



ENSURING ACCESS TO NEW TREATMENTS FOR EBOLA VIRUS DISEASE

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Médecins Sans Frontières/Doctors Without Borders (MSF) is an international, independent medical humanitarian organization that delivers medical care to people affected by conflict, disease outbreaks, natural and human-made disasters, and exclusion from health care. Founded in 1971, MSF has operations in over 70 countries today.

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The MSF Access Campaign was launched in 1999, on the heels of MSF being awarded the Nobel Peace Prize. Rooted in MSF's medical operations, the MSF Access Campaign analyzes and advocates for access to lifesaving medicines, diagnostic tests, and vaccines for people in MSF programs and beyond.

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Front cover photo:

An EVD survivor puts her hand print on a survivors' wall erected by MSF at its EVD treatment centre in Monrovia, Liberia. Contributions by patients, survivors and their communities, were crucial to the R&D of treatments for EVD. © Malin Lager/MSF

Back cover photo:

François Mufolo, MSF epidemiologist, talks with the village chief and community members in Bobua in Equateur province, Democratic Republic of Congo, where an EVD outbreak occurred in 2020. © Caroline Thirion/MSF

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EXECUTIVE SUMMARY

Ebola virus disease (EVD) is a severe, often fatal, illness that is caused by the Ebola virus and transmitted between humans or to humans from animals. While there are six different species in the genus *Ebolavirus*, *Zaire ebolavirus* is the species responsible for most outbreaks of EVD. Named after Zaire (now Democratic Republic of the Congo [DRC]), the country where the first recorded outbreak of EVD occurred in 1976, *Zaire ebolavirus* also caused the largest EVD outbreak on record in West Africa in 2014-16 which killed more than 11,000 people.

As of 2023, the world has two effective treatments approved by the US Food and Drug Administration (FDA) for disease caused by *Zaire ebolavirus*. After nearly half a century without any treatments, this breakthrough was made possible thanks to an unprecedented global collaborative effort by a wide range of stakeholders, including public researchers, ministries of health in affected countries, the World Health Organization (WHO), pharmaceutical corporations and non-governmental organisations (NGOs). Médecins Sans Frontières (MSF) teams, the people in our care, and their communities were also a part of these efforts.

Public contributions to biomedical research and development (R&D) have always been integral to new medicines' development, but the role, scale and breadth of public contributions were particularly noteworthy in the case of treatments for EVD. The culmination of this was the publicly funded and managed Pamoja Tulinde Maisha (PALM) clinical trial that demonstrated the superior efficacy of two EVD treatment candidates. A monoclonal antibody (mAb) cocktail of atoltivimab, maftivimab, and odesivimab, known as REGN-EB3 and marketed by Regeneron Pharmaceuticals (Regeneron) as Inmazeb, was approved by the FDA in October 2020. In December 2020, the FDA also granted approval to a second monoclonal antibody treatment, ansvimab, known as mAb114 and marketed by Ridgeback Biotherapeutics (Ridgeback) as Ebanga. mAb114 was originally isolated from a blood sample taken from an EVD survivor in DRC.

In August 2022, the WHO made a strong recommendation for their separate use in the first ever therapeutic guidelines for EVD. The guidelines also included a conditional recommendation against the use of ZMapp and remdesivir, the two other treatment candidates in the PALM trial.

Although the approval of these products was a great achievement, the process of ensuring that people who need them can access them is at a standstill. As crucial contributors to the R&D of these treatments, survivors, affected countries and NGOs should have a say in this process. However, we see that decisions related to access and affordability are currently left only to the private corporations holding legal rights and regulatory data, and to the goodwill of these corporations and national governments. The US government has set up its own emergency stockpile of EVD treatments which contains nearly all currently available treatments. As a result, these treatments have not been adequately rolled out as lifesaving public health tools for people in countries where outbreaks occur and are instead retained primarily as biosecurity tools. Other actors such as the European Union (EU) have also shown interest in establishing their own stockpile as part of their pandemic preparedness efforts. More than two years since their approval and five outbreaks of EVD later, the recommended medicines are still far from being used to their full potential in outbreak response.

In addition, as of April 2023, the format, size, governance, and location of a UN/WHO global stockpile of EVD treatments were still under discussion. The offered price per treatment course has not been disclosed but is likely to be exorbitant based on the estimated price paid by the US for its stockpile. The ambitions for the size of the UN/WHO stockpile may have to be considerably scaled down due to price barriers and lack of supply. It is uncertain at this stage whether a global UN/WHO stockpile will be established in the near future, leaving people, countries and treatment providers like MSF without direct access to the two medicines whose development they contributed to for future outbreaks of this deadly disease.

REPORT SCOPE AND METHODS



Members of an MSF medical team attend to a 16-year-old patient at a treatment centre in Sierra Leone. © Fabio Basone/MSF

This report focuses on treatments for disease caused by *Zaire ebolavirus*. Currently, there are no approved treatments for disease caused by any of the other species of Ebola virus, but the lessons learned from the R&D of existing treatments and the recommendations made within this report are of direct relevance to treatments targeting other species that may be developed in the future.

The report compiles and analyses information that can contribute to a thorough consideration of decisions regarding management, volume, allocation and pricing of treatments in a global stockpile of treatments for EVD. We consider R&D contributions, estimated manufacturing

costs, market dynamics and ownership of technologies and intellectual property (IP) related to mAb114 and REGN-EB3.

The report pays particular attention to contributions from the US government because it was the largest public funder in terms of cash outlays. The US is also currently the largest purchaser of these treatments. Although the UN/WHO has expressed ambition for a globally coordinated procurement mechanism and the European Union has interest in establishing its own stockpile, both of these are for the moment greatly outweighed by the size of the US government stockpile of EVD treatments.

While it continues to pose a significant global public health concern, Ebola virus is also one of several pathogens being discussed as a “pathogen of pandemic potential” across a multitude of global pandemic preparedness discussions. Hence, although the US government has played an instrumental role in the development of these new therapies and remains a key stakeholder, numerous other actors worldwide – particularly endemic country governments and affected communities – must be at the centre of access discussions as they carve out their own pandemic and outbreak preparedness actions.

The Product Details Supplement annexed to this report provides more extensive information for the two treatments, including:

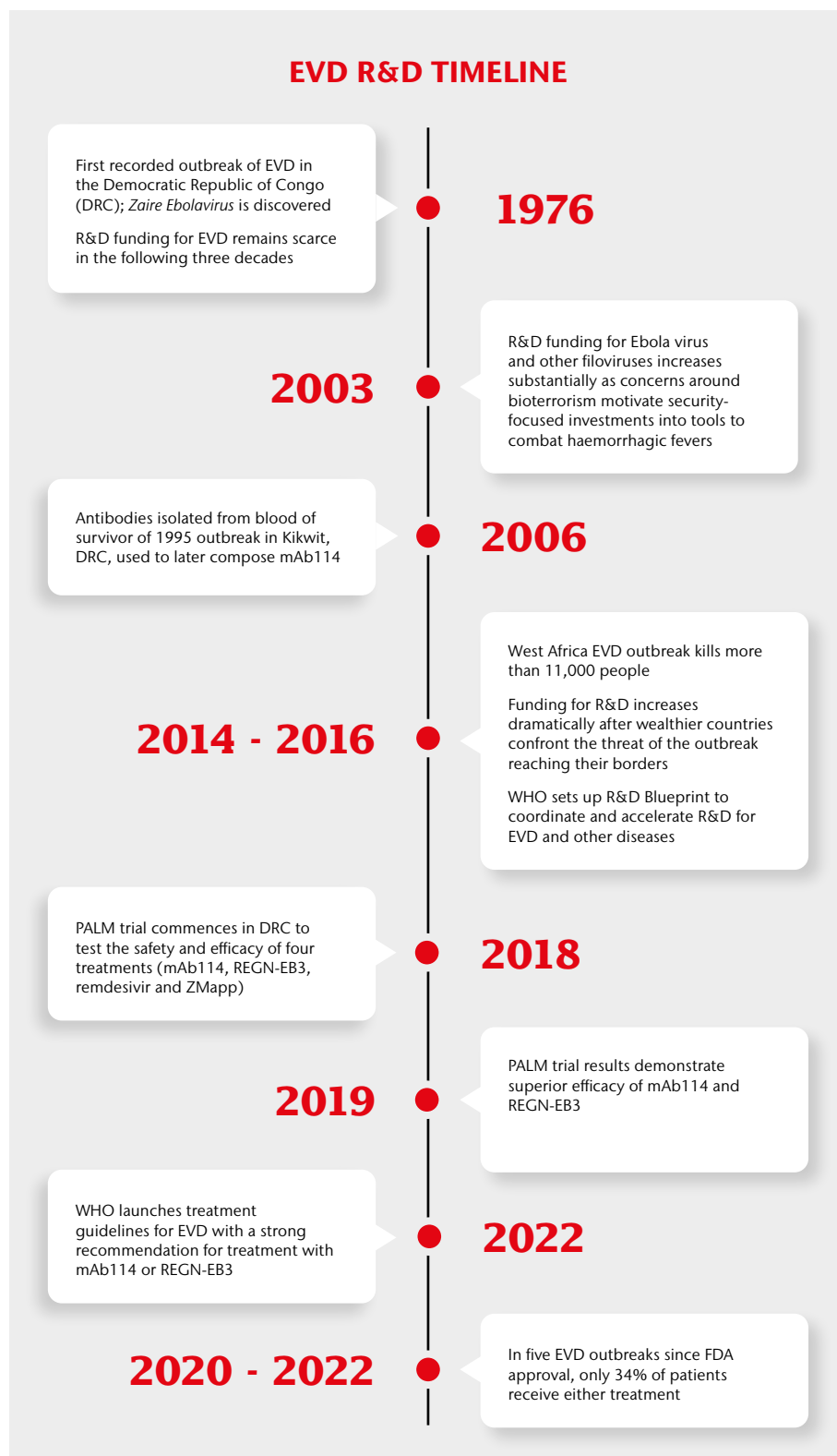
- background on the pharmaceutical corporations that hold IP licenses and regulatory approvals on each treatment;
- an overview of each treatment’s discovery;
- a summary of what is known about the manufacturing process of each treatment – including estimated manufacturing costs;
- a non-exhaustive list of patents identified on the EVD treatments; and
- the details of known public and private sector funding and resources behind each treatment.

Information was collected via a desk review of public reports, public databases, documents shared among the partners of the PALM clinical trial; interviews with manufacturers (including extensive interviews with Ridgeback and Regeneron); and informal conversations with different US government agencies, including the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA). Interviews were conducted by MSF staff and a research consultant. Both manufacturers were provided an opportunity before publication to comment on our findings on public and private contributions to R&D and manufacturing estimates. We did not receive any response from them.

Much of this analysis performance relies on third party information, estimates or incomplete data. Pharmaceutical corporations generally refuse to reveal their actual costs of researching, developing and manufacturing a medicine, including how much taxpayer funding they received to develop the medicine. Despite a 2019 World Health Assembly resolution that mandates improved transparency of markets for medical products, we still do not know the prices of each product, what corporations are charging each purchaser, clinical trial costs and other relevant information included in the resolution. Even public funders such as governments are not transparent with funding and resource information in ways that would best serve price negotiations and enable public accountability. For example, several grants identified in the Product Details Supplement do not include actual grant amounts. The costs of publicly funded clinical trials are also not disclosed. Finally, we were confronted with opacity from suppliers about the number of doses that have been manufactured and sold. It is unclear whether this reflects a choice on the part of the manufacturers or results from the terms of their supply agreements with the US government.

DELIVERING NEW TREATMENTS FOR EVD: A COLLECTIVE EFFORT

The R&D of EVD treatments after decades of neglect was possible due to the collective effort of a breadth of actors. This included contributions from governments of the US, Canada, Switzerland, Germany, France, China; pharmaceutical corporations; critical research efforts by public research institutions; ministries of health, public researchers and medical professionals in endemic countries; contributions from EVD survivors; and support from WHO and NGOs such as the International Medical Corps (IMC), the Alliance for International Medical Action (ALIMA) and MSF. Several unprecedented multi-stakeholder consortia involving both public and private actors emerged from this joint effort, ultimately generating the safety and efficacy data relied upon for approval of two new treatments. Among these were the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) ethical protocol for EVD treatments, the Partnership for Research on Ebola Virus in Liberia II (PREVAIL II) clinical trial in West Africa and the PALM clinical trial in DRC.



EVD TREATMENTS R&D TIMELINE

1976-2013

Although the Ebola virus was discovered in 1976, R&D funding for medical tools to diagnose, prevent, or treat the disease was scarce until the early 2000s. Because EVD was perceived as a disease causing mostly small-scale outbreaks in poor rural communities in central Africa, R&D efforts for diagnostics, treatments, and vaccines had been extremely limited, as is the case with many neglected tropical diseases (NTDs).¹ In 2002, global R&D funding towards filoviruses (Ebola, Marburg, and others) was still low, estimated at US\$5.2 million.² However, it increased substantially in 2003, when concerns around bioterrorism motivated security-focused investments into medical countermeasure tools to combat haemorrhagic fevers, particularly by the US government.³ In 2006, 11 years after the 1995 EVD outbreak in Kikwit, DRC, several antibodies were isolated from the blood of a survivor, where mAb114 later showed the most promising effect in non-human primate studies.⁴

2014-2017

When the 2014-2016 EVD outbreak began in West Africa, people were without any specific and targeted medical countermeasures, as had been the case during outbreaks in previous decades.

It was during the epidemic in West Africa, when wealthier countries faced the threat of the outbreak reaching their borders, that funding for R&D increased dramatically. It was also during this time that the first real clinical trials were set up with the aim of helping develop better tools to tackle EVD. Based on the lessons learnt from preparing for and responding to epidemics including EVD, WHO set up their Blueprint for R&D. The blueprint aimed to coordinate and accelerate R&D, bringing together multidisciplinary experts to develop R&D roadmaps followed by target product profiles (TPPs) to be used as a guidance for future epidemic response for identified priority diseases such as EVD.

In the early phases of the outbreak in 2014, Regeneron isolated several antibodies from transgenic mice immunised with the glycoprotein of Ebola virus and combined three of these to compose REGN-EB3.⁵

2018 - present

When MSF teams responded to another outbreak in DRC in 2018, they were equipped with new tools and improvements in the medical management of EVD. These included new investigational treatments, two then-experimental vaccines that later received regulatory approval (FDA, EMA and WHO Prequalification in 2019 for rVSV-ZEBOV from Merck, and EMA and WHO Prequalification in 2020 for Ad26.ZEBOV/MVA-BN-Filo from Johnson & Johnson), as well as simpler diagnostics.

By August 2018, at the start of the EVD outbreak in DRC, treatment providers like MSF had access to five investigational treatments (mAb114, favipiravir, REGN-EB3, remdesivir, ZMapp) via the MEURI ethical framework. This framework, established by WHO in collaboration with a committee of international experts, allowed treatment providers to access investigational treatments outside of a clinical trial setting if specific criteria were met. A few months later, the use of treatments for EVD switched from the MEURI protocol to the PALM randomised clinical trial – a critical step since clinical trials can generate the scientific data needed to draw conclusions on the effectiveness and safety of treatments.

PALM trial

It was only in November 2018 – over 40 years after the virus was discovered – that the first-ever multidrug randomised controlled trial (RCT) for EVD treatments launched in DRC. The PALM trial tested the safety and efficacy of four investigational treatments. This included three monoclonal antibody (mAb) therapies (mAb114, REGN-EB3, and ZMapp) and one nucleotide analogue antiviral (remdesivir).⁶

The challenges of conducting a scientifically rigorous and ethically sound clinical trial in a conflict zone within DRC should not be underestimated. The level of collaboration behind the PALM clinical trial was unprecedented. Conducted through an international research consortium coordinated by the WHO, the trial was co-sponsored and co-funded by the Institut National de Recherche Biomédicale (INRB; part of the DRC Ministry of Health) and the National Institute of Allergy and Infectious Diseases (NIAID; part of the US National Institutes of Health [NIH]). Patients were enrolled across four treatment centres in Beni, Katwa, Butembo and Mangina. The treatment centres were managed by the INRB and the DRC Ministry of Health, and by three medical humanitarian organisations – ALIMA, IMC and MSF.⁷ MSF-operated EVD treatment centres in Butembo and Katwa, in North Kivu, DRC, enrolled patients for the trial during February 2019 for a short period before operations were suspended following attacks on the medical facilities. Other critical partners in the trial included BARDA, the US Centers for Disease Control and Prevention (CDC), MSF's epidemiological research arm Epicentre, the University of Minnesota (USA), and the WHO.⁸

In August 2019, with 681 patients enrolled in the study, the trial's independent data and safety monitoring board recommended that two of the treatments be dropped from the study (remdesivir and ZMapp).⁸ After analysing data from 499 patients, the board announced that REGN-EB3 and mAb114 – both mAb therapies – were deemed more effective, and that moving forward, all patients would be randomised to receive one of these two treatments in an extension phase of the study. The results were published in December 2019; an analysis of 681 patients confirmed that the proportion of deaths among those who received mAb114 and REGN-EB3 was significantly lower than among those who received ZMapp and remdesivir. In October 2020, the FDA approved REGN-EB3,

marketed by Regeneron as Inmazeb, as the first EVD treatment.⁹ In December 2020, the FDA also granted approval to a second treatment, mAb114, marketed by Ridgeback as Ebanga.¹⁰

While Ridgeback has filed for registration of REGN-EB3 in DRC in 2022, neither treatment is currently registered in any endemic country. This means that the treatments are not adequately available where outbreaks regularly occur and can still only be administered by designated treatment providers in accordance with the MEURI protocol.¹¹ For now, the treatments can be accessed only through ad-hoc donations by companies or the US government.

To support the national and global efforts to increase access to and affordability of products for treatment of EVD, WHO issued the first invitation to manufacturers of EVD treatments to submit an expression of interest (EOI) for product evaluation to the WHO prequalification (WHO PQ) unit in 2021.¹² As of April 2023, no company has submitted their portfolio for WHO PQ. Regeneron has informed WHO that they are in the process of compiling their information for submission.¹³

WHO EVD treatment guidelines

In August 2022, the WHO launched their first-ever EVD treatment guidelines with a “strong recommendation for treatment with mAb114 or REGN-EB3 for patients with real time polymerase chain reaction (RT-PCR) confirmed Ebola virus disease (EVD) and for neonates of unconfirmed EVD status, 7 days or younger, born to mothers with confirmed EVD”. The guidelines included a conditional recommendation against the use of ZMapp and remdesivir.¹⁴

Based on the available evidence regarding the efficacy of mAbs against Ebola virus and their optimal use in the early stages of the disease demonstrated in the PALM trial, MSF believes that the current guidelines do not go far enough in their recommendations. The treatments could and should be used in a more liberal way to prevent disease and reduce mortality based on the available evidence regarding the efficacy of mAbs against EVD. Currently, due to the limited availability of these drugs, post-marketing investigations for use in other indications, including post exposure, has not been feasible.

Expanding the recommendation would entail adopting a much wider indication for their use. This includes 1) as post-exposure prophylaxis in high-risk contacts who do not show signs of EVD or have a positive PCR test, and 2) as a treatment for individuals with signs and symptoms compatible with EVD and whose contact history is strongly suggestive of Ebola virus infection, and for individuals who test positive on a rapid diagnostic test (RDT), while awaiting PCR test results.^a

Restricting use of the treatments to only PCR-confirmed cases delays their administration and thus jeopardises their effect. The restrictive guidelines also, therefore, prevent the accurate estimation of the true supply needs for the two treatments.

Since the FDA approvals in 2020, real-life access to the two treatments has proven to be limited during outbreaks. A recent study authored by scientists from BARDA and NIH revealed that only 53 out of 158 patients (34%) with confirmed Ebola infection during the five outbreaks in DRC and Guinea between 2020 and 2022 received treatment with either REGN-EB3 or mAb114.¹⁵ While logistical hurdles may have contributed to the low coverage, the treatment coverage should be closer to 100% for confirmed cases admitted to a treatment centre.¹⁶

An application has been submitted for inclusion of the treatments in the 2023 update of the WHO Model List of Essential Medicines; MSF has endorsed their inclusion. However, as of April 2023, MSF and other EVD outbreak responders such as the WHO did not have an overview of how to gain reliable and sustainable access to the recommended treatments for patients.



Uganda Ebola disease outbreak, 2022-23

In September 2022, Ugandan health authorities declared an outbreak of disease caused by *Sudan ebolavirus*, the first documented outbreak caused by this species since 2012. At the onset of the outbreak, no approved vaccine or treatments were available, as the approved medical countermeasures for disease caused by *Zaire ebolavirus* are not effective for disease caused by other species of *Ebolavirus*. The outbreak led to a rush in investment to try to bring promising candidates whose development had stalled due to a lack of interest and funding, into clinical trials. However, when the outbreak was declared over 113 days later after 164 cases (142 confirmed and 22 probable) and 77 deaths (55 confirmed and 22 probable), no clinical trial for either vaccines or treatments had started. Disappointingly, even after the experience with the development of medical tools for disease caused by *Zaire ebolavirus*, the international community has yet to learn and move from responsiveness to preparedness for R&D for outbreak-prone diseases.

Photo caption: An MSF health promoter talks with a shopkeeper in Madudu, close to the epicentre of the 2022 Ebola disease outbreak in Uganda. © Sam Taylor/MSF

^a A 2022 meta-analysis of diagnostic accuracy studies reported an overall sensitivity of 86.1% and specificity of 97% in EVD RDTs, and an overall sensitivity of 96.2% and specificity of 96.8% for PCR tests. Given their high specificity, RDTs could be used as a 'rule in' test, but should not be used to rule out disease due to a substandard sensitivity. See more: <https://doi.org/10.1016/j.cmi.2022.09.014>

R&D CONTRIBUTIONS



A technician from the Public Health Agency of Canada testing a patient's blood sample. © Sylvain Cherkaoui/Cosmos

We have identified 20 sources of direct or indirect public funding for research, development, manufacturing and/or procurement. Due to a lack of transparency across the R&D system, we cannot confirm whether these are reflective of all public contributions, nor can we confirm any private contributions. For many of these grants and agreements, we also do not know how much money has been contributed. However, among the 8 grants and agreements that do publicly disclose funding totals, we identified approximately \$800 million in public contributions.

We detail these contributions not only to emphasise the extent of public contributions for the development of the treatments, but also to underscore how access to the treatments in endemic countries remains insufficient despite these contributions.

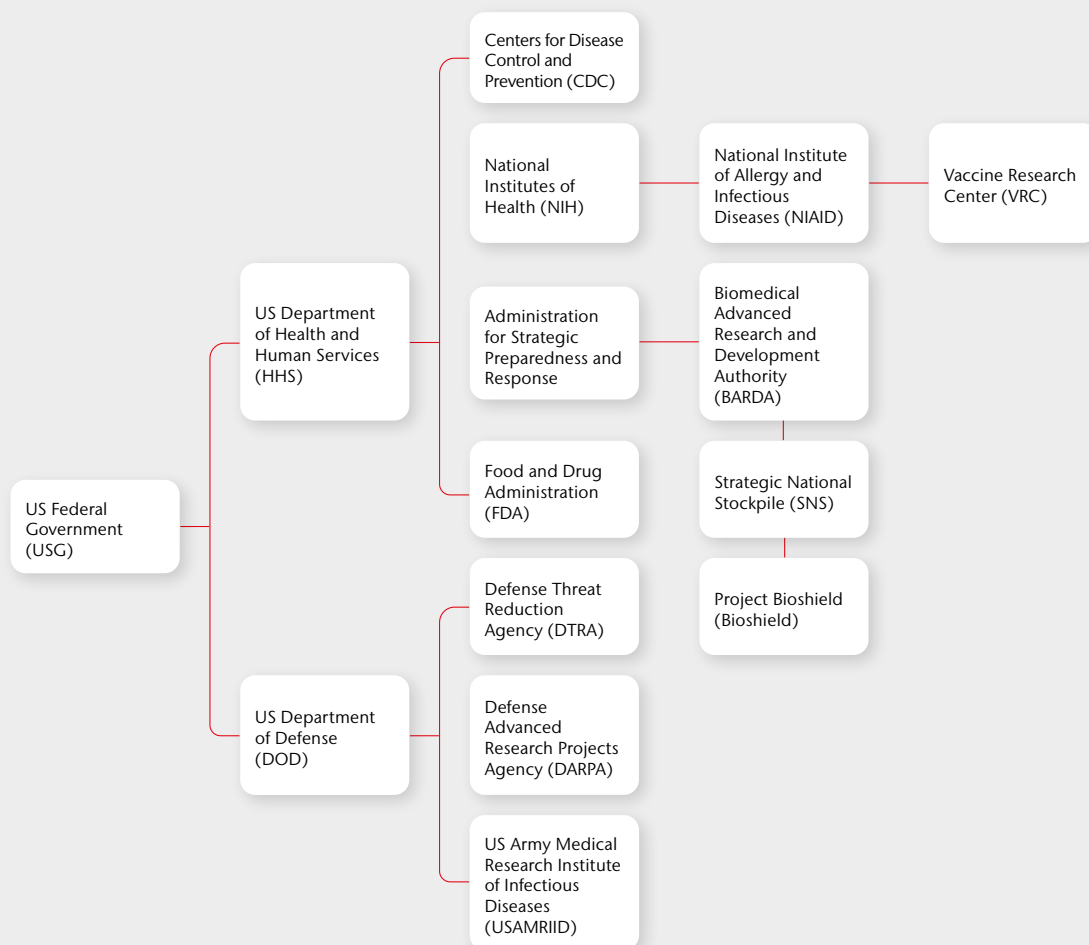
US GOVERNMENT R&D CONTRIBUTIONS

The US government has contributed hundreds of millions of dollars in direct R&D funding towards the four PALM trial EVD treatment candidates. Additionally, the US government has committed to purchase approved products (detailed in the

“Stockpiling EVD treatments” section) in advance as an additional incentive to support product development. As far as mAb114 and REGN-EB3 are concerned, we estimate that at least \$800 million were invested towards their development and procurement (detailed in the Product Details Supplement). The US has also granted public rewards and incentives to several treatment candidates and has contributed in-kind support.

As is true for several other countries, Ebola virus has been identified by the US government as a biodefence material threat, and the mobilisation of funding for US government research, development and manufacturing support have therefore been motivated by biodefence priorities.¹⁷ US government support for EVD R&D has come primarily from two departments: the Department of Health and Human Services (HHS) and the Department of Defense (DoD). Although being considered as part of the biodefence agenda has catalysed the research for an otherwise neglected disease, the immense public funding driven by domestic biosecurity objectives has also resulted in these new treatments being considered primarily as biosecurity tools rather than as public health tools for outbreaks that primarily impact people in low- and middle-income countries (LMICs).

Figure 1: US government agencies funding EVD treatment research, development and procurement



Direct funding from US HHS and DoD

Sitting within HHS, the Administration for Strategic Preparedness and Response (ASPR) is charged with “saving lives and protecting Americans from 21st century health security threats” and has played an integral role in the R&D of the EVD treatments through BARDA.¹⁸ This agency has supported the development of mAb114 and REGN-EB3. The Strategic National Stockpile (SNS) and Project Bioshield also sit within ASPR and have in part incentivised EVD treatment development by assuring developers of a market through supply commitments. The SNS stores medicines for emergency use, including those developed by BARDA. (See “Stockpiling EVD treatments” for more details).

HHS funding for R&D for EVD treatments has also come via agencies and programmes under the NIH, the US government’s medical research agency. This includes the preclinical development of mAb114, carried out in-house by NIAID and the Vaccine Research Center (VRC). NIAID also co-financed and sponsored the PALM clinical trial and led the PREVAIL II RCT of ZMapp during the 2014–16 EVD outbreak in West Africa.

In addition to HHS, the US DoD has supported R&D for EVD treatments through the Defense Advanced Research Projects Agency (DARPA), the Defense Threat Reduction Agency (DTRA), and other entities such as the US Army Medical Research Institute of Infectious Diseases (USAMRIID).³

Non-financial US government support

The contributions of the US government are greater than direct funding alone. R&D for EVD treatments may also have benefitted from a variety of US federal resources including laboratory equipment, human resources, technical expertise and federally funded public university research facilities. For example, beyond direct monetary support, BARDA has also provided valuable technical assistance and managed clinical research and manufacturing networks for both its public and private partners.¹⁹ Additionally, cooperative research and development agreements (CRADAs) also represent significant in-kind support. Direct payments are typically not allowed under CRADAs, but CRADAs grant the use of US government personnel, services and highly specialised facilities. Unfortunately, the value of these public contributions is unknown. CRADA financial details are exempt from disclosure under the Freedom of Information Act.

Although it is difficult to identify, track and estimate the value of in-kind inputs, both treatments benefitted from significant in-kind public contributions to their R&D.

US rewards and incentives

Beyond direct funding and in-kind support, prospective and approved EVD treatments may also qualify for additional incentives and rewards from the FDA, including priority review vouchers and special designations explicitly designed to spur innovation and access.

Priority Review Vouchers

The Priority Review Voucher (PRV) programme grants clinical trial sponsors that successfully register an eligible medicine or vaccine a 'voucher' (or a PRV) for priority review of another product that would not qualify for an accelerated review on its own merit. In the US, there are two types of PRV programmes relevant to EVD, namely PRVs following approval of products treating tropical diseases and PRVs following approval of certain medical countermeasures.^{20,21} A PRV reduces the targeted review time for an application by four months, valuable additional time on the market for companies with high-grossing products. PRVs can be used by the recipient or sold, with vouchers regularly selling for around \$100 million.²²

Both Regeneron and Ridgeback were awarded PRVs for their respective treatments under the medical countermeasures PRV programme.^{11,23} As far as we are aware, these two PRVs have not been used yet or sold to a third party.

The Orphan Drug Designation Programme

The FDA's Orphan Drug Designation programme awards corporations with a tax credit on qualifying clinical R&D expenditures (25% on expenses incurred in 2018 or later, and 50% on expenses before 2018); a seven-year period of market exclusivity upon FDA approval; and a waiver of the FDA user fee.²⁴ Both REGN-EB3 and mAb114 were designated orphan drugs at the request of the pharmaceutical corporations.^{25,26}

Additional incentives

EVD treatments are also eligible for additional incentives under other FDA programmes. For example, both REGN-EB3 and mAb114 were granted Breakthrough Therapy Designations, entitling Ridgeback and Regeneron to heightened FDA consultation with senior managers, rolling review, and potential for priority review and accelerated approval.^{10,27,28}

The role of patents and other IP exclusivities in limiting access to mAb114

Patents have been granted and are being pursued in several countries by multiple entities for mAb114 and REGN-EB3 (see Product Details Supplement).

For instance, a patent with broad claims has been granted to Regeneron in the US in September 2017 (US 9,771,414) and September 2018 (US 10,081,670).^{29,30} An equivalent patent application has been filed under the WIPO Patent Cooperation Treaty (PCT) system and in multiple countries.³¹ The broad claims of this patent cover the antibodies themselves, their production methods, antibodies which bind to the same epitope as the antibodies covered by the patent, and their use in combination with other antivirals or vaccines. To date, Regeneron has not engaged in any licensing or technology transfer agreements with entities in endemic countries despite the substantive support it got from these countries in conducting R&D on REGN-EB3.

The example of mAb114 further illustrates how exclusive IP rights have played a role in limiting access to the medicine in countries where it is needed most. HHS, which hosts NIH, was granted a patent in the US on mAb114 with very broad claims.³² This usually grants the patent-holder exclusivity over the patented compound for 20 years starting from the date of filing.

During the PALM trial in DRC, in December 2018, it was reported that Ridgeback signed a patent licensing agreement with NIAID of NIH which would allow the company to further develop mAb114.³³ However, the licensee Ridgeback, which has been called a “molecule-flipping” company, cannot be described as a “traditional” pharmaceutical company.³⁴ Among other things that separate it from such a company is the fact – particularly material here – that it has no in-house production capacity or R&D

division. In fact, in 2022, it entered into an agreement with Emergent BioSolutions for the manufacturing, sale and distribution of mAb114 in the North America market.³⁵ Ridgeback continues to be the sole supplier of mAb114 for the rest of the world.

The patent licensing agreement between NIH and Ridgeback in 2018 was non-exclusive, due to the fact that NIH at the time envisioned the granting of a second license for mAb114.³⁶ However, in March 2021, without explicit public justification, NIH announced its plans for an exclusive patent licensing agreement with Ridgeback on mAb114.³⁷ Critics considered this move controversial because exclusive licensing may result in severe access restrictions if the licensee does not find sufficient commercial incentive to produce the treatment and/or sell it in certain markets. This was a particular concern for EVD treatments given the limited anticipated commercial return as a consequence of uncertain and restricted general public demand, and especially concerning in light of the fact that Ridgeback had already obtained the exclusive right to use technical data developed from government-sponsored clinical trials and been awarded a PRV for mAb114.³⁸

Crucially, for biological treatments, access to the originator mAb (as the comparator product) is critical for the entry of alternative producers. Biosimilarity to the comparator product must be demonstrated for regulatory approval; without this, biosimilar developers would need to conduct clinical trials to demonstrate the safety and effectiveness of their product. Data exclusivity represents another hurdle for developers. An application for registration of a biosimilar product can only be made after the data exclusivity period: in the US, data exclusivity for biologics is for 12 years.

Granting exclusive rights and licensing a patent to only one company which has neither a track record nor actual in-house capacity to manufacture and supply is deeply problematic.

These IP management steps taken by the US government on mAb114 unnecessarily concentrated the power to determine how patients in endemic LMICs could get access to the treatment in the hands of a single US company. Any evaluations or criteria relied on by the US government to make this decision are not publicly known.

In recent communications with MSF, Ridgeback continues to avoid disclosure of important information on supply and pricing and currently only offers mAb114 through an ad-hoc donation programme.

The example demonstrates how in this case patents and exclusivity rights were not used as tools to incentivise product development, but rather created monopolies blocking reliable access to treatments for EVD. While a more open-science and public-good approach with a global vision could have been explored, the US government and pharmaceutical corporations regrettably favoured a market-incentive-based model that does not address people's needs in endemic countries.

While a more open-science and public-good approach with a global vision could have been explored, the US government and pharmaceutical corporations regrettably favoured a market-incentive-based model that does not address people's needs in endemic countries.

To change the current situation with respect to the monopoly around mAb114, a possible first step is to identify alternative manufacturers, ideally in endemic countries or the African region, which could receive a licence and knowledge/technology transfer.

When IP and other exclusivities act as barriers to pursuing such an option, governments should consider using flexibilities enshrined under international law. One such flexibility is compulsory licensing on patents, which exists within the TRIPS Agreement and has been used by governments in the past to overcome patent barriers in order to support better access options through production or importation of medicines for endemic countries. It is necessary to overcome these exclusivities in order to address sole supplier issues.

As public health needs for access to treatments for NTDs such as EVD do not represent a lucrative market, relying on market dynamics based on exclusivities is the wrong strategy to support access. Instead, a more direct policy intervention is needed to ensure that technologies, data and know-how needed to produce these monoclonal antibody therapies are made available to capable manufacturers dedicated to producing and supplying them for endemic countries.

Attaching conditions to public funding to ensure access and transparency

Since public money funded most if not all the R&D for both products, public funders, including the US government, were in an ideal position to demand a set of binding and publicly available access conditions in exchange for their funding.

This could have included the following conditions to ensure access and availability to the final products:

- Affordable and transparent pricing requirements for end products (a cost of goods plus reasonable margin or no profit-no loss during a public health emergency could have served as models);
- Non-exclusive licensing/technology transfer requirement to ensure diversity of manufacturing and supply;
- Funders' retention of rights linked to the research funded in the event that the manufacturers' supply does not meet demand in a timely manner or is not reasonably priced (making reference to so-called "march-in rights");
- Transparency requirements, including publication of full R&D costs, clinical trial costs, clinical trial protocols and disaggregated preclinical and clinical trial results data, subsequent IP licensing, sub-licensing and technology transfer agreements, prices and cost of production, and information on supply capacity and delivery schedules;
- Access plans and transparent indicators which encompass registering and making available the drugs, vaccines or diagnostics, particularly where clinical trials were hosted; and

- Timely access to comparator drugs, tests, assays or vaccines needed for comparison studies, regulatory approvals and/or R&D.

As the details in the contracts between NIH and Ridgeback are not publicly available, we cannot ascertain if any of these conditions were actually included in the contract. Critically, the full contractual terms of the R&D funding and IP licensing agreements should have been published in their entirety by NIH.

OTHER PUBLIC AND NON-PROFIT CONTRIBUTIONS (NON-US GOVERNMENT)

Non-US governmental agencies, NGOs, other public and philanthropic actors and EVD patients and survivors have also made essential contributions to the discovery and preclinical and clinical development of EVD treatments.

The DRC's INRB played a key role in the development of mAb114. Both the PALM clinical trial and the establishment of the MEURI ethical protocol for EVD investigational treatments would not have been possible without the support of the Congolese Ministry of Health, WHO, and several NGOs, including ALIMA, IMC, and MSF and its research arm Epicentre. Similarly, the PREVAIL II RCT in West Africa (prior to the PALM RCT) was the result of a joint effort between several actors, including governmental agencies in affected countries (Liberia, Sierra Leone and Guinea), the French National Institute of Health and Medical Research (INSERM), and NGOs such as IMC and the French Red Cross.⁸

The contributions of EVD patients and survivors to the R&D of treatments for EVD through the provision of clinical samples and participation in clinical trials have been critical. Regeneron used the sequence data from a virus isolated from an EVD survivor in making REGN-EB3, and mAb114 was identified by screening the immune cells of another EVD survivor.^{39,40} Further, the PALM clinical trial, and the pivotal evidence it generated, would not have been possible without the participation of EVD-affected communities in the DRC. During past EVD outbreaks, including the 2014-2016 outbreak in West Africa, clinical samples were collected and sent to laboratories around the world, enabling research and knowledge generation globally.

The management of clinical samples taken from EVD patients and survivors in affected countries is also an important issue in discussions regarding access to treatments for EVD. There was no clear articulation or effective regulation of the obligations of researchers and pharmaceutical corporations that used clinical samples to guarantee fair and equitable sharing of final products with the people and countries that provided them. The agreements that governed the export and use of samples abroad were often not publicly shared, and there is no evidence that they included any provisions on access, availability and affordability of the products that would later be developed.⁴¹

The contributions of EVD patients and survivors to the R&D of treatments for EVD through the provision of clinical samples and participation in clinical trials have been critical.



A lab assistant with blood samples from suspected EVD cases. © Sylvain Cherkaoui/Cosmos

Clinical samples access and benefit-sharing framework

At the international level, the Council for International Organizations of Medical Sciences' (CIOMS) ethical guidelines for medical research involving humans has long stated the importance of ensuring post-clinical trial access and benefit sharing (ABS) with people in low-resource settings who contributed in the clinical trial efforts.⁴² However, the non-binding nature of these guidelines and the unclear position on price, affordability and availability limit their application by pharmaceutical corporations.

An ABS mechanism for access to the influenza virus, including affordability of medical products, is included in the WHO Pandemic Influenza Preparedness (PIP) framework, which has been in place since 2011.⁴³ This mechanism is helpful for influenza virus-related treatments, as it provides an enforceable mechanism for WHO to request the private sector for financial contributions and reserved supplies to meet public health needs of LMICs, in exchange for access

to the influenza virus needed for product development. Although the PIP framework does not apply to EVD treatments directly, the experience of the PIP framework based on an enforceable ABS mechanism is a valuable reference to consider establishing similar mechanisms for other epidemic- and pandemic-prone diseases beyond influenza.

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, a legally binding supplementary agreement to the Convention on Biological Diversity, entered into force in 2014.⁴⁴ Ratified by 138 countries and the EU, the Nagoya Protocol aims to establish an accountable ABS mechanism such that monetary and non-monetary benefits arising from the utilisation of genetic resources are shared with their country of origin. Whether and how the Nagoya Protocol applies to specific real-world situations is complex and depends

on several variables, including the status of ratification and implementation in a given (origin or recipient) country, and the type of sample and its collection date. The full implementation of the ABS mechanism according to the Nagoya Protocol requires considerably improved collaboration, compliance, national legislation and political will from all stakeholders involved in sample collection and sharing, and in clinical trials. Moreover, some countries, including the US, have not signed the Nagoya Protocol.⁴⁵

Despite gaps in effectiveness and implementation of the Nagoya Protocol and ABS mechanisms at international and national levels, the principles and spirit of these tools could guide the governance with respect to access and sharing of clinical samples, access to clinical trial data, sequencing data, information and control over decisions affecting the availability and affordability of final treatments.

In 2022, the WHO initiated the BioHub programme aiming to “offer a reliable, safe, and transparent mechanism for WHO Member States to voluntarily share novel biological materials” concerning pathogens with pandemic potential, under standard conditions including ABS provisions.⁴⁶ While it remains unclear how the final rules and conditions would be established to manage and govern IP and ABS obligations, this emerging mechanism could potentially play an important role in the development of novel EVD tools in the future.

In addition, the ongoing WHO Pandemic Accord and International Health Regulations (IHR) review discussions may prove to be an important opportunity to substantiate an ABS mechanism for future pandemics and public health challenges, including EVD outbreaks.

PRIVATE SECTOR CONTRIBUTIONS

When pharmaceutical corporations refuse to disclose their R&D costs on a given medicine and reported company-wide R&D costs are not disaggregated, it is difficult to verify the amount of private sector expenditure that went into R&D; this is the case for these EVD treatments. Nevertheless, the evidence available regarding the size and nature of public contributions as well as Ridgeback’s late entry in mAb114’s development suggest that Regeneron and Ridgeback have invested very little in the therapies’ discovery and R&D.

Regeneron has shared that the bulk of R&D costs for REGN-EB3 were covered by their collaboration with the US government.⁴⁷ Private sector funding has not been disclosed for mAb114, but the treatment was fully publicly funded until December 2018, when it was licensed to Ridgeback.

STOCKPILING EVD TREATMENTS

A range of economic, scientific, epidemiological, political, and security factors – ones very likely to emerge again in the context of pandemic preparedness – contribute to the current access situation for EVD treatments.

First, as compared to traditional small-molecule pharmaceuticals, mAbs are expensive to produce, particularly at small scale. Second, it is likely that general global need for such treatments at any given time will be limited to a small number of treatments distributed across a handful of endemic countries situated largely on the African continent. Third, in most cases, these countries and many other procurers, such as WHO, are unable to purchase standing stock at the prices believed to have been offered to the US. Fourth, much of the R&D financing for these products has come from the US government, in part due to health and national security concerns, affording it a particular role in procurement. Fifth, the willingness of the US government as the only procurer to exercise leverage over the price is counterbalanced by an increased willingness to spend resulting from the national security grounds for procurement. Additionally, there will be no need to commercialise this product or incur marketing or advertising costs.

As a consequence of all these factors, the treatments are for the moment expected to be manufactured and procured primarily for storage in the US and potential UN/WHO and EU stockpiles in the future. It is important to bear in mind that these factors are also likely to arise with respect to medical tools developed for other pathogens with pandemic potential or those that may be considered biosecurity threats, but have limited, and geographically restricted distribution at any given moment.

The US government, via BARDA and SNS, is expected to be by far the largest purchaser of the new EVD treatments. Overall, the SNS has approximately \$600 million per year to purchase drugs and other medical countermeasures, funded by Project Bioshield.^{b,48} Procurement contracts with BARDA and SNS were initially signed with Regeneron and MappBio for REGN-EB3 and ZMapp respectively, following a call for proposals with a goal of procuring up to 753,000 treatment courses.⁴⁹ This number represents a maximum target, not what will be procured.

ZMapp did not advance in the PALM clinical trial and was not eventually stockpiled. The US government committed to purchasing 50,000 treatment courses of REGN-EB3 from Regeneron for \$345 million.^{64,91} By our calculations, this equates to an estimated price of \$6,900 per treatment course. This is nearly 10 times higher than our own estimate of the manufacturing costs for a treatment course of REGN-EB3 (\$750).

Purchase of mAb114 will take more time due to delays in production. Ridgeback has no in-house production capacity, and has licensed the treatment to Emergent BioSolutions for only the US and Canada markets. Representatives of Emergent BioSolutions have confirmed that the company is now the only manufacturer of mAb114 and that they will not be able to release any new doses before 2024. The production of new doses by Emergent BioSolutions is expected to be supported via a grant by BARDA, leading to their purchase by the US government by 2025. However, there is a possibility that a small number of treatment courses has already been stockpiled by the US government.

^b The scope of the SNS includes chemical and radiological medical countermeasures (MCMs). However, chemical and radiological stockpile items are typically less expensive than treatments for infectious diseases, and therefore tend to account for a relatively small proportion of overall expenditure.

When the SNS decides to purchase a therapy, BARDA is required to prepare an Independent Government Cost Estimate (IGCE) before negotiating how much it will pay the potential manufacturer. IGCEs take into account actual company expenses and a proposed profit, and could therefore provide valuable insight into manufacturing costs and pricing, but BARDA is not required to make IGCEs publicly available. In 2014, however, BARDA revealed that “fair and reasonable costs” for IGCEs are based on the price of similar products on the market; and in the case of mAb therapies, IGCEs are based on “historical as well as current market costs for similar products such as commercial antibodies used for other diseases.”⁵⁰

Using the price of current mAbs in the market to inform the price of future EVD treatments is problematic because the commercial prices for many mAb therapies in the US target non-communicable diseases such as cancer and are artificially high due to pharmaceutical company pricing decisions. They are not at all a reflection of their manufacturing costs. Prices for medicines in the US are generally set based on what the market can bear, an exercise further protected by patent monopolies, with no price controls or required links to any cost inputs such as R&D or manufacturing costs.

The EU has also shown interest in establishing stockpiles of vaccines and treatments for EVD as part of its RescEU programme, a common reserve of resources at EU level aimed at boosting the preparedness and response capacity for different types of crises, including pandemics.⁵¹ Such stockpiles could be established and managed by entities in EU member states with European Commission funding. The use of the stockpiled materials would fall under the EU Civil Protection Mechanism coordinated by the European Commission. The EU Civil Protection Mechanism can and does provide assistance to countries outside the EU. As the stockpiles are yet to be established, neither their potential size is clear, nor if there would be a willingness to make these materials available for use outside the EU when needed. At the moment, the two companies have also not filed for registration of the treatments at the European Medicines Agency (EMA).

UN/WHO STOCKPILE: PRICE AND GOVERNANCE

Now that two EVD treatments have been approved by FDA, a humanitarian stockpile should be established in preparation for outbreaks that will need doses at short notice.

Discussions are underway regarding the establishment of a global humanitarian UN/WHO stockpile for EVD treatments under the International Coordinating Group on Vaccine Provision (ICG), a mechanism led by the four member agencies MSF, WHO, International Federation of the Red Cross and Red Crescent Societies (IFRC) and United Nations Children’s Fund (UNICEF), that aims to manage and coordinate the supply of emergency vaccines and antibiotics to countries during significant disease outbreaks. The ICG is already responsible for managing the provision of EVD vaccines.⁵² Key decisions regarding who will manage the UN/WHO EVD treatments stockpile, what volumes will be maintained, what prices will be paid per treatment and who will pay, are yet to be made.

In August 2022, WHO sent multiple requests for quotations to Ridgeback and Regeneron for potential orders of different amounts of mAb114 and REGN-EB3 respectively.⁵³ Discussions on procurement and access were initiated between Ridgeback and the WHO but failed to materialise into any concrete agreement partly because Ridgeback has no plans to produce the treatment in the short term. Instead of contributing to a UN/WHO stockpile, Ridgeback has decided to restrict its access programme to its own “Rapid Response Team”, whereby a team of experienced EVD workers affiliated to or trained by the INRB in DRC are paid by the corporation to offer diagnosis and treatment with mAb114 free of charge during outbreaks.⁵⁴ The number of treatment courses stocked for future interventions through this programme has not been disclosed but, as additional doses of mAb114 will only be produced in 2024, it currently presumably consists of the leftover doses from the PALM trial. Based on our communications with Ridgeback,

this programme seems limited to DRC and does not respond to the needs of other organisations potentially involved in the treatment of EVD, including MSF.

Regeneron has yet to respond to WHO’s request. Should Regeneron offer WHO a price similar to that which it is estimated to have offered to the US government (\$6,900 per treatment course), the ambitions for the size of the UN/WHO stockpile would likely need to be considerably reduced. This limited size would stand in stark contrast to the tens of thousands of treatment courses already procured by the US government. This may leave WHO and others in a challenging position when responding to future outbreaks if the US government is not willing to share these doses in a timely and appropriate manner. Regeneron has systematically declined our requests to disclose its supply details for REGN-EB3.⁵⁵

MANUFACTURING COSTS

To help inform stockpiling discussions, we provide estimated manufacturing costs for EVD treatments below.

Calculating the manufacturing costs of medical tools relies on a complex list of costs that varies depending on the type of product. In the case of mAbs, the cost to produce the active pharmaceutical ingredients (APIs) represents by far the highest share of the overall manufacturing costs.⁵⁶ Other costs include product formulation and packaging. In some cases, combining several antibodies into a single mixture to form a mAb cocktail can also contribute to the overall manufacturing costs. Additional costs not directly linked to manufacture include overhead, distribution,

and licensing fees. The actual manufacturing costs for mAb114 and REGN-EB3 have not been disclosed by the manufacturers, so we are again relying on estimates. (Specific manufacturing cost estimates for mAb114 and REGN-EB3 can be found in the Product Details Supplement.)

The main drivers behind mAb manufacturing costs, expressed in dollars per gram, are the size of the batch (or grams of antibodies produced per litre of ‘medium’ in the bioreactor) and the productivity of the antibody (or how easily the antibody can be cultured).⁵⁷ For the purposes of this report, in line with another publication, we assume that a conservative estimate of the cost to manufacture mAb API in 2023 is no more than \$100 per gram for a “large” annual production of around 300kg per

year, and no more than \$250 per gram for a “small” annual production of around 50kg per year.⁵⁹

The cost to manufacture a full treatment course depends on this unit cost multiplied by the dosage needed to treat one person, expressed in milligrams of mAb per kilogram of body weight. Notably, the dosage of REGN-EB3 is particularly high (150mg/kg), three times more than that of mAb114 (50mg/kg) in part because it is a cocktail of three antibodies. For a person weighing 50kg, a full treatment course of REGN-EB3 is 7.5g. This could be produced for as low as \$750 with current production methods. Similarly, for a person weighing 50 kg, a full treatment course of mAb114 is 2.5g. This could be produced for as low as \$250.

Figure 2: Estimated costs to manufacture Ebola treatments for one 50kg adult

	REGN-EB3	mAb114
Dosage	150mg/kg	50mg/kg
Dose for 50kg patient	7.5g	2.5g
Estimated manufacturing costs	Small-scale production	\$1,875
	Large-scale production	\$750
		\$625
		\$250

Although still more expensive than the production of small molecules, the production costs for mAbs are expected to fall further below \$50/g for large scale production in the future as new technologies emerge.⁵⁸ A reduction in the required dose due to enhancements leading to increased effectiveness of the product could also bring down the price of the products significantly.

Given the tremendous amount of public involvement and investment in the research, development, manufacturing and procurement of mAb114 and REGN-EB3, these products should be priced accordingly, and no higher than at-cost plus a reasonable profit margin, based on verified or independently estimated manufacturing costs. Public contributors, including EVD-affected countries, should have a say in the plans to develop these stockpiles and determine volumes and governance issues.

EVD AND PANDEMIC PREPAREDNESS



A sign outside an MSF health facility in Conakry, Guinea, which translates to “All together against Ebola, always remain vigilant”. © Albert Masias/MSF

Access challenges with EVD treatments are a telling example of why the current global health architecture needs to be challenged and improved in order to ensure access to medicines for those who need it most. At the moment, WHO member states are negotiating a new instrument on pandemic prevention, preparedness and response, and in parallel revising the IHR and establishing a new global coordination platform for access to medical countermeasures. These processes provide an

opportunity to address the present gaps of ensuring access to medical products tackling existing pathogens with pandemic potential and possible new outbreaks. It is critical to reflect upon the multiple lessons learned from the access challenges to treatments for EVD, so that these processes can break from the status quo and establish effective mechanisms to ensure equitable access to lifesaving medical products based on health needs of people.

CONCLUSION AND RECOMMENDATIONS

EVD is a disease with a high mortality rate and devastating effects for people, families, communities and societies. The discovery, research and development of the first-ever effective treatments for the disease, mAb114 and REGN-EB3, are the result of a massive collaborative effort, involving patients/survivors, NGOs, affected governments, donor governments, pharmaceutical corporations, and numerous public resources. Although this should have revolutionised the management of EVD in endemic countries, the biosecurity imperatives for the R&D of these treatments have instead resulted in a situation where the treatments are being stockpiled in non-endemic countries, rather than used widely as lifesaving tools during outbreaks in countries where they occur.

The lack of access to the recommended treatments was already evident in recent outbreaks of EVD caused by the *Zaire ebolavirus*.

The granting of IP and other exclusive rights that cover clinical samples, underlying technologies, the products themselves as well as their pre-clinical and clinical use, coupled with a lack of transparency on critical information including R&D and manufacturing costs, mean that, in practice, EVD treatment globally is controlled by two pharmaceutical corporations. This control enables these corporations to ignore the multi-stakeholder effort that went into developing these products and restricts their potential to save lives.

After multiple requests to the companies, both from MSF and the WHO, we still have no overview on how to procure these lifesaving treatments. Outbreak responders need a clear answer from involved companies and stockpile owners on how to access mAb114 and REGN-EB3 in a timely, reliable and sustainable manner for the people who need them.

These shortcomings will reoccur when mAbs are developed for other diseases with pandemic potential if corrective action is not taken urgently. The following actions could help ensure transparency of processes and decisions made regarding stockpiles for EVD treatments, improve access and availability of treatments for everyone who needs them, and recalibrate R&D for future treatments for diseases with epidemic and pandemic potential:

Urgent access and stockpile considerations

- **UN/WHO** should create an international stockpile of EVD treatments based on health needs and linked to the ICG EVD vaccine stockpile in order to simplify distribution and procurement of both vaccines and therapeutics following outbreaks;
- **Africa CDC and national health authorities from endemic countries** should be involved in the design of the UN/WHO stockpile, including in discussions related to its size and availability of treatment courses;
- **Ridgeback and Regeneron** should urgently disclose their current and planned supply capacities, and transparently make the offered price available to potential buyers. Instead of donating treatments on a case-by-case basis, the companies should make them available to the UN/WHO stockpile to facilitate better outbreak-response planning;
- **Ridgeback and Regeneron** should submit their products for evaluation by WHO PQ without further delay to facilitate timely access to the treatments. The manufacturers, FDA and national regulatory authorities in endemic countries should consider the WHO Collaborative Registration Procedure route to accelerate registration of the treatments;⁵⁹
- **Ridgeback, Regeneron and WHO** should ensure that commercial negotiations for the replenishment of the UN/WHO stockpile are open to observers from international and endemic country NGOs, patient groups and endemic country governments;
- **WHO and the governments holding or establishing stockpiles** should regularly share information on demand forecast, inventories and prices of mAb114 and REGN-EB3. In the event of an EVD outbreak becoming a public health emergency of international concern (or if the UN/WHO stockpile is too small to tackle an outbreak), the US government and other governments or actors establishing stockpiles should make doses of the licensed treatments immediately available to UN/WHO upon request. Given the anticipated scenario of EVD treatment supply being split amongst these

multiple stockpiles, a mechanism should be established that triggers automatic reallocation from the larger stockpiles to the UN/WHO in the event of an unexpected large outbreak that exceeds the latter's response capacity. Such a model combining a WHO stockpile with doses from national stockpiles is already in place for smallpox vaccination stockpiles;⁶⁰ and

- **Ridgeback and Regeneron** should support post-marketing investigations of the treatments for use in other indications, including post-exposure use, through making the treatments available for such investigations.

Supply and price considerations in the medium term

- **Pharmaceutical manufacturers** should price their products no higher than at-cost plus a reasonable profit margin, based on independently estimated manufacturing costs; and
- **Endemic countries** which continue to face challenges in accessing treatments for EVD should consider **alternative mAb suppliers**, including LMIC manufacturers and not-for-profit manufacturers. If IP monopolies hinder the introduction of alternative manufacturers, they should also consider the use of necessary public health flexibilities to overcome these monopolies and to reduce the dependence on a single supplier of EVD treatments.

R&D and IP management considerations

- **WHO and member states** should reflect the key lessons learned from access challenges with treatments for EVD in the ongoing processes of strengthening pandemic prevention, preparedness and response, including the negotiation for a legally binding pandemic accord and amendment of IHR. Particularly, these processes need to include measures addressing ongoing access challenges for medical products tackling outbreaks caused by existing pathogens with pandemic potential and possible new outbreaks. The norm-setting processes should concretely address coordination of stockpiling at global and national levels, to ensure proportionality and equity;

- **Affected country governments**, via national research institutions and regional bodies such as Africa CDC, should lead the decision-making process on R&D priority setting and increase collaboration in R&D for EVD treatments based on public health needs in cooperation with WHO;
- **WHO** should ensure that decisions on the follow-on R&D agenda, including the prioritisation of other EVD treatments in the pipeline and the development of target product profiles (TPPs), are made under the auspices of the WHO R&D Blueprint strategy. TPPs for second-generation EVD treatments should include priority considerations for lower-dose pan-Ebola mAbs and small molecule treatment candidates. Medical practitioners, including NGOs treating EVD, should be part of the R&D priority setting process;
- **R&D funders** should be guided by the R&D priorities and TPPs set forth by WHO in their funding decisions. They should favour proposals based on open science and a not-for-profit model of R&D, production and supply in LMICs over conventional profit-driven and monopoly-based models of R&D and IP management. In funding agreements, they should include explicit and enforceable conditions to ensure priority access by people in the most affected countries and to ensure accountability in access in general. The conditions should include clear requirements and accountability for public disclosure of full R&D costs including clinical trial costs; clinical trial protocols and disaggregated preclinical and clinical trial results data; foreground and background IP and all licensing details; prices and cost of production, and information on supply capacities and delivery schedules; non-exclusive IP licensing of all technologies developed with the funding in favour of LMIC manufacturers; equal partnership and ownership in R&D with entities in LMICs; and technology transfer to LMIC actors;
- **All governments** should take steps to fully implement the WHO transparency resolution; and
- **Governments of affected countries, major donor countries and WHO** should provide access to clinical samples and genetic sequencing of relevant pathogens once clear ABS conditions are established in material transfer agreements. Additionally, they should improve norms and regulations concerning ABS to ensure fair and equitable benefit sharing and access to the end products by both communities that provided clinical samples for EVD research and all affected communities at country and global level. Public and private research entities should follow ABS principles in their research activities to support access by affected communities.

ANNEX: PRODUCT DETAILS SUPPLEMENT

mAb114 (EBANGA)

General information

- **Therapeutic class:** Single human Ebola monoclonal antibody (mAb)
- **Dosage and administration:** 50mg/kg in a single intravenous infusion
- **IP and licensing:** The Vaccine Research Center (VRC) of the US National Institutes of Health (NIH) is the owner of a primary patent on mAb114. It granted a patent license in December 2018 to Ridgeback Biotherapeutics (Ridgeback), a private US-based pharmaceutical corporation, founded in 2015 in Miami, Florida.⁶¹ Ridgeback is a very small company with limited staff and no in-house production capabilities. The licensing agreement between NIH and Ridgeback was originally non-exclusive, as NIH at the time envisioned the granting of a second license for mAb114. However, in March 2021, NIH announced its plans for an exclusive patent licensing agreement with Ridgeback on mAb114.⁴⁰ In July 2022, Emergent BioSolutions entered into an agreement with Ridgeback, and is now in charge of manufacturing, sale and distribution of mAb114 in the North American market.³⁷ As a result, Ridgeback continues to be the sole supplier of mAb114 for the rest of the world. The licensing agreement between Ridgeback and the NIH may have contained up-front payments and/or royalties.^c
- **Status:** mAb114 is one of two EVD treatments (along with REGN-EB3) that was deemed more effective in the PALM RCT. mAb114, now marketed as Ebanga, was approved by the FDA in late December 2020.

Discovery/use of clinical samples

mAb114 was isolated from the immune cells of a male survivor of the 1995 EVD outbreak in Kikwit, DRC. The discovery is the result of a collaboration between scientists in Switzerland (IRB, Humabs), DRC (INRB) and USA (NIH, USAMRIID). The survivor, 28 years old at the time of the outbreak, was one of only two survivors in a family of 15.⁶² The blood sample was drawn from the survivor in 2006 in the US following a standard specimen collection protocol of the NIH to obtain human biological samples for research studies.⁶³ Subsequent immune cell isolation and antibody cloning was performed in Switzerland at the Institute for Research in Biomedicine by European researchers.

Manufacturing

Manufacturing process

mAb114 is produced in a Chinese hamster ovary cell culture. Until 2020, mAb114 was exclusively produced in a small-sized bioreactor (1,000 litres) with a high yield by the NIH, or with contract manufacturers paid by the NIH.

^c The NIH requires licensees to bring inventions to practical application, and applicants must submit a development plan. The standard license also includes a provision for an initial royalty payment followed by payments based on license-specific benchmarks. The specific license terms agreed to by Ridgeback, however, are not publicly available. A model NIH license may be viewed here: <https://www.ott.nih.gov/sites/default/files/documents/pdfs/NIH-Patent-License-Nonexclusive-Sublicense-model-102015.pdf>

Ridgeback has no in-house production capacity and relies on contract manufacturers to release doses. Since July 2022, Emergent BioSolutions has become the sole producer of mAb114, following its agreement with Ridgeback, but will not be able to release a batch before 2024.

Hence, the stock of mAb114 administered over the last years were produced under the supervision of the NIH for use in clinical trials.

Manufacturing cost

The dosage to treat a person with mAb114 (50mg/kg) is one-third the dosage required for REGN-EB3 (150mg/kg). The manufacturing costs for a treatment course of mAb114 are therefore expected to be significantly lower comparatively.

To produce one treatment course of mAb114, we estimate that it should cost less than \$250 and \$625 with large- and small-scale production, respectively (Table 1).

Table 1. Estimated cost to produce one treatment course of mAb114

Scale of production	Yield (kg of mAbs per year)	Estimated manufacturing cost per gram	Estimated cost to produce one treatment course
Small (manufacturing in 2,000L bioreactors)	50 (equivalent to 20,000 treatment courses)	< \$250	< \$625
Large (manufacturing in 10,000L bioreactors)	300 (equivalent to 120,000 treatment courses)	< \$100	< \$250

Assuming a treatment course for a person weighing 50kg.

Public funding and resources

The R&D and manufacturing for mAb114 has benefitted from substantial public taxpayer support. The US government is the largest contributor (predominantly through the NIH), with additional contributions from Europe, the DRC and elsewhere.

US (HHS)

- NIH: R&D of mAb114 was led by the VRC and others at the NIAID, part of the NIH. The blood samples from the survivor of the 1995 EVD outbreak were collected at an NIH facility. It is not always possible to disaggregate NIH VRC expenditures that are specific to mAb114. Support for safety clinical trials of mAb114 and the PALM RCT of mAb114 in DRC was provided by NIAID.
- BARDA: late-stage pharmaceutical development and manufacturing scale-up benefited in 2020 from a grant by BARDA. Additional support to scale up manufacturing is being provided to

Ridgeback and Emergent BioSolutions from 2022 onwards.

- FDA: mAb114 was granted breakthrough therapy designation in September 2019. It also received a PRV and an orphan drug designation.
- DOD: support was provided to manufacture mAb114 for preclinical and clinical studies.
- USAMRIID: Animal studies, using a model developed by the NIH and the US Army, were conducted by USAMRIID in Fort Detrick, Maryland, US.

Europe

- Immune cell isolation and antibody cloning was performed in Switzerland at the Institute for Research in Biomedicine by researchers funded by the European Research Council.

DRC

- Two employees of the DRC INRB are co-inventors of mAb114.
- Organisations providing treatment in DRC, including Ministry of Health, NGOs and WHO, implemented the PALM trial confirming efficacy of mAb114.

See Tables 2 and 3 for more details on the direct and indirect public contributions to mAb114's R&D, organised by funder.

Table 2. Direct public funding and resources for mAb114

Funder	Item	Recipient	Amount
HHS BARDA ⁶⁴	Support GMP scale up to enable procurement	Emergent BioSolutions, Ridgeback	<i>Unknown</i>
HHS NIAID 1ZIAAI005081 ⁶⁵	Ebola Virology	Sullivan (NIAID/VRC)	\$12.1m
HHS NIAID 1ZIAAI005079 ⁶⁶	Ebola Vaccine Development <i>Assumed to also support antibodies</i>	Sullivan (NIAID/VRC)	\$23.5m
HHS NIAID 1ZIAAI005082 ⁶⁷	Ebola Vaccine Immune Correlates and Mechanism of Protection <i>Assumed to also support antibodies</i>	Sullivan (NIAID/VRC)	\$13.9m
Funder unknown ⁶⁸	Isolation and cloning of mAb114 performed in Switzerland by HuMABs (now Vir Biotechnology) and Institute for Research in Biomedicine	Vir Biotechnology Institute for Research in Biomedicine	<i>Unknown</i>
HHS NIAID NCT03478891 2018 ⁶⁹	Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-EBOMAB092-00-AB (mAb114), Administered Intravenously to Healthy Adults		<i>Unknown</i>
HHS NIAID NCT03719586 2019 ⁷⁰	Investigational Therapeutics for the Treatment of People with Ebola Virus Disease (PALM RCT)		<i>Unknown</i>
NIAID/VRC Intramural Research Program ⁷¹	Non-human primate studies of mAb114	USAMRIID	<i>Unknown</i>
DOD US Army ⁷²	mAb114 Manufacturing (up to 3 runs of 500L each)	Ology Biosciences	\$8.4m
DOD DARPA ^{73,74,75}	Manufacture of mAb114 for Phase 1 trial	NIAID/VRC, Medimmune, Catalent	<i>Unknown</i>
HHS (BARDA) 2019 75A50119C00059 ⁷⁶	For R&D and manufacture of mAb114	Ridgeback	\$14m
HHS (BARDA) 2020 75A50120C00009 ⁷⁷	For R&D and manufacture of mAb114	Ridgeback	\$20.2m

Table 3. Indirect public funding and resources for mAb114

Funder	Item	Recipient	Amount
FDA ²⁶	Orphan Drug Act subsidies	Ridgeback	US FDA user fee waiver, benefits including 50% R&D tax credit (2016-17) 25% R&D tax credit (2018 onward) ⁷⁸
FDA ¹⁰	MCM PRV	Ridgeback	Often worth > \$100m ⁷⁹

Private funding and resources

Ridgeback played no role in the preclinical and clinical development of mAb114. Given Ridgeback's limited staff and in-house capabilities, the corporation has contracted out the production of mAb114 and hired a third party to prepare the therapy's US FDA application. This is the only private sector investment for mAb114 known as of March 2023.

Summary of selected patent information

A patent with broad claims covering four variants of the antibody, their respective fragments, their cell lines, and antibodies which bind to the same epitope as the antibody and its variants, has been granted in the US to the HHS, which hosts NIH.³³ This enables NIH to manage the IP licensing related to mAb114.

REGN-EB3 (INMAZEB)

General information

- **Therapeutic class:** Combination of three human Ebola mAbs (atoltivimab, maftivimab, and odesivimab)
- **Dosage and administration:** 150mg/kg in a single intravenous infusion
- **Pharmaceutical corporation:** Regeneron Pharmaceuticals (Regeneron) is a publicly traded biotechnology corporation founded in 1988.⁸⁰ The company's products and research pipeline focus on infectious and rare diseases. Regeneron is headquartered in Tarrytown, New York, US. In 2022, Regeneron reported more than \$12 billion in sales.⁸¹
- **Status:** REGN-EB3 is one of the two EVD treatments (along with mAb114) that was deemed more effective in the PALM RCT. REGN-EB3, now marketed as Inmazeb, was approved by the US FDA in 2020 and recommended by the WHO in 2022.

Discovery/use of clinical samples

Recombinant glycoproteins of the Makona strain of the *Zaire ebolavirus* were used as immunogen to generate REGN-EB3. This strain is an early isolate from the 2014-16 outbreak. It was isolated in a clinical sample of an EVD survivor – a Guinean woman known as C15 – taken by an MSF team, and sequenced by the Bernard Nocht Institute in Germany.³⁹ These target proteins were injected into genetically modified mice, developed by Regeneron (VelocImmune^d), where target-antibodies (REGN-EB3) were generated.

Manufacturing

Manufacturing process

REGN-EB3 is produced in a Chinese hamster ovary cell culture.⁸² The three different antibodies are combined to create the mAb cocktail. Regeneron has production facilities in Rensselaer, New York, US, and the corporation's facility in Limerick, Ireland, may also be capable of producing the medicine.^{83,84} REGN-EB3 is currently produced in large-sized bioreactors with a high yield, in accordance with their contract with the US government to produce the treatment for the US Strategic National Stockpile.⁸⁵ Production of up to 50,000 treatment courses intended to be procured by the US stockpile was initiated.⁶⁶

Manufacturing cost

Large-scale production (manufacturing in 10,000 litre bioreactors) may yield around 300kg of mAbs per year, which is equivalent to 25,000 treatment courses of REGN-EB3. Assuming that a manufacturing cost of less than \$100 per gram could be reached for the API, we estimate that it should cost less than \$750 to produce the API for one treatment course of REGN-EB3 (Table 4).

^d VelocImmune is a mouse-based technology owned by Regeneron that produces human mAbs. Regeneron uses this technology for a wide variety of projects, including for arthritis research and to produce cancer monoclonal antibodies. It was not developed specifically for EVD. For more information, see: <https://www.regeneron.com/technology>.

Table 4. Estimated cost to produce one treatment course of REGN-EB3

Scale of production	Yield (kg of mAbs per year)	Estimated manufacturing cost per gram	Estimated cost to produce one treatment course
Small (manufacturing in 2,000L bioreactors)	50 (equivalent to 6,667 treatment courses)	< \$250	< \$1,875
Large (manufacturing in 10,000L bioreactors)	300 (equivalent to 40,000 treatment courses)	< \$100	< \$750

Assuming a treatment course for a person weighing 50kg.

Public funding and resources

The R&D of REGN-EB3 has benefitted from substantial public taxpayer support. The US government is the largest contributor (predominantly through BARDA), with additional contributions from Europe, the DRC and other actors.

US (HHS)

- BARDA: Regeneron received two BARDA contracts worth more than \$700 million for the preclinical and clinical development of REGN-EB3 and its procurement by the US Strategic National Stockpile.
- NIH: Support for the PALM RCT of REGN-EB3 in DRC was provided by NIAID.
- FDA: REGN-EB3 was granted US FDA Orphan Drug Designation on 14 July 2016. Upon FDA approval, Regeneron was also awarded a medical countermeasure PRV.
- USAMRIID: Animal studies were conducted by USAMRIID in Fort Detrick, Maryland, US.

Europe

The Ebola virus sequence (C15), of which recombinant glycoprotein was used as an immunogen to create REGN-EB3, was isolated by the French National Institute of Health and Medical Research's (INSERM) Reference Center for Viral Hemorrhagic Fevers (Lyon, France) and sequenced by the German Ministry of Health's Bernhard Nocht Institute for Tropical Medicine (Hamburg, Germany). A digital version of the sequence was published online by the Bernhard Nocht Institute.

DRC

Organisations providing treatment in DRC, including Ministry of Health, NGOs and WHO, implemented the trial confirming efficacy of REGN-EB3.

See Tables 5 and 6 for more details on the direct and indirect public contributions to REGN-EB3's R&D, organised by funder.

Table 5. Direct public funding and resources for REGN-EB3

Funder	Item	Recipient	Amount (in US\$)
HHS BARDA HHSO100201500013C Sep 2015 – Jun 2017 ⁸⁶	Anti-Ebola Antibody Therapeutics Development Program, including safety study and non-human study at USAMRIID	Regeneron	Up to \$45.9m
HHS BARDA HHSO100201700016C Sep 2017 – Jul 2027 ⁸⁷	Ebola Regulatory and Stockpile Funding for final regulatory work and production of the US Strategic National Stockpile	Regeneron	\$693.1m as of March 2023 Up to \$756.4m contract value
HHS NIAID NCT03719586 2019 ⁷¹	Investigational Therapeutics for the Treatment of People with Ebola Virus Disease (PALM RCT)		Unknown

Table 6. Indirect public funding and resources for REGN-EB3

Funder	Item	Recipient	Amount
Bernhard Nocht Institute, Germany ⁸⁸	Isolation and sequencing of <i>H.sapiens</i> -wt/GiN/2014/Makona-Kissidougou-C15 (Makona, used to generate antibodies)	Regeneron (via Genbank KJ660346)	
FDA ²⁵	Orphan Drug Act subsidies	Regeneron	US FDA user fee waiver, benefits including 50% R&D tax credit (2016-17) 25% R&D tax credit (2018 onward) ⁷⁹
FDA ²³	MCM PRV	Regeneron	Often worth > \$100m ⁸⁰

Private funding and resources

It is difficult to quantify how much private sector actors, including Regeneron, have financially contributed to the R&D of REGN-EB3, as most of this information is not public. However, Regeneron's filings with the US Securities and Exchange Commission (SEC) provide some insight. In these regulatory filings, Regeneron states that for one of its ongoing BARDA contracts to develop 10 new biodefense antibody therapies (signed in 2017 and unrelated to REGN-EB3), 80% of its R&D and pilot manufacturing costs are covered by the US government.⁸⁹ Although Regeneron does not provide a similar figure for its contributions to REGN-EB3 R&D, they admit that the bulk of the R&D costs for the treatment have been funded through their collaboration with the US government.⁹⁰

Summary of selected patent information

A patent with broad claims has been granted to Regeneron in the US in September 2017 (US 9,771,414) and September 2018 (US 10,081,670).^{29,30} An equivalent patent application has been filed under the WIPO Patent Cooperation Treaty (PCT) system and in multiple countries.³¹ The broad claims of this patent cover the antibodies themselves, their production methods, antibodies which bind to the same epitope as the antibodies covered by the patent, and their use in combination with other antivirals or vaccines. To date, Regeneron has not engaged in any licensing or technology transfer agreements with entities in endemic countries.

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