Scale up supply of experimental Ebola drugs

Estimates of the probable impact of the outbreak show that existing stocks of potentially useful medicines are insufficient, says **Oliver Brady**.

With the worst-ever outbreak of Ebola raging in West Africa, a World Health Organization (WHO) committee last week concluded that it is ethical to use unproven drugs and vaccines to try to combat the disease, as long as doctors obtain patients' informed consent. There are no medicines currently approved for routine use against Ebola, either to treat infected people or to protect those they come into contact with, so we are in uncharted territory. Two logical and immediate questions are: what investigational drugs and vaccines are available, and what volume of each would be required?

At the front line, options for therapy and post-exposure treatment include passive immunization with monoclonal or polyclonal antibodies, and antiviral agents. For broader protection, several vaccines have been tested on non-human primates.

With the backing of the WHO, policy-makers and funders are now trying to decide which of these options to accelerate into active service. They need good estimates of how many of these drugs and vaccines to manufacture and distribute to control an Ebola outbreak.

Together with colleagues, I have been trying to provide such estimates.

We have separated the people who require help into four categories. Most urgently, there are those who have already become infected with Ebola virus and people close to them, such as family members. Next are the medical and support staff who treat patients, and those who handle the corpses. At less immediate risk but still important to protect are essential non-medical staff in the region of the outbreak, such as humanitarian-aid workers and people who provide key local services. A case can be made that protection should also be offered to key domestic government workers and others providing essential logistical support. Finally, we have already seen isolated cases of Ebola spread far from its West African source by travellers, and policy-makers should consider protection for these imported cases.

The scientific literature holds some information about probable levels of exposure in these groups (see http://go.nature.com/1le6ua). This provides the best available evidence base for political and private funding decisions on the volume of drugs or vaccines that would be required.

To make this information available, my colleagues and I have constructed a spreadsheet that calculates the total number of people that might require treatment for a given outbreak (see http://go.nature.com/vv98gv). This value is customizable depending on factors such as which of the above categories are to be targeted.

The intention is not to provide exact numbers of doses required, but rather to scope potential demand for a number of realistic scenarios.

This demand is likely to be higher than many people realize. For example, our analysis suggests that, even under a conservative scenario, up to 30,000 people would have so far required treatment or prophylaxis in the current outbreak — significantly more than in any previous outbreak. The difference reflects the scale of the current emergency, which has made the jump from rural to urban areas. The WHO warned last week that reported numbers of cases and deaths "vastly underestimate" the size of the problem.

To estimate the demand for therapeutic or prophylactic agents more accurately, more-detailed data on patient contact rates and health-care-worker exposure must be collected or made available by the relevant organizations. These factors are likely to change as the Ebola epidemic spreads, treatment centres become available and people are quarantined.

UNDER A CONSERVATIVE SCENARIO, UP TO 30,000 PEOPLE WOULD HAVE SO FAR REQUIRED TREATMENT OR PROPHYLAXIS.

Our estimates may need to be increased if, with the transition from rural to urban environments, infected people are coming into contact with more people. Under such conditions, tracking a person's contacts for the full recommended 21 days after exposure to the disease becomes logistically challenging, and it may be necessary to refine which contacts are defined as epidemiologically significant. Policy-makers should consider the role of strategies such as mass vaccination and greater use of personal protective equipment.

Our analysis is crude and has very clear limitations. But it does demonstrate that for treatment and prevention interventions to be rolled out evenly and fairly, stocks must be scaled up substantially. It seems that supplies of the monoclonal-antibody therapy ZMapp are already exhausted, and available stocks of many other investigational drugs are limited to treatment courses for tens or hundreds of people, rather than the required thousands or tens of thousands.

It is clear that the scale of the current outbreak presents a change in the development landscape for those invested in Ebola therapeutics. As well as the direct disease burden, the unfolding epidemic in West Africa has revealed the huge potential for indirect costs brought about by political destabilization and crippled health-care services.

The use of ZMapp has already raised issues of equity of access to potentially life-saving therapies. But as WHO assistant director-general Marie-Paule Kieny has said: "I don't think that there could be any fair distribution of something that exists in such a small quantity."

The scale of the ongoing outbreak may tilt the politics and economics to speed the development of a drug or vaccine. But it also makes it difficult to scale up production and distribution. All involved must rise to meet the challenge. ■

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Interactive table explanation

Depending on how the exact aims of each therapeutic are divided between the four categories, one can estimate provisionally the total numbers required by changing values for each category using the toggles in the interactive chart provided (http://goo.gl/i2tikH). In this, parameter values are controlled in the top two charts. The first chart (top left) controls the main parameters for categories 1 to 4 while the second (top right) tailors specific parameters for occupational workers in category 2.

In the bottom two charts the selected parameters are applied to reported case numbers from the current outbreak (bottom left) and historical outbreaks (bottom right). For the purpose of historical outbreaks, only those with total number of cases >1 are considered. The case number for the current outbreak is accurate as of 19 August 2014, but is likely to increase and existing reports suggest that the number of reported Ebola cases is a significant underestimate[1]. Division of the results into current and historical outbreaks is intended to highlight the disparity in therapeutic need presented by the current outbreak as it differs considerably in size, extent and burden (figure 1).

Evidence and justification for occupational exposure rate

Occupational exposure rates are estimated based on the treatment of patients with Ebola virus disease (EVD) in a dedicated Ebola virus Treatment Centre (ETC). Treatment in other healthcare settings is not considered, since treatment in other settings is not recommended and the occupational exposure of healthcare and other workers in other settings may be highly variable. In small health care centres there may be a low ratio of health workers to EVD patients. For example the 1976 DRC outbreak and the Kikwit outbreak in 1995 started in healthcare settings with few healthcare staff and the number of EVD cases far exceeded the number of healthcare staff [2,3]. Conversely, in large urban hospitals, a single unrecognised EVD case may have contact with a large number of health care and ancillary staff[4]: for example in outbreaks of highly pathogenic avian influenza A/H5N1, as many as 30 healthcare workers have been exposed to a single unrecognised case [5,6].

The mean occupational exposure rates are based on current Médecins Sans Frontières standards for the EVD outbreak in West Africa. The following figures are per 10 ETC beds: 4 clinical teams that work 8 hour shifts (with one team on rest day). Each team is composed of 1 doctor, 3 nurses and 3 ancillary staff. In addition to these teams that work directly in the ward, 4 transport staff (not on team shift work) are also included. In total, this equates to a total of 3.2 healthcare workers per bed. All these values can be adjusted in the interactive chart.

Estimation of the number of beds occupied per outbreak

Individuals that are at high risk of infection due to their occupation may be exposed to multiple patients over the course of an epidemic. As a result, it is more accurate to calculate occupational exposure per bed rather than per patient to avoid overestimates of a single healthcare worker coming into contact with multiple patients. The peak number of beds occupied is dependent on the rate of patient admission to

hospital over the course of the outbreak.

To estimate the number of beds occupied per outbreak we obtained the number of cases reported at each time point for ten EVD outbreaks[2-4,7-12]. A simulation model was run over the time period where patients were admitted to the hospital (assumed to be when the cases were reported) and removed 8 days later (simulating either death or recovery)[2]. The total number of patients in the hospital over the course of the epidemic was recorded and the maximum occupancy over the course of the outbreak was obtained to give the per bed exposure.

This approach assumed all patients were being treated in one hospital with unlimited bed capacity. We therefore only applied this approach to geographically restricted outbreaks with lower case numbers. To normalise among outbreaks of different size, peak bed volume was divided by the total number of cases for each outbreak to give an average number of beds per reported case of 0.44 (standard deviation 0.17). This provided the justification for the estimates of the range of beds per patient in the table calculation of 0.1-0.8, thus approximately encompassing two standard deviations around the mean of 0.44.

Conservative scenario

We considered the following conservative scenario for the example calculation in the main text: 9 EVD patient contacts per patient, 100:44 total EVD patients to peak required beds ratio, staff composition as above (4 teams of 1 doctor, 3 nurses and 3 ancillary staff plus 4 transport staff), 5,000 essential non-medical service providers, 250 domestic contingency. This is considered a conservative estimate as it is based on data mostly from outbreaks in rural areas, unlike the urban setting that the virus is circulating in, which are likely to underestimate particularly the number of contacts per EVD patient.

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Figure 1: The 23 reported outbreaks of EVD through time. The area of each circle and its position along the y-axis represents the number of cases. EVD = Ebola Virus Disease.

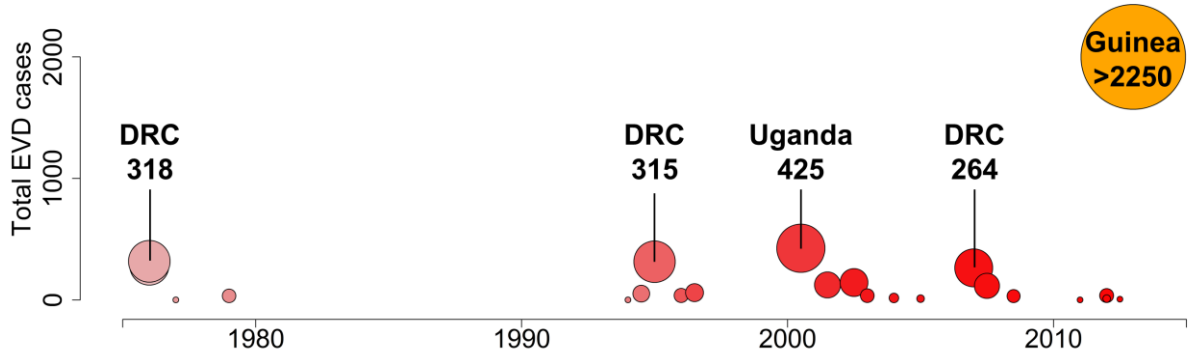

Figure 2: Density plot of historical EVD outbreak total case number. Underlying rug plot shows individual data points.

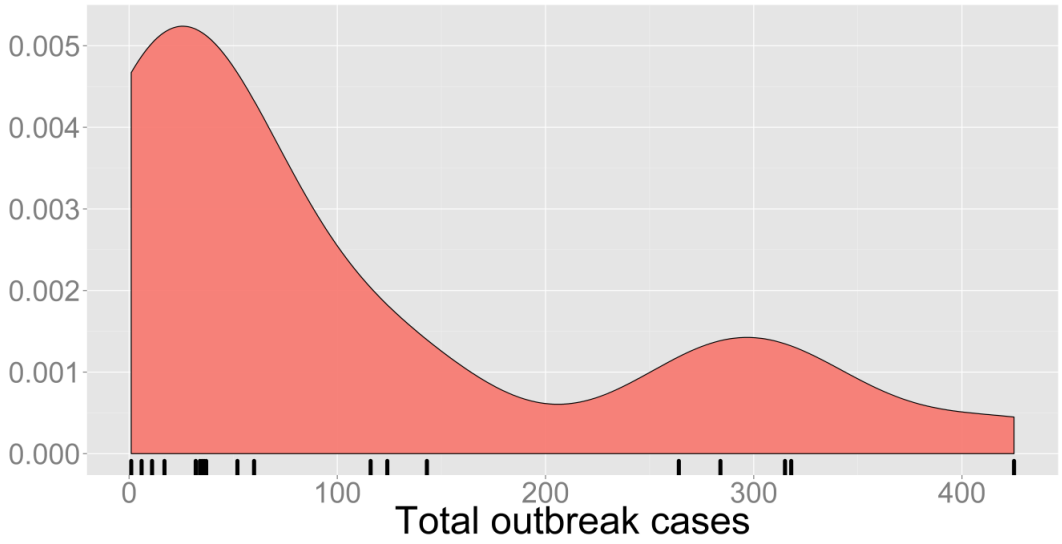

Figure 3: Density plot of contacts per EVD patient from contact tracing studies. Underlying rug plot shows individual data points.

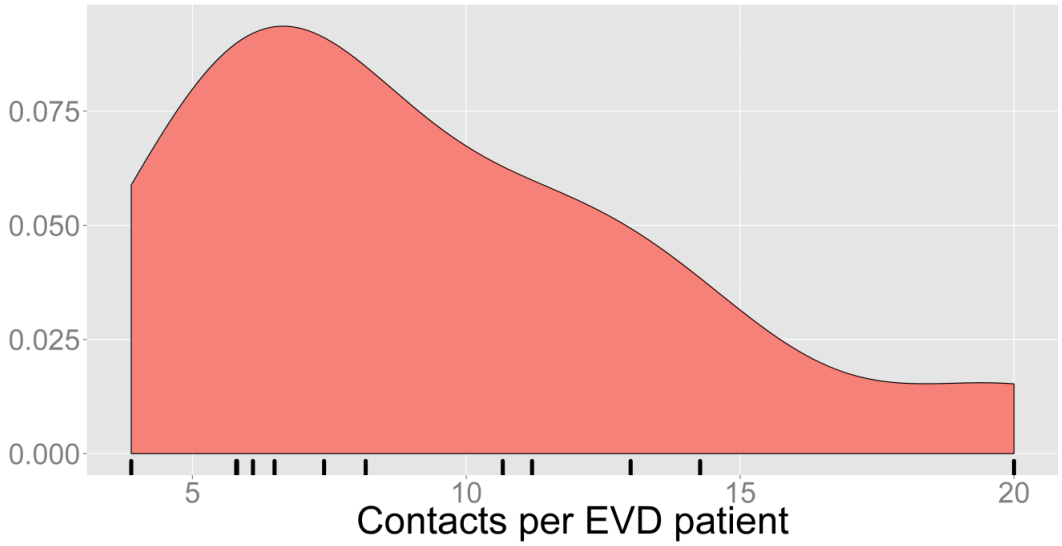

Table 1: Historical EVD outbreaks (suspected and confirmed cases, n = 23) * The latest WHO figures report 2240 cases of EVD as of 19 August 2014, however reports suggest that reporting capacities have been far exceeded and that the actual number may be much higher [1]. DRC = Democratic Republic of the Congo. ROC = Republic of the Congo. EVD = Ebola Virus Disease.

Outbreak epicentre	**Total number of cases**	**Source**
South Sudan, 1976	284	(WHO/International study team 1978)[13]
DRC, 1976	318	(International Commission 1978)[2]
DRC, 1977	1	(Heymann, Weisfeld et al. 1980)[14]
South Sudan, 1979	34	(Baron RC, McCormick JB et al. 1983)[15]
Côte d'Ivoire, 1994	1	(Le Guenno, Formenty et al. 1995)[16]
Gabon, 1994	52	(Centers for Disease Control 2014)[17]
DRC, 1995	315	(Khan, Tshioko et al. 1999)[3]
Gabon, 1996	37	(Georges, Leroy et al. 1999)[11]
Gabon, 1996	60	(Georges, Leroy et al. 1999)[11]
Uganda, 2000	425	(Okware, Omaswa et al. 2002)[7]
Gabon, 2001	124	(World Health Organization 2003)[12]
ROC, 2002	143	(World Health Organization 2003)[12]
ROC, 2003	35	(Boumandouki, Formenty et al. 2005)[4]
South Sudan, 2004	17	(Onyango, Opoka et al. 2007)[8]
ROC, 2005	11	(Kuhn and Calisher 2008)[9]
DRC, 2007	264	(Leroy, Epelboin et al. 2009)[18]
Uganda, 2007	115	(Wamala, Lukwago et al. 2010)[10]
DRC, 2008	32	(World Health Organisation 2009)[19]
Uganda, 2011	1	(Shoemaker, MacNeil et al. 2012)[20]
DRC, 2012	36	(Albarino, Shoemaker et al. 2013)[21]
Uganda, 2012	11	(Albarino, Shoemaker et al. 2013)[21]
Uganda, 2012	6	(Albarino, Shoemaker et al. 2013)[21]
Guinea, 2013	>2250*	(World Health Organization 2014)[22]

Table 2: Ebola contact tracing studies. Every effort was made to exclude accidental occupational contacts where possible. EVD = Ebola Virus Disease.

Outbreak	EVD patients	EVD patient contacts	Contacts per EVD patient	Source	Contact definition
DRC, 1976	61	498	8.2	(International Commission 1978)[2]	Live in contiguous household and share common eating facilities
DRC, 1976	62	459	7.4	(International Commission 1978)[2]	Live in contiguous household and share common eating facilities
DRC, 1976	18	117	6.5	(International Commission 1978)[2]	Live in contiguous household and share common eating facilities
DRC, 1976	5	29	5.8	(International Commission 1978) [2]	Live in contiguous household and share common eating facilities
South Sudan, 1976	38	232	6.1	(WHO/International study team 1978)[13]	Same household, intra-family
South Sudan, 1979	34	132	3.9	(Baron RC, McCormick JB et al. 1983)[15]	Intra-family, but includes family nursing
Gabon, 1996	15	300	20	(Milleliri, Tévi-Benissan et al. 2004)[23]	Physical contact
Uganda, 2000	393	5680	14.3	(Lamunu, Lutwama et al. 2004)[24]	Physical contact
Uganda, 2000	5	56	11.2	(Lamunu, Lutwama et al. 2004)[24]	Physical contact
Uganda, 2000	27	157	5.8	(Lamunu, Lutwama et al. 2004)[24]	Physical contact
Republic of the Congo, 2005	12	128	10.7	(Nkoghe, Kone et al. 2011)[25]	Slept in same household within the previous month, direct contact, touched linen or bodily fluids
Uganda, 2011	1	13	13	(Shoemaker, MacNeil et al. 2012)[20]	Physical onset after illness onset at home

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