EBOLA AND OTHER AFRICAN VIRAL HAEMORRHAGIC FEVERS

In response to the 2014 West African Ebola epidemic, last year's G-FINDER survey tracked funding for Ebola R&D for the first time, capturing FY2014 investments. This year, the survey scope was expanded to include four more African VHFs: Marburg, Lassa fever, Rift Valley fever and Crimean-Congo haemorrhagic fever. Of these additional diseases, only Marburg received any significant R&D investment in its own right. Funding for R&D into the remaining three VHFs – as well as that for R&D targeting multiple VHFs – has been combined into a single category for analysis.

In this year's G-FINDER report, funding for Ebola and other African VHFs (for both 2014 and 2015) has been analysed separately from the neglected diseases traditionally included in G-FINDER. This is a change from last year's report, when Ebola funding was included in the neglected disease analysis. This revised approach reflects the different nature of the threat posed by Ebola and other emerging infectious diseases – and the unique characteristics of the resulting market failure – compared to 'traditional' neglected diseases, and means that the unprecedented global response to the Ebola epidemic does not distort our understanding of the R&D funding landscape for neglected diseases.

For an analysis of how the neglected disease funding landscape changes when funding for Ebola and other African VHFs is included, please see the textboxes at the beginning of the Diseases and Funders sections of this report.

$631 MILLION

TOTAL SPEND ON EBOLA AND OTHER AFRICAN VHF R&D IN 2015

THIS WAS EQUIVALENT TO

21%

OF GLOBAL R&D FUNDING FOR NEGLECTED DISEASE R&D

MORE MONEY WAS INVESTED IN R&D FOR EBOLA AND OTHER AFRICAN VHFS IN 2015 THAN IN ANY NEGLECTED DISEASE EXCEPT HIV/AIDS

Viral haemorrhagic fevers can be caused by a diverse range of viruses, although the majority of these fall within four distinct taxonomic families: Arenaviridae, Bunyaviridae, Flaviviridae and Filoviridae. Although they share many common features, the diseases that fall under this definition vary significantly in terms of geographic distribution and the threat they pose to humans.

Based on the G-FINDER criteria, we have included five diseases within the scope of our tracking efforts, all of which predominantly occur on the African continent: Ebola virus disease, Marburg virus disease, Crimean-Congo haemorrhagic fever (which has also been documented in southern and central Europe, the Middle East and central Asia), Rift Valley fever and Lassa fever. Collectively referred to in our analysis as 'African VHFs', these diseases represent the five most important zoonotic viral haemorrhagic fevers for humans.[95]

The initial signs and symptoms of most VHFs may include fever, fatigue, dizziness, muscle aches, loss of strength, and exhaustion; the similarity of these symptoms to those of many other acute febrile illnesses can make early clinical diagnosis challenging. Signs of progression to severe disease include bruising, internal and external bleeding, organ failure and shock.

Ebola virus disease and Marburg virus disease are caused by filoviruses. The natural reservoir of both viruses is believed to be infected fruit bats; once introduced into the human population, person-to-person transmission is the primary mechanism for the spread of infection.[96] Both are severe, acute illnesses that can be fatal if untreated; the case fatality rate for Ebola can be as high 90% in some outbreaks, and for Marburg is over 80%.[97,98]

The Global Burden of Disease Study estimates that Ebola was responsible for 295,350 DALYs and 5,498 deaths in the developing world in 2015 (although this mortality figure is higher than the 3,311 confirmed, probable and suspected deaths reported by the WHO for 2015).[99,100] This is fewer deaths than were caused by any of the neglected diseases within the scope of G-FINDER which are potentially fatal, and around the same morbidity as trachoma.

Crimean-Congo haemorrhagic fever and Rift Valley fever are both caused by viruses of the bunyavirus family, and are transmitted to humans via ticks and mosquitoes, respectively. In documented outbreaks of CCHF, fatality rates in hospitalised patients have ranged from 9% to as high as 50%.[101] Only 1 in 10 RVF cases go on to severe disease and haemorrhagic fever occurs in less than 1% of all cases, but the fatality rate among this group is around 50%.[102]

Lassa fever is caused by an arenavirus, and is primarily spread to humans through contact with infected rodents. Its onset is more gradual, and the case fatality rate is 1-15%.[103] There are an estimated 100,000 to 300,000 Lassa virus infections per year in west Africa, with approximately 5,000 deaths.[104]

No licensed drugs or vaccines exist for Ebola, so treatment is restricted to supportive and symptomatic therapy, and outbreak containment relies on prevention and control strategies. Early diagnosis is critical for both successful treatment and epidemic control, but is hampered by the lack of appropriate tests. The first ever rapid POC screening tests for Ebola were given emergency approval at the height of the 2014 epidemic, but laboratory confirmation is still required.[105] There is a need for inexpensive but accurate rapid POC tests for screening, as well as smaller, faster, more mobile molecular tests suitable for the African setting.[106] Novel and re-purposed drugs are currently being evaluated for treatment of Ebola, including the monoclonal antibody cocktail ZMapp™ (Phase III), and favipiravir (Phase II).[107] There are also several vaccine candidates in clinical development, the most advanced of these being rVSV-ZEBOV (Phase III) and ChAd3-EBOZ (Phase II).[107] However, despite the fact that clinical trials were fast-tracked during the recent outbreak, the lack of new cases presents a challenge for further development.

There are no approved drugs, vaccines, or cheap and reliable POC tests available for Marburg. All drug candidates (including BCX4430 and AVI-7288) and vaccine candidates are in very early stages of development (pre-clinical or Phase I). Current diagnostics include ELISA testing, PCR, and IgM-capture ELISA, which can confirm cases of Marburg within a few days of symptom onset. Virus isolation can also be performed but is limited to the few biosafety level 4 laboratories available in affected regions.[108]

No approved vaccine exists for Crimean-Congo haemorrhagic fever, and treatment is limited to ribavirin, which has limited efficacy and can have severe side-effects.[109] Diagnosis of CCHF through laboratory testing or an RT-PCR kit is available, with POC diagnostic assays still in early stage development. There are no treatments in the development pipeline, although protein antigen specific platform vaccines are in early stages of development.[110]

An inactivated vaccine for Rift Valley fever has been developed for experimental use but remains unregistered. There are a number of alternative candidates currently in the pipeline, one of which (RVF MP-12) has completed Phase II clinical trials.[111] Treatment for severe cases of RVF is generally limited to supportive care, and definitive diagnosis is limited to laboratory-based tests including RT-PCR, ELISA and virus isolation; we have not been able to identify any drug or diagnostic candidates specifically for RVF currently in development.

As for CCHF, there is no approved vaccine for Lassa fever, and treatment is reliant on ribavirin, which has limited efficacy.[112] A number of experimental antiviral drugs have been tested in vitro or in small animal models (favipiravir, T-705; ST-193; and small interfering RNAs), but none has progressed into clinical trials.[113] A number of vaccine candidates are also in development, all in pre-clinical stages.[113] The ReLASV® Antigen Rapid Test for Lassa received CE certification from European regulators in 2014 for diagnostic use in the EU and other international markets, however it is still not approved by the FDA.[114]

A total of $631m was invested in R&D for Ebola and other African VHFs in 2015. The vast majority of this was Ebola-specific ($574m, 91%). $17m (2.7%) was invested in Marburg-specific R&D, and $40m (6.4%) in other and/or multiple African VHFs (with the majority of this latter category being multi-filovirus R&D that included Ebola as a target).

Table 41. African VHF R&D funding 2014 (US$ millions)

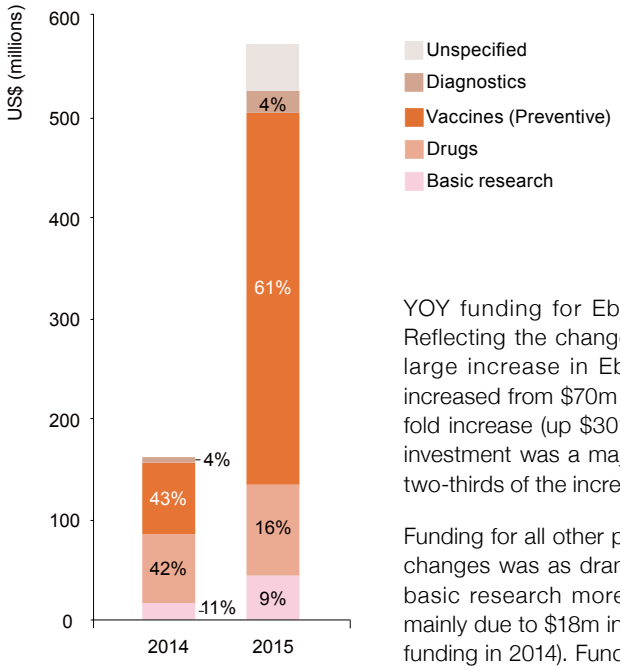
Disease	Basic Research		Vaccines (Preventive)	Diagnostics	Unspecified	Total	%
	Drugs						
Ebola	44	90	370	23	47	**574**	91
Marburg	4.0	3.0	5.7	2.8	1.7	**17**	2.7
Other and/or multiple VHFs	12	10	12	2.4	4.0	**40**	6.4
Total	59	103	388	28	53	631	100

In addition to the sheer volume of funding, one of the most remarkable – if not entirely unexpected – findings in this year's report is the massive increase in funding for Ebola R&D compared to 2014. We have restricted our analysis of YOY funding changes to Ebola alone, as it was the only VHF included in both the FY2014 and FY2015 surveys, although funding for African VHFs other than Ebola undoubtedly also increased.

Funding for Ebola R&D more than tripled (up $411m, 258%) from 2014 levels. The magnitude of this increase, which came primarily from public and industry funders, is unprecedented in any of the neglected diseases traditionally tracked by G-FINDER. For context, the 2015 *increase* in funding for Ebola alone (from already significant levels in 2014) was larger than the *collective* 2015 global investment in developing country-relevant R&D for dengue, bacterial pneumonia & meningitis, helminths, salmonella infections, hepatitis C, leprosy, cryptococcal meningitis, trachoma, rheumatic fever, Buruli ulcer and leptospirosis combined.

In 2015, the vast majority of R&D funding for Ebola and other African VHFs was focused on vaccines ($388m, 61%), with smaller amounts going to drugs ($103m, 16%), basic research ($59m, 9.4%) and diagnostics ($28m, 4.4%). This was a marked change from 2014, when vaccines and drugs each received a similar share of Ebola R&D funding (accounting for 43% and 42%, respectively), possibly reflecting the fact that vaccine clinical trials for Ebola started later and are more expensive to conduct.

Figure 26. African VHF R&D funding by product type 2014-2015



YOY funding for Ebola R&D increased for all product areas. Reflecting the change noted above, the vast majority of the very large increase in Ebola funding went to vaccine R&D, which increased from $70m in 2014 to $370m in 2015 – a more than five-fold increase (up $301m, 436%). The significant growth in industry investment was a major factor, with industry responsible for nearly two-thirds of the increase in Ebola vaccine investment.

Funding for all other product areas also grew, although none of the changes was as dramatic as that for vaccines. Funding for Ebola basic research more than doubled (up $26m, 149%) to $44m, mainly due to $18m in new investment from the UK MRC (after zero funding in 2014). Funding for Ebola drug development increased by $22m (up 33%) to $90m, as a result of increased US public sector investment, while Ebola diagnostic funding nearly tripled (up $15m, 263%) to $23m.

FUNDERS

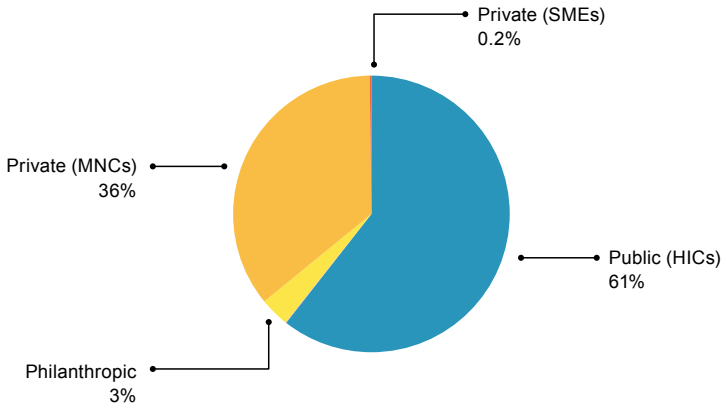
The public sector was the source of nearly two-thirds ($383m, 61%) of all reported funding for R&D into Ebola and other African VHFs in 2015. Industry provided just over a third ($226m, 36%), and the philanthropic sector just 3.4% ($22m).

This was a major change from the sectoral funding breakdown for 2014 Ebola investments (when the public sector funding share was 72%, industry 21% and philanthropic funders 7.3%), and is almost unparalleled amongst the diseases covered by the G-FINDER survey. Only hepatitis C and bacterial pneumonia & meningitis, for example, have greater of share of industry involvement – two diseases where there is significant overlap with commercially-driven R&D activities, neither of which receives anywhere close to the same level of funding. It is also one of the lowest shares of philanthropic funding seen in any of the diseases covered by the G FINDER survey.

More than three-quarters ($298m, 78%) of all public sector funding for Ebola and other African VHF R&D in 2015 came from US Government agencies. This share actually fell compared to 2014, despite the massive increase in US Government investment, as other countries also began to ramp up their investment in Ebola and other African VHF R&D. European governments in particular increased their share of public funding from 12% in 2014 to 22% in 2015.

Reported funding from LMIC governments represented less than 1% of total public funding for Ebola and other African VHF R&D in 2015. This figure is likely an underestimate – due to participation rates by African organisations in the G-FINDER survey – but may also reflect a focus on outbreak response and containment, rather than R&D. Virtually all industry investment came from MNCs, and was directed towards Ebola vaccine development (many SMEs are actively undertaking R&D in this area – particularly in drug development – but the majority of funding for these efforts comes from the public sector).

Figure 27. African VHF R&D funding by sector 2015



Public sector funding for Ebola R&D nearly tripled compared to 2014 (up $210m, 182%). This was driven by US Government funders (up $149m, 151%), but there was also a more than five-fold increase in European public funding for Ebola R&D (up $63m, 452%), much of which came from the EU's IMI Ebola+ initiative.

The increase in industry investment in Ebola R&D (up $194m, 614%) was nearly as large as that from the public sector, with almost all of this increase going to vaccine development (up $193m, 614%). Philanthropic funding for Ebola increased modestly (up $7.0m, 59%), with much of this increase also for vaccine R&D (up $5.6m, 271%).

TOP FUNDERS

In 2015, the top 12 funders accounted for 98% of funding for Ebola and other African VHF R&D. Although we generally avoid commenting on the aggregate industry contribution when discussing top funders (as it consists of the collective investment of many organisations), the funding picture here is remarkable: aggregate industry was by far the largest funder of Ebola and other African VHF R&D, providing over a third of all funding, twice the investment of the next largest funder (the US NIH).

In addition to the US NIH, two other US Government agencies (US BARDA and US DOD) round out the top three non-industry funders; they are also joined in the top 12 by the US CDC. Collectively, these four US Government agencies and the aggregate pharmaceutical industry were responsible for 83% ($524m) of all global investment in R&D for Ebola and other African VHFs in 2015.

Looking only at Ebola R&D funding for the sake of accurate comparison to 2014, the largest increase among the non-industry top funders in 2015 came from US BARDA (up $78m, 297%). This was followed by the US DOD (up $46m, 423%), and a ten-fold funding increase from the EU (up $40m, 900%, largely due to new investment under the IMI Ebola+ initiative). The two other organisations with increases in the double-digit millions were the US NIH (up $20m, 32%) and the UK MRC, whose $18m investment in Ebola basic research (from zero investment in 2014) put it in the top 12 for the first time.

Just two funders in the top 12 for 2015 reported reducing their investment in Ebola R&D, with small decreases coming from the Gates Foundation (down $4.0m, -34%) and Inserm (down $2.1m, -40%).

Table 42. Top African VHF R&D funders 2015

Funder	US$ (millions)		2015 % of total
	2014	2015	
Aggregate industry	34	226	36
US NIH	64	113	18
US BARDA	26	104	16
US DOD	11	73	12
EU	4.5	45	7.2
UK MRC	-	18	2.9
US CDC	-	8.3	1.3
Wellcome Trust	0.1	8.0	1.3
Gates Foundation	12	7.8	1.2
Inserm	5.3	6.4	1.0
UK DFID	1.5	4.6	0.7
MSF	-	3.5	0.6
Subtotal of top 12^	163	618	98
Disease Total	164	631	100

^ Subtotals for 2014 top 12 reflect the top funders for those respective years, not the top 12 for 2015
- No reported funding
Funding organisation did not participate in the survey for this year. Any contributions listed are based on data reported by funding recipients so may be incomplete

FUNDING FLOWS

R&D funding flows for Ebola and other African VHFs differ markedly from those for traditional neglected diseases in two main ways: the proportion of funding that is invested internally, and the way external funding is distributed.

More than half (54%) of all funding for Ebola and other African VHFs is invested in internal R&D programmes. This is almost double the self-funding share for neglected diseases (28%), and largely reflects the high level of industry investment.

Almost all external (grant or contract) funding was provided directly to researchers and developers, with fund managers essentially absent from the picture: PDPs received a single grant ($3.7m to FIND for diagnostic R&D), and no funding given to other intermediary organisations was specifically earmarked for African VHFs.[x] Accordingly, a much larger share (42%) of external funding for Ebola and other African VHFs was given directly to SMEs and MNCs than is normally the case in neglected disease R&D, where fund managers play a larger role and direct funding to industry accounts for less than 10% of all external funding.

[x] We note that some core funding given to intermediaries may subsequently be used to fund R&D for Ebola and other African VHFs. For example, EDCTP issued a diagnostic-focused call in 2015 for neglected and emerging infectious diseases, including Ebola (although ultimately no Ebola projects were selected)