FIGHTING EBOLA & MARBURG: UNFINISHED BUSINESS

The ongoing threat from Ebola & Marburg

The Ebola and Marburg viruses are both filoviruses capable of causing severe haemorrhagic fever, each identified by the WHO as priority pathogens with the potential to cause a pandemic. Six species of Ebolavirus have been identified, the two most common being the Zaire and Sudan ebolaviruses. The largest Ebola outbreak since the virus was first discovered in 1976 was caused by Zaire Ebolavirus between 2014-2016 in West Africa, alongside more recent outbreaks in the Democratic Republic of Congo (DRC) (Zaire) between 2020-2022, and Uganda in 2022 (Sudan).

There have been more than a dozen recorded outbreaks of Marburg virus since its discovery in 1967, the deadliest of which caused 227 deaths in 2004 in Angola – but nothing on the scale of the West African or DRC Ebola epidemics. As recently as June 2023, there were outbreaks of Marburg in Equatorial Guinea and Tanzania.

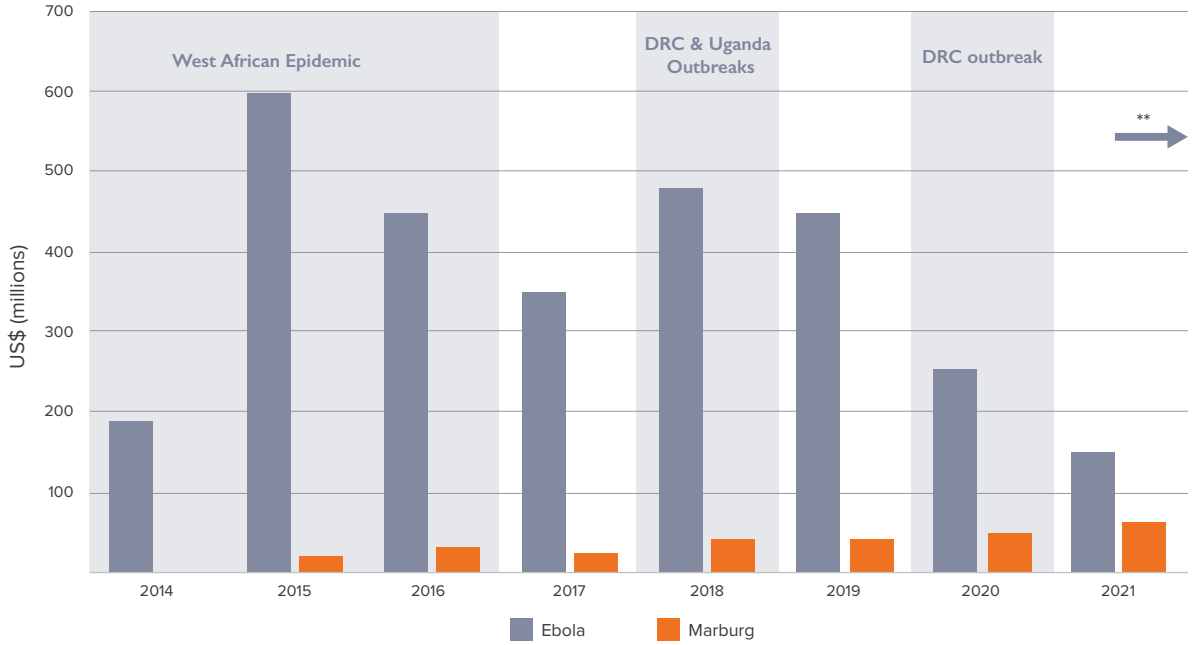
While there are two approved vaccines and two monoclonal antibodies for Zaire ebolavirus, no licensed vaccines or biologics exist to protect against Marburg or Sudan ebolavirus, leaving the world vulnerable to a potential pandemic-scale outbreak in the future.

KEY TAKEAWAYS

- Newly registered Ebola vaccines, treatments and diagnostics are exclusively targeted at the Zaire virus, which was responsible for the 2014 West African pandemic and the 2019 epidemic in the Democratic Republic of Congo.
- We still lack good tools for controlling the Sudan species of Ebola, which caused a recent outbreak in Uganda, and Marburg virus – a related pathogen responsible for outbreaks in Equatorial Guinea and Tanzania.
- Recent outbreaks have fuelled product development for Sudan ebolavirus and Marburg, with several promising vaccine candidates in the pipeline for each pathogen.
- Funding for filoviral R&D remains extremely dependent on the US government, presenting potential risks to continuity and low- and middle-income country (LMIC) access.
- Late-stage clinical trials require candidate products to be deployed immediately following the detection of an outbreak, and can be cut short by a successful public health response. Preparation via animal models, stockpiling products and prioritising testing of promising candidates are key to maximising this window.
- Previous efforts against Zaire ebolavirus and COVID-19 are supporting the next round of vaccine development, demonstrating the spillover benefits from vaccine R&D.

How R&D funding responded to previous outbreaks

FIGURE 1 **Ebola & Marburg R&D funding, 2014-2021**



** Outbreaks of Marburg have since occurred in Tanzania and Equatorial Guinea in 2023, as has an outbreak of Sudan ebolavirus in Uganda

Shaded regions represent outbreaks of Ebola[i]

R&D funding for Ebola[i]

Funding for Ebola R&D peaked in 2015 – at the height of the West African outbreak – at $595m,[ii] trending downwards until the DRC outbreak inspired a second – slightly lower – peak at $476m in 2018. Since then, funding has fallen by more than two-thirds, dropping to just $150m in 2021 as the DRC outbreak was brought under control.

These shifts in funding reflect both active outbreaks and the movement of products through the pipeline, with the large drops in funding in recent years resulting from the successful registration of the ERVEBO and Zabdeno/Mvabea vaccines and the biologics Inmazeb and Ebanga.

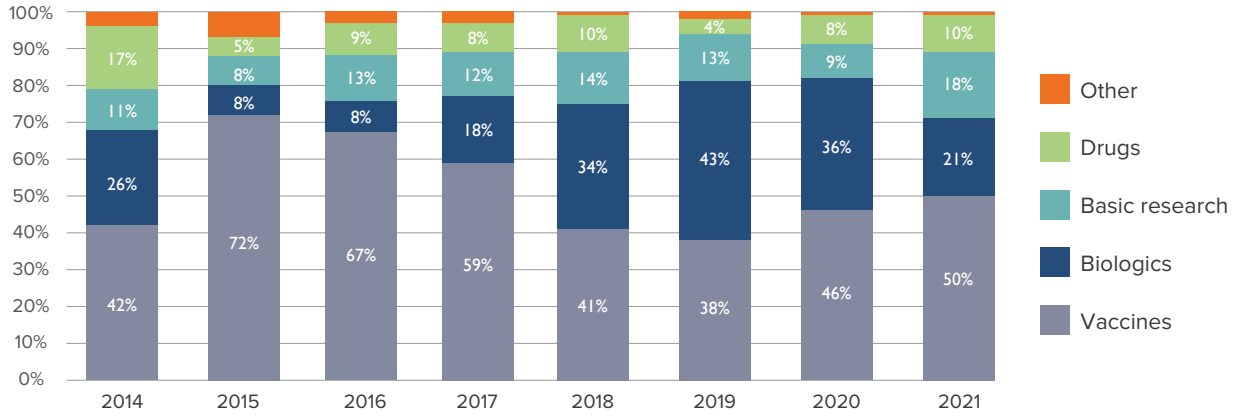
Almost three-quarters of 2021 funding came from just two organisations – the US National Institutes of Health (NIH) and US Biomedical Advanced Research and Development Authority (BARDA) – which together provided 57% of Ebola funding since 2014. Funding from industry – the third largest source of investment – fell to an all-time low of just $24m in 2021, down from a peak of $258m in 2015. This leaves funding vulnerable to shifts in US policy and means that products developed via US public funding will not provide guaranteed access for LMICs.[2]

Vaccine R&D has historically dominated the Ebola funding landscape, accounting for over half the total, but its share has started to drop in recent years. Ebola vaccine funding peaked at $426m in 2015 (72% of all Ebola R&D funding) and has fallen every year since. The peak, and subsequent drop in Ebola vaccine R&D funding can largely be traced to the movement of the successful candidates through clinical development and into post-registration studies. Vaccine funding's recent decline coincided with an increase in the share (and absolute value of) biologics funding, which spiked in 2018, rising by $100m, before increasing again to a peak of $193m in 2019. This funding then dropped drastically in 2020 (down $100m), as the Ebola monoclonal antibodies completed clinical trials and received FDA approval in late 2020, though the limited access so far granted to LMICs means they have yet to see much use in response to subsequent outbreaks.

i Funding data for 2014 focused exclusively on Ebola, with Marburg and combined filoviral R&D added in the 2015 survey.

ii All dollar amounts are given in inflation-adjusted 2021 US dollars at 2021 exchange rates.

FIGURE 2 **Ebola R&D funding by product, 2014-2021**



R&D funding for Marburg

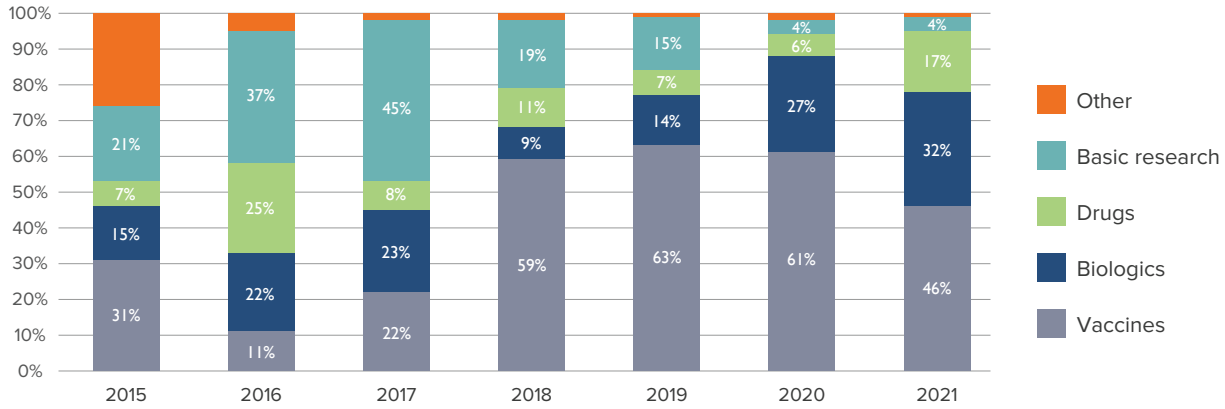
Funding for Marburg R&D has remained more consistent, but at a significantly lower level than for Ebola. It experienced a gradual upward trend from $19m in 2015 to $46m in 2020, followed by a substantial jump between 2020 and 2021, reaching an all-time high of $61m. This 2021 leap in Marburg funding was split roughly equally between drug and biologics R&D, while vaccine funding declined slightly after four consecutive years of increases.

This comparative lack of focus on Marburg partly reflects the – so far – much smaller outbreaks it has caused: the largest historical Ebola outbreak (beginning in West Africa in 2014) infected 28,610 people, while the largest Marburg outbreak (Angola, 2004-2005) infected 252. This disparity reflects Ebola's slightly higher case fatality rate – since, without routine surveillance, non-fatal cases are less likely to be identified – and its slightly longer incubation period, which leaves infected individuals with more time to spread the disease prior to becoming symptomatic.

Almost all Marburg R&D has been funded by the US government, which provided 99% of the total in 2021, and similar proportions in prior years. This, in turn, was dominated by the US BARDA (38% in 2021) and Department of Defense (DOD) (37%), followed by the US NIH at 24% (after having been responsible for almost all Marburg funding prior to 2018).

Correspondingly, NIH-backed basic research funding dominated the Marburg landscape prior to 2018, with the shift towards vaccines coinciding with the 2018 arrival of BARDA and DOD funding. Their funding has been directed towards several candidates in preclinical trials and Phase I of clinical development. Marburg biologics funding saw its third consecutive year of growth in 2021, a $21m increase across 2020 and 2021, thanks to investment into Phase I development of a pan-Marburg biologic.

FIGURE 3 **Marburg R&D funding by product, 2015-2021**



How has R&D funding translated into new and potential vaccines?

In December 2019, MSD's ERVEBO became the first FDA-approved Ebola vaccine, and shortly after, in 2020, the European Medicines Authority gave marketing authorisation to Janssen's multivalent heterologous prime-boost vaccine, a two-dose regimen of Zabdeno and Mvabea. These vaccines have subsequently saved many thousands of lives during recent outbreaks, with the Janssen regimen administered to more than 50,000 people in the DRC and Rwanda during the 2018-2020 outbreak. In a late 2021 outbreak in the DRC, more than 1,800 people were vaccinated with existing stockpiles of ERVEBO in a campaign that began just five days after the first case was detected. The availability of a vaccine meant the spread of these outbreaks was able to be controlled – with only 11 cases detected in the October 2021 DRC outbreak – as compared to up to 29,000 in pre-vaccine outbreaks.

These registered vaccines, however, only provide protection against the Zaire virus, and have been shown to be ineffective against Sudan ebolavirus and Marburg. While both are less lethal than the (pre-vaccine) Zaire species, each still has the potential to spark a future epidemic. The availability of a vaccine at the onset of these recent outbreaks would have helped to control the spread and save lives.

The early 2023 Sudan ebolavirus outbreak has sparked an urgency in testing promising vaccine candidates, three of which have been identified and are being trialled through the Tokomeza Ebola trial[3] – ChAd3-SUDV (Sabin Vaccine Institute), ChAdOx1 biEBOV (Oxford University & The Jenner Institute), and VSV-SUDV (IAVI & Merck). While doses of these vaccines arrived in Uganda 79 days after the outbreak was announced,[4] successful efforts to control the outbreak halted the progress of vaccine trials. In June 2023, IAVI began Phase I trials of their candidate vaccine against Sudan Ebolavirus (rVSVΔG-SUDV-GP, based on MSD's ERVEBO platform), with funding from the US BARDA.[5] The recent outbreaks serve as a reminder of the need to coordinate with local communities, design fast-moving multi-arm or adaptive trials, and the need to prepare for, rather than react to outbreaks by completing early-stage testing and stockpiling doses.

Similarly, the WHO has been evaluating potential vaccine candidates against Marburg, to be trialled in Equatorial Guinea, which announced its first ever outbreak in February 2023. Outcomes of an emergency meeting called by the WHO identified five candidate vaccines,[6] three of which have been identified as priorities for trialling during the current outbreak – Janssen's adenovirus-based candidate; Sabin Vaccine Institute's ChAd3-MARV, based on the same underlying research as its Sudan species candidate both of which have competed Phase 1b clinical trials[7] and Public Health Vaccines' VSV-MARV – also based on the NIH research[8] underlying MSD's Sudan candidate, which is still in preclinical development but has shown protection in non-human primates.

How soon can we close the gaps in our defences against Ebola and Marburg?

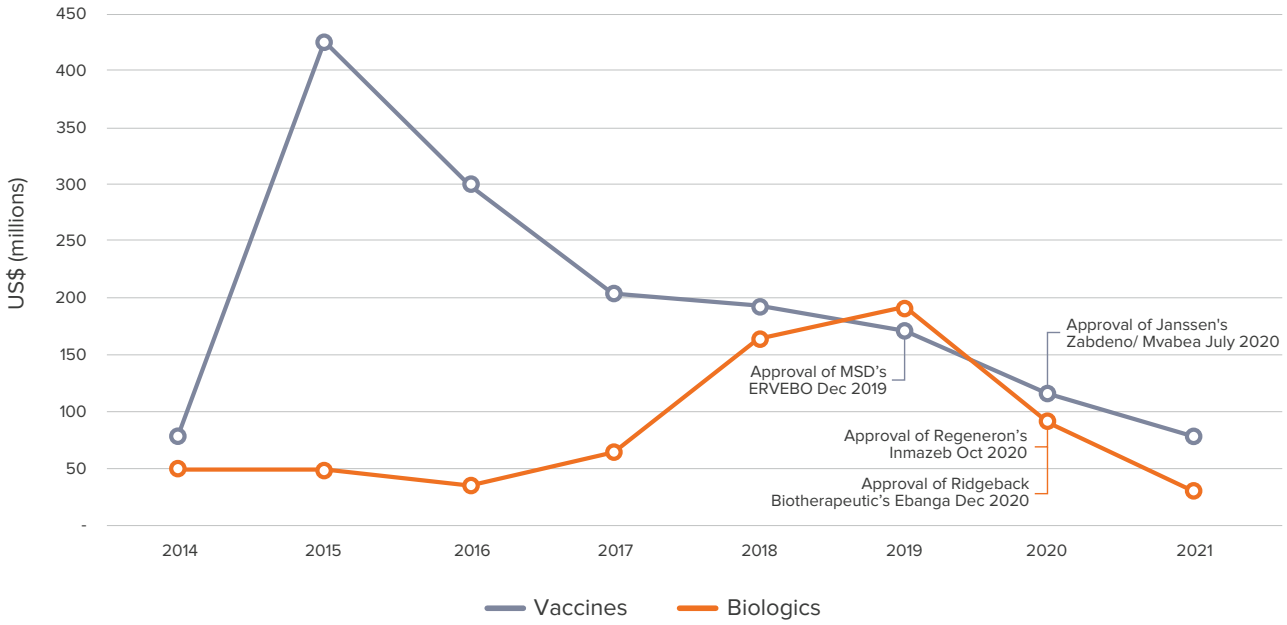
While none of the products approved for fighting Zaire ebolavirus appear to work against Sudan ebolavirus or Marburg, these new candidates draw heavily on earlier efforts against the West African Ebola and global COVID-19 pandemics. Of the three most promising Sudan ebolavirus vaccine candidates, one is based on the adenovirus platform used to develop Astra Zeneca's COVID-19 vaccine, while another is based on MSD's ERVEBO Zaire vaccine. This underlines the spillover benefits offered by vaccine development, where technologies developed in response to one pathogen can accelerate progress against others.

Despite the relatively rapid development of MSD's Ebola vaccine (five years to licence), the initial response to Ebola was too slow to complete vaccine development in time to assist with the West African epidemic, which killed over 11,000 people. There remains an inherent tension between the needs of product developers to recruit a trial group while the outbreak is ongoing and the understandable desire to stamp it out as quickly as possible. The early weeks of an outbreak are vital for product development, and the relatively rapid arrival of candidate product

samples in some recent outbreaks is a sign that we may be starting to learn the lessons of the earlier fight against Zaire ebolavirus. Between outbreaks, we should encourage the further development of animal models and dose stockpiles, and consider regulatory change to allow early access based on animal rules.

We can see the effectiveness of Ebola product development – with multiple point-of-care and rapid diagnostic tests now available, and two approved biologic products – in the vast reductions in mortality following the vaccine rollout. But, the relatively low mortality figures from recent outbreaks of Sudan ebolavirus – 55 fatalities in Uganda – and Marburg – 12 deaths in Equatorial Guinea, and 6 in Tanzania – probably also point to the expertise developed by public health institutions in both East and West Africa for controlling the spread of outbreaks via non-pharmaceutical interventions. The quality of the public health response has bought funders time to finish the work they began – too slowly – in ending the string of outbreaks in the DRC; they should take advantage of it, and the knowledge and expertise we gained in developing treatments for other recent pandemics, to finish the job and end the pandemic threat from filoviruses of all kinds.

FIGURE 4 **Ebola vaccine and biologic R&D funding in relation to product registration**



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