of Oxford study [1] showing the rVSV-ZEBOV-GP vaccine was immunogenic, with higher titres of neutralising antibodies produced at higher vaccine doses. Preliminary vaccination efficacy results followed in April 2019 that concluded "*…the rVSV-ZEBOV vaccine should contribute to bringing the current Ebola outbreak in the DRC to an end, and to controlling future outbreaks as effectively and rapidly as possible*" [G]. In a benefit to medical practice and policy, interim recommendations by WHO SAGE in May 2019 [H] indicated that rVSV-ZEBOV-GP should be offered as a priority to vaccinate those at high risk. Over 303,000 people received the rVSV-ZEBOV-GP vaccine between August 2018 and May 2020, [Ii]. An academic study lead by the Yale School of Public Health estimated that the deployment of rVSV-ZEBOV-GP during this outbreak reduced both geographical spread and risk by up to 70%, compared with projections without any vaccination campaign [J]. Whereas in the earlier West African outbreak approximately 900 health-care workers were infected and 513 died due to Ebola, in this outbreak in the DRC nearly 30,000 frontline healthcare workers, laboratory workers, surveillance teams and burial teams were offered the single dose vaccine with an efficacy calculated as 97.5% [G].

WHO Ebola outbreak response capabilities were further improved through the results of the first in human clinical trials [3, 4] on the Ad26.ZEBOV/MVA-BN-Filo Ebola vaccine as these led to this vaccine becoming the second WHO recommended vaccine for use for control of Ebola outbreaks. Following the initial use of rVSV-ZEBOV-GP vaccine in 2014/2015, there were two reasons that further vaccine development was essential. One major concern was the limited supply of the (then) currently employed vaccine (rVSV-ZEBOV-GP) referred to in [H]. The other was that this vaccine was quite reactogenic giving a high proportion of vaccinees a marked febrile reaction. Given that vaccinees are often contacts of people with Ebola, there were concerns of public uptake of the vaccine and that there may be diagnostic confusion and unnecessary containment and screening for Ebola. The prompt results of the Ad26.ZEBOV/MVA-BN-Filo Phase I vaccine trial [3] and Medicines and Healthcare products Regulatory Agency review of vaccine manufacturing, meant it was possible to move at pace from the Phase 1 first in human (3) to subsequent African trials, which were vital if patient benefit from a second Ebola vaccine was to be realised during this DRC epidemic. Though still at the investigational vaccine development stage, in May 2019 the WHO SAGE advised that individuals with indirect exposure to Ebola in the DRC be immunised with the Ad26.ZEBOV/MVA-BN-Filo vaccine [H] which was subsequently deployed in large scale population intervention study for outbreak control in the DRC. Between October 2019 and April 2020, 20,339 people received the first dose of the Ad26.ZEBOV/MVA-BN-Filo vaccine, and 9,560 of them received the second dose [I(i)]. The Ad26.ZEBOV/MVA-BN-Filo schedule was given European Medicines Agency licensure in July 2020 [Ki and Kii].

The progression of the Ad26.ZEBOV/MVA-BN-Filo vaccine to licensure and effect on WHO guidance was built on numerous reports and recommendations that refer to the University of Oxford-led research, including:

- the WHO SAGE October 2018 background paper [F] refers directly to the evidence on duration of the antibody response in [4] "*the information on the duration of protection for… candidate Ebola vaccines is up to 360 days post vaccination for the … Ad26.ZEBOV/MVA-BN-Filo vaccines*" and summarises the results from all three University of Oxford-led Ebola vaccine trials [1, 3 and 5].
- the May 2019 WHO SAGE Interim Ebola Recommendations [H], which recommend that lower risk populations be vaccinated with the Ad26.ZEBOV-GP vaccine, referred to the WHO Ebola Vaccines Decision framework April 12, 2019 [L] which described, reviewed and assessed the safety and immunogenicity of the Phase I and II trial data for the Ad26.ZEBOV/MVA-BN-Filo vaccine [3, 5] as being stronger than that for an alternate vaccine being considered for testing in the field.

The work of Snape in leading the Phase I clinical trial of the Ad26.ZEBOV/MVA-BN-Filo vaccines in a dramatically expedited study [3], followed by extended safety and immunogenicity studies [4, 5] led directly to the availability of a second crucial tool in the fight against Ebola. The Director of the Department of Research and Production, National Laboratory for Public Health of

Congo, Brazzaville confirmed that "*The double use of …[both]…. vaccines rapidly brought the epidemic to an end…..the development of two successful vaccines against EVD is highly significant for global health*" [M].

DRC Ebola outbreak, June 2020 - November 2020
Days before the 10th outbreak was declared over, the 11th Ebola outbreak was declared, which resulted in 119 cases and 55 deaths. Despite occurring during the COVID-pandemic, vaccination efforts began just four days after the outbreak occurred and more than 40,000 people at high risk were vaccinated with the rVSV-ZEBOV-GP vaccine [I(ii)].

5. Sources to corroborate the impact

[A] US Department of Health and Human Services Centers for Disease Control and Prevention (CDC) Summary of the cost of the Ebola epidemic in 2013-15 in West Africa.

[B] Henao-Restreoi et al (2015) Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet* 386: 857015066 DOI: 10.1016/S0140-6736(15)61117-5

[C] WHO news release announcing conditional authorization of rVSV-ZEBOV-GP vaccine by the European Medicines Agency and WHO movement towards pre-qualification (18 October 2019)

[D] WHO prequalification of rVSVΔG-ZEBOV-GP, November 2019 https://extranet.who.int/pqweb/content/ervebo

[E] Email testimonial from regional representative for Africa for Epicentre, the research arm of Médecins Sans Frontières (MSF).

[F] Background paper for WHO SAGE deliberations, summarising the results from [1], [2], [3] and [4], October 2018.

[G] WHO preliminary report on the expanded access/compassionate use of rVSV-ZEBOV-GP in the DRC, April 2019.

[H] WHO SAGE committee on Immunization: Interim recommendations on vaccination again Ebola Virus Disease (EVD), May 2019.

[I] WHO reports on Ebola Virus Disease in the DRC: (i) Situation Report update, 23 June 2020; (ii) Disease outbreak news update, 18 November 2020.

[J] Wells CR, Pandey A, Parpia AS, Fitzpatrick MC, Meyers LA, Singer BH, Galvani AP (2019) Ebola vaccination in the Democratic Republic of the Congo.. *Proc. Natl. Acad. Sci. USA*. 116(20):10178-10183. DOI: 10.1073/pnas.1817329116.

[K] European Medicines Agency licensure of Ad26.ZEBOV/MVA-BN-Filo
i) Zabdeno https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno and
ii) Mvabea https://www.ema.europa.eu/en/medicines/human/EPAR/mvabea

[L] WHO Research and Development Blueprint https://www.who.int/blueprint/priority-diseases/key-action/ebola-vaccine-candidates/en/ Ebola vaccine candidates, 12 April 2019

[M] Statement by the Director of the Department of Research and Production, National Laboratory for Public Health of Congo, Brazzaville, advisor to the Prime Minister of Guinea during the 2013-2015 Ebola outbreak.