# HERD IMMUNITY TO EBOLAVIRUSES IS NOT A REALISTIC TARGET FOR CURRENT VACCINATION STRATEGIES

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**Abstract**

The recent West African Ebola virus pandemic, which affected >28,000 individuals increased interest in anti-Ebolavirus vaccination programs. Here, we systematically analyzed the requirements for a prophylactic vaccination program based on the basic reproductive number ($R_0$, i.e. the number of secondary cases that result from an individual infection). Published $R_0$ values were determined by a systematic literature research and ranged from 0.37 to 20. $R_0$s ≥4 realistically reflected the critical early outbreak phases and superspreading events. Based on the $R_0$, the herd immunity threshold ($I_c$) was calculated using the equation $Ic=1–(1/R_0)$. The critical vaccination coverage ($V_c$) needed to provide herd immunity was determined by including the vaccine effectiveness (E) using the equation $Vc=Ic/E$. At an $R_0$ of 4, the $I_c$ is 75% and at an E of 90%, more than 80% of a population need to be vaccinated to establish herd immunity. Such vaccination rates are currently unrealistic because of resistance against vaccinations, financial/ logistical challenges, and a lack of vaccines that provide long-term protection against all human-pathogenic Ebolaviruses. Hence, outbreak management will for the foreseeable future depend on surveillance and case isolation. Clinical vaccine candidates are only available for Ebola viruses. Their use will need to be focused on health care workers, potentially in combination with ring vaccination approaches.

**Key words:** Ebola virus; Ebolavirus; Vaccines; Herd immunity; Basic Reproduction Number

## Introduction

Four Ebolaviruses (Ebola virus, Sudan virus, Bundybugyo virus, Taï Forrest virus) are endemic to Africa and can cause severe disease associated humans (1). Reston viruses are endemic to Asia and considered to be non-pathogenic in humans (1). However, very few genetic changes may result in human-pathogenic Reston viruses (1-3). Since the discovery of the first two members of the *Ebolavirus* family in 1976 in Sudan (today South Sudan) and Zaïre (today Democratic Republic of Congo), Ebolaviruses had until 2013 only caused small outbreaks in humans affecting up to a few hundred individuals (4,5). The recent Ebola virus outbreak in West Africa (2013-2016) resulted in 28,616 confirmed, probable, and suspected cases of Ebola virus disease and 11,310 deaths (5), which may still underestimate the actual numbers (6). It was the first Ebolavirus outbreak that affected multiple countries, was introduced to another country via air travel, and resulted in disease cases outside of Africa (4,5). The outbreak emphasized the health threats posed by Ebolaviruses and the importance of protection strategies (5,6).

Vaccination programs are effective in controlling infectious diseases, as demonstrated by the WHO-driven smallpox eradication (7). However, eradication seems to be an unrealistic aim for zoonotic viruses like the Ebolaviruses that circulate in animal reservoirs (8). Only herd immunity could prevent future outbreaks and protect individuals that cannot be vaccinated due to health issues (7). The herd immunity threshold ($l_c$) describes the number of society members that need to be protected (l) to prevent outbreaks. It is based on the basic reproductive number $R_0$ (number of secondary cases caused per primary case) of a pathogen (9-13).

Here, we performed a systematic analysis to determine the critical vaccine coverage ($V_c$) required to prevent Ebolavirus outbreaks by a prophylactic mass vaccination program based on the $R_0$ associated with Ebolavirus infection in humans. The results were further critically considered in the context of 1) the status of current Ebolavirus vaccine candidates and 2) the feasibility of a large-scale prophylactic Ebolavirus vaccination program taking into account a) the preparedness to participate in vaccination programs in the affected societies, b) logistic challenges, and c) costs.

## Methods

### Ebolavirus nomenclature

The nomenclature in this manuscript follows the recommendations of Kuhn et al. (14). The genus is *Ebolavirus*. The species are *Zaire ebolavirus* (type virus: Ebola virus), *Sudan ebolavirus* (type virus: Sudan virus), *Bundibugyo ebolavirus* (type virus: Bundibugyo virus), and *Taï Forest ebolavirus* (type virus: Taï Forest virus).

### Identification of studies that report on the basic reproductive number ($R_0$) of Ebolaviruses

To identify scientific articles that have calculated the basic reproductive number ($R_0$) for Ebolaviruses, we performed a literature search using PubMed (www.ncbi.nlm.nih.gov/pubmed) for the search term combinations "Ebola R0", "Ebola basic reproductive number", and "Ebola basic reproduction number" (retrieved on 29th September 2017).

### Determination of herd immunity thresholds and their implications for Ebolavirus diseases prevention strategies

Based on the basic reproductive number $R_0$, i.e. the number of secondary cases that result from an individual infection, the herd immunity threshold ($I_c$) was calculated using equation 1

$$I_c = 1 - (1/R_0) \qquad \text{(eqn 1)}$$

where $I_c$ indicates the proportion of a society that needs to be protected from infection to achieve herd immunity. Next, the critical vaccination coverage ($V_c$) that is needed to provide herd immunity was determined by including the vaccine effectiveness (E) using equation 2

$$V_c = I_c / E = [1 - (1/R_0)]/ E \qquad \text{(eqn 2)}$$

(9-13).

## Results

### Basic reproductive number ($R_0$) values for Ebolaviruses

The PubMed search for "Ebola R0" provided 18 hits, the search for "Ebola basic reproductive number" provided 42 hits, and the search for "Ebola basic reproduction number" provided 35 hits (Figure 1; Data Sheet 1). After removal of the overlaps and inclusion of an additional article (identified from the reference list of (12)) this resulted in 51 articles, 35 of which provided relevant information on Ebolavirus $R_0$ values (Figure 1; Data Sheet 1).

$R_0$ data were only available for Ebola virus and Sudan virus outbreaks. (Data Sheet 1). 29/35 studies analyzed data from the recent West African Ebola virus outbreak (Data Sheet 1). The others reported on Ebola virus outbreaks in the Democratic Republic of Congo. Four studies also included data from the Sudan virus outbreak 2000/2001 in Gulu, Uganda. We also considered a review that summarized all available data until February 2015 (4) (Data Sheet 1).

$R_0$ indicates the number of new infections caused by an infected individual, and when greater than 1 an outbreak will spread. $R_0$s ranged from 0.36 to 12 for Ebola virus and from 1.34 to 3.54 for Sudan virus (Data Sheet 1). Three studies directly compared the Ebola virus outbreak in Kikwit (1995, DR Congo) and the Sudan virus outbreak in Gulu (2000/ 2001, Uganda) (15-17), but did not reveal fundamental differences between the $R_0$s (Data Sheet 1, Data Sheet 2).

Different approaches to calculate $R_0$s lead to varying results (13). Accordantly, $R_0$ values calculated for the Sudan virus outbreak 2000/ 2001 in Gulu using identical data ranged from 1.34 to 3.54 (Data Sheet 1, Data Sheet 2). Additionally, virus transmission is influenced by socio-economic and behavioral factors including the health care response, society perceptions, religious practices, population density, and/ or infrastructure (13,18). Concordantly, $R_0$s determined in different districts of Guinea, Liberia, and Sierra Leone during the West African Ebola virus epidemic ranged from 0.36 to 3.37 (19). High reproductive numbers (≥4) are typically observed at the beginning of Ebolavirus outbreaks, prior to the implementation of control measures (20-23). Also, the spread of Ebolaviruses may be substantially driven by "superspreaders" who infect a high number (up to 15-20) of individuals (18,24-27). Hence, a vaccination program should establish herd immunity against Ebolaviruses that spread with an $R_0$ of ≥4.

### Herd immunity threshold ($I_c$)

At an $R_0$ of 4, the $I_c$ (eqn 1) is 75%, which means that 75% of a population need to be immune to provide herd immunity (Figure 2A, Data Sheet 3). The $I_c$ further rises to 80% at an $R_0$ of 5, to 90% at an $R_0$ of 10, and to 95% $R_0$ of 20 (Figure 2A, Data Sheet 3). This shows that high proportions of a population need to be immune to establish effective herd immunity.

### Critical vaccine coverage ($V_c$)

As there is currently no approved vaccine for the prevention of Ebolavirus disease, we calculated a range of $V_c$ (eqn 2) scenarios that reflect the efficacy range covered by approved vaccines. Attenuated replication-competent measles virus vaccines have been reported to protect up to 95% of individuals from disease after one dose, which increased to up to 99% after a second dose (28). The efficacy of varicella zoster virus vaccines, another attenuated

replication-competent vaccine, was recently calculated to be 81.9% after one dose and 94.4% after two doses (29). Inactivated seasonal influenza virus split vaccines have been reported to have a substantially lower efficiency of 50-60% (30-32). Hence, we considered a $V_c$ range between 50% and 100% (Figure 2B, Data Sheet 3). Vaccines, which provide high protection (ideally after a single vaccination), and high vaccination rates are required to prevent Ebolavirus outbreaks. If we assume an $R_0$ of 4 and a vaccination efficacy E of 90%, more than 80% of a population need to be vaccinated to establish herd immunity. If the $R_0$ rises to 5 a vaccine coverage of 80% would be required, even if a vaccine with 100% efficacy was available (Figure 2B, Data Sheet 3).

## Discussion

We performed an analysis of the Ebolavirus vaccine requirements to achieve the $V_c$ needed for prophylactic mass vaccination programs. Vaccines need to prevent Ebolavirus outbreaks that spread at an $R_0 \geq 4$, which reflects the critical early outbreak phases prior to the implementation of control measures and superspreading events (18-27). At an $R_0$ of 4, 80% of individuals need to be vaccinated with a vaccination efficacy of 90% to achieve herd immunity. Hence, highly effective vaccines and a high vaccination coverage are essential for successful prophylactic mass vaccination programs against Ebolaviruses.

Clinical vaccine candidates providing protection against all three to four human-pathogenic Ebolaviruses (Ebola virus, Sudan virus, Bundibugyo virus, potentially Taï Forest virus) do not currently exist (Data Sheet 4), although pre-clinical data suggest that the development of such vaccines may be feasible (5). Current vaccine candidates may also not provide the long-term protective immunity (≥10 years) necessary for sustainable protection against spillover events from animal reservoirs. Two studies reported immune responses 12 months after vaccination with different Ebola virus vaccine candidates (34,35). One of them described seroconversion in >90% of individuals after a single injection of rVSV-ZEBOV, a vesicular stomatitis virus-based Ebola virus vaccine. No or only a minor drop in antibody titers and neutralization capacity was reported 360 days after vaccination (34). A study investigating rVSV-ZEBOV and ChAd3-EBO-Z, a chimpanzee adenovirus type-3 vector-based Ebola virus vaccine, found lower seroconversion rates (rVSV-ZEBOV: 83.7%; ChAd3-EBO-Z: 70.8%) and reported the highest antibody response after one month and a decline afterwards (35). Thus, it is not clear, whether the vaccine-induced immunity covers the time frames >18 months that Ebolavirus survivors may remain contagious for (5,34,35,38-42). Notably, antibody responses may not always reliably indicate the protective efficacy of vaccines (36,37) (L. Lobel, unpublished data). Ebola virus recurrences and reinfections indicate that also natural Ebolavirus infections may not necessarily provide sustained protective immunity, which may further complicate the development of vaccines that provide long-term protection (43,44).

Limited acceptance of vaccinations may also limit Ebolavirus vaccination programs. In a rVSV-ZEBOV ring vaccination trial, only 5,837/ 11,841 patient contacts could be vaccinated. 34% of the contacts refused the vaccination (45). In a survey in Sierra Leone during the West African Ebola epidemic, 106/ 400 respondents (26.6%) were prepared to pay for a vaccination, while 290 respondents (72.5%) would have accepted a free vaccination (46). Hence, a $I_c$ of 75% (necessary to prevent an outbreak that spreads with an $R_0$=4 (Data Sheet 3)) would not be achievable, even under the threat of an ongoing epidemic.

The median maximum fee that survey participants in Sierra Leone during the West African Ebola epidemic were prepared to pay for a vaccine was about 5,000 leones ($0.65 as of 11th January 2018) (46). The international organization GAVI (www.gavi.org) is providing $5 million for the development of rVSV-ZEBOV, which is expected to pay for 300,000 vaccine doses (about $16.70/ dose) (47). Within a rVSV-ZEBOV ring vaccination trial, 11,841 contacts requiring vaccination from 117 clusters were identified over a ten-month period, i.e. about 101 individuals per confirmed Ebola virus disease patient (45). Hence, 300,000 doses will enable to vaccinate the contacts of approximately 2,970 Ebola virus disease patients. If an effective vaccine (which provided protection against all human-pathogenic Ebolaviruses) was available, a vaccination program would comprise about 462 million individuals in the countries that have been affected by Ebolavirus outbreaks (Data Sheet 5). Notably, the

211 countries, which have been affected by Ebolavirus outbreaks so far, have large rural
212 populations ranging from 13% (Gabon) to 84% (Uganda) (Data Sheet 5). Vaccination
213 programs in rural areas are associated with logistical issues including transport difficulties,
214 lack of equipment and trained medical specialists, and cultural and language barriers (48,49).
215
216 In conclusion, the achievement of a $V_c$ of 75% that is necessary to prevent an outbreak that
217 spreads with an $R_0$ of 4 with a vaccine that has an efficacy of 100% is currently unrealistic
218 because of limited vaccine acceptance in the affected populations and because of financial
219 and logistical challenges. In addition, concurrent diseases such as HIV and cancer, along with
220 potential side effects of vaccination, may remove significant numbers of potential vaccinees
221 (5,50). Moreover, vaccines that provide long-term immunity against all three (or including
222 Taï Forest virus, four) human-pathogenic Ebolaviruses, which would be needed to protect
223 populations effectively from large Ebolavirus outbreaks in endemic areas, do not exist.
224 Therefore, outbreak control of Ebolaviruses will for the foreseeable future depend on
225 surveillance and the isolation of cases. Clinical vaccine candidates are only available for
226 Ebola viruses and will need to be focused on health care workers, who are often involved in
227 disease transmission (22), potentially in combination with the vaccination of patient contacts.

## References

1. Michaelis M, Rossman JS, Wass, M.N. Computational analysis of Ebolavirus data: prospects, promises and challenges. Biochem Soc Trans (2016) 44:973-8.
2. Pappalardo M, Juliá M, Howard MJ, Rossman JS, Michaelis M, Wass MN. Conserved differences in protein sequence determine the human pathogenicity of Ebolaviruses. Sci Rep (2016) 6:23743. doi:10.1038/srep23743
3. Pappalardo M, Reddin IG, Cantoni D, Rossman JS, Michaelis M, Wass MN. Changes associated with Ebola virus adaptation to novel species. Bioinformatics (2017) 33:1911-5.
4. Van Kerkhove MD, Bento AI, Mills HL, Ferguson NM, Donnelly CA. A review of epidemiological parameters from Ebola outbreaks to inform early public health decision-making. Sci Data (2015) 2:150019. doi: 10.1038/sdata.2015.19
5. Keshwara R, Johnson RF, Schnell MJ. Toward an Effective Ebola Virus Vaccine. Annu Rev Med (2017) 68:371-86.
6. Rojek A, Horby P, Dunning J. Insights from clinical research completed during the west Africa Ebola virus disease epidemic. Lancet Infect Dis (2017) 17:e280-e292.
7. Bonanni P, Sacco C, Donato R, Capei R. Lifelong vaccination as a key disease-prevention strategy. Clin Microbiol Infect (2014) 20(Suppl 5):32-6.
8. Judson SD, Fischer R, Judson A, Munster VJ. Ecological Contexts of Index Cases and Spillover Events of Different Ebolaviruses. PLoS Pathog (2016) 12:e1005780. doi:10.1371/journal.ppat.1005780
9. Anderson RM. The concept of herd immunity and the design of community based immunization programs. Vaccine (1992): 10:928-35.
10. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. Clin Infect Dis (2011) 52:911-6.
11. Plans-Rubió P. The vaccination coverage required to establish herd immunity against influenza viruses. Prev Med (2012) 55:72-7.
12. Gittings K, Matson KL. Establishing herd immunity against Ebola through vaccination. Vaccine (2016) 34:2644-7.
13. Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, et al. The basic reproduction number (R0) of measles: a systematic review. Lancet Infect Dis (2017) 17:e420-e428.
14. Kuhn JH, Becker S, Ebihara H, Geisbert TW, Johnson KM, Kawaoka Y, et al. Proposal for a revised taxonomy of the family Filoviridae: classification, names of taxa and viruses, and virus abbreviations. Arch Virol (2010) 155:2083-103.
15. Chowell G, Hengartner NW, Castillo-Chavez C, Fenimore PW, Hyman JM. The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. J Theor Biol (2004) 229:119-26.
16. Legrand J, Grais RF, Boelle PY, Valleron AJ, Flahault A. Understanding the dynamics of Ebola epidemics. Epidemiol Infect (2007) 135:610-21.
17. Chen T, Ka-Kit Leung R, Liu R, Chen F, Zhang X, Zhao J, et al. Risk of imported Ebola virus disease in China. Travel Med Infect Dis (2014) 12:650-8.
18. Skrip LA, Fallah MP, Gaffney SG, Yaari R, Yamin D, Huppert A, et al. Characterizing risk of Ebola transmission based on frequency and type of case-contact exposures. Philos Trans R Soc Lond B Biol Sci (2017) 372(1721). pii: 20160301. doi:10.1098/rstb.2016.0301
19. Krauer F, Gsteiger S, Low N, Hansen CH, Althaus CL. Heterogeneity in District-Level Transmission of Ebola Virus Disease during the 2013-2015 Epidemic in West Africa. PLoS Negl Trop Dis (2016); 10:e0004867. doi:10.1371/journal.pntd.0004867
20. Althaus CL. Rapid drop in the reproduction number during the Ebola outbreak in the Democratic Republic of Congo. PeerJ (2015) 3:e1418. doi:10.7717/peerj.1418
21. Althaus CL, Low N, Musa EO, Shuaib F, Gsteiger S. Ebola virus disease outbreak in Nigeria: Transmission dynamics and rapid control. Epidemics (2015) 11:80-4.

22. Rosello A, Mossoko M, Flasche S, Van Hoek AJ, Mbala P, Camacho A, et al. Ebola virus disease in the Democratic Republic of the Congo, 1976-2014. Elife (2015) 4. pii: e09015. doi:10.7554/eLife.09015
23. Kucharski AJ, Eggo RM, Watson CH, Camacho A, Funk S, Edmunds WJ. Effectiveness of Ring Vaccination as Control Strategy for Ebola Virus Disease. Emerg Infect Dis (2016) 22:105-8.
24. Volz E, Pond S. Phylodynamic analysis of ebola virus in the 2014 sierra leone epidemic. PLoS Curr. 2014;6. pii: ecurrents.outbreaks.6f7025f1271821d4c815385b08f5f80e. doi:10.1371/currents.outbreaks.6f7025f1271821d4c815385b08f5f80e
25. Osterholm MT, Moore KA, Kelley NS, Brosseau LM, Wong G, Murphy FA, et al. Transmission of Ebola viruses: what we know and what we do not know. MBio (2015) 6:e00137. doi:10.1128/mBio.00137-15
26. Althaus CL. Ebola superspreading. Lancet Infect Dis. (2015) 15:507-8.
27. Lau MS, Dalziel BD, Funk S, McClelland A, Tiffany A, Riley S, et al. Spatial and temporal dynamics of superspreading events in the 2014-2015 West Africa Ebola epidemic. Proc Natl Acad Sci U S A (2017) 114:2337-42.
28. Holzmann H, Hengel H, Tenbusch M, Doerr HW. Eradication of measles: remaining challenges. Med Microbiol Immunol (2016) 205:201-8.
29. Rieck T, Feig M, An der Heiden M, Siedler A, Wichmann O. Assessing varicella vaccine effectiveness and its influencing factors using health insurance claims data, Germany, 2006 to 2015. Euro Surveill (2017) 22. pii: 30521. doi:10.2807/1560-7917.ES.2017.22.17.30521
30. Beyer WE, Nauta JJ, Palache AM, Giezeman KM, Osterhaus AD. Immunogenicity and safety of inactivated influenza vaccines in primed populations: a systematic literature review and meta-analysis. Vaccine. (2011) 29:5785-92.
31. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis (2012) 12:36-44.
32. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med (2013) 11:153. doi:10.1186/1741-7015-11-153
33. Ledgerwood JE, Costner P, Desai N, Holman L, Enama ME, Yamshchikov G, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. Vaccine (2010) 29:304-13.
34. Heppner DG Jr, Kemp TL, Martin BK, Ramsey WJ, Nichols R, Dasen EJ, et al. Safety and immunogenicity of the rVSVΔG-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. Lancet Infect Dis (2017) 17:854-66.
35. Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. N Engl J Med (2017) 377:1438-47.
36. Dorigo-Zetsma JW, Leverstein-van Hall MA, Vreeswijk J, de Vries JJ, Vossen AC, Ten Hulscher HI, et al. Immune status of health care workers to measles virus: evaluation of protective titers in four measles IgG EIAs. J Clin Virol (2015) 69:214-8.
37. Hahné SJ, Nic Lochlainn LM, van Burgel ND, Kerkhof J, Sane J, Yap KB, et al. Measles Outbreak Among Previously Immunized Healthcare Workers, the Netherlands, 2014. J Infect Dis (2016) 214:1980-6.
38. Diallo B, Sissoko D, Loman NJ, Bah HA, Bah H, Worrell MC, et al. Resurgence of Ebola Virus Disease in Guinea Linked to a Survivor With Virus Persistence in Seminal Fluid for More Than 500 Days. Clin Infect Dis (2016) 63:1353-6.

327 39. Sissoko D, Duraffour S, Kerber R, Kolie JS, Beavogui AH, Camara AM, et al.
328 Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease
329 survivors: a longitudinal analysis and modelling study. Lancet Glob Health (2017) 5:e80-e88.
330 40. Li JX, Hou LH, Meng FY, Wu SP, Hu YM, Liang Q, et al. Immunity duration of a
331 recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost
332 immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-
333 controlled, phase 1 trial. Lancet Glob Health (2017) 5:e324-34.
334 41. Winslow RL, Milligan ID, Voysey M, Luhn K, Shukarev G, Douoguih M, et al. Immune
335 Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored
336 Ebola Vaccines at 1 Year. JAMA (2017) 317:1075-7.
337 42. Zhu FC, Wurie AH, Hou LH, Liang Q, Li YH, Russell JB, et al. Safety and
338 immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy
339 adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2
340 trial. Lancet (2017) 389:621-8.
341 43. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus
342 relapse causing meningoencephalitis: a case report. Lancet (2016) 388:498-503.
343 44. MacIntyre CR, Chughtai AA. Recurrence and reinfection--a new paradigm for the
344 management of Ebola virus disease. Int J Infect Dis (2016) 43:58-61.
345 45. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et
346 al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease:
347 final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça
348 Suffit!). Lancet (2017) 389:505-18.
349 46. Huo X, Shi G, Li X, Lai X, Deng L, Xu F, et al. Knowledge and attitudes about Ebola
350 vaccine among the general population in Sierra Leone. Vaccine (2016) 34:1767-72.
351 47. Henao-Restrepo AM, Preziosi MP, Wood D, Moorthy V, Kieny MP; WHO Ebola
352 Research, Development Team. On a path to accelerate access to Ebola vaccines: The WHO's
353 research and development efforts during the 2014-2016 Ebola epidemic in West Africa. Curr
354 Opin Virol (2016) 17:138-44.
355 48. Alexander KA, Sanderson CE, Marathe M, Lewis BL, Rivers CM, Shaman J, et al. What
356 factors might have led to the emergence of Ebola in West Africa? PLoS Negl Trop Dis
357 (2015) 9:e0003652. doi:10.1371/journal.pntd.0003652
358 49. Moon S, Sridhar D, Pate MA, Jha AK, Clinton C, Delaunay S, et al. Will Ebola change
359 the game? Ten essential reforms before the next pandemic. The report of the Harvard-
360 LSHTM Independent Panel on the Global Response to Ebola. Lancet (2015) 386:2204-21.
361 50. Kagina BM, Wiysonge CS, Lesosky M, Madhi SA, Hussey GD. Safety of licensed
362 vaccines in HIV-infected persons: a systematic review protocol. Syst Rev (2014) 3:101. doi:
363 10.1186/2046-4053-3-101

364 **Figure legends**
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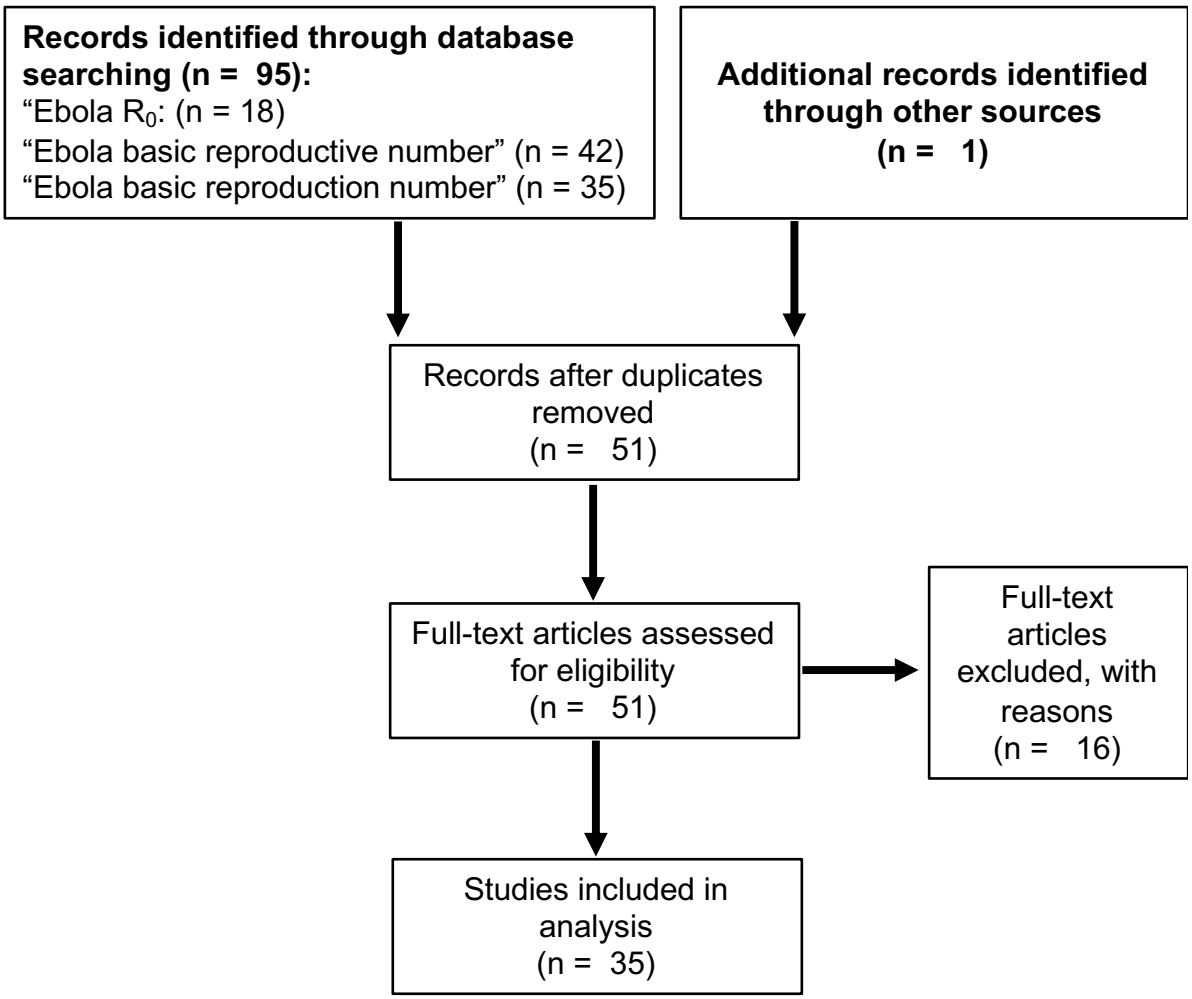
## Figure 1




366
367
368 **Figure 1**. Summary of the literature search using PubMed (www.ncbi.nlm.nih.gov/pubmed)
369 to identify articles that report on the basic reproductive number ($R_0$) of Ebolaviruses.
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**Figure 2**

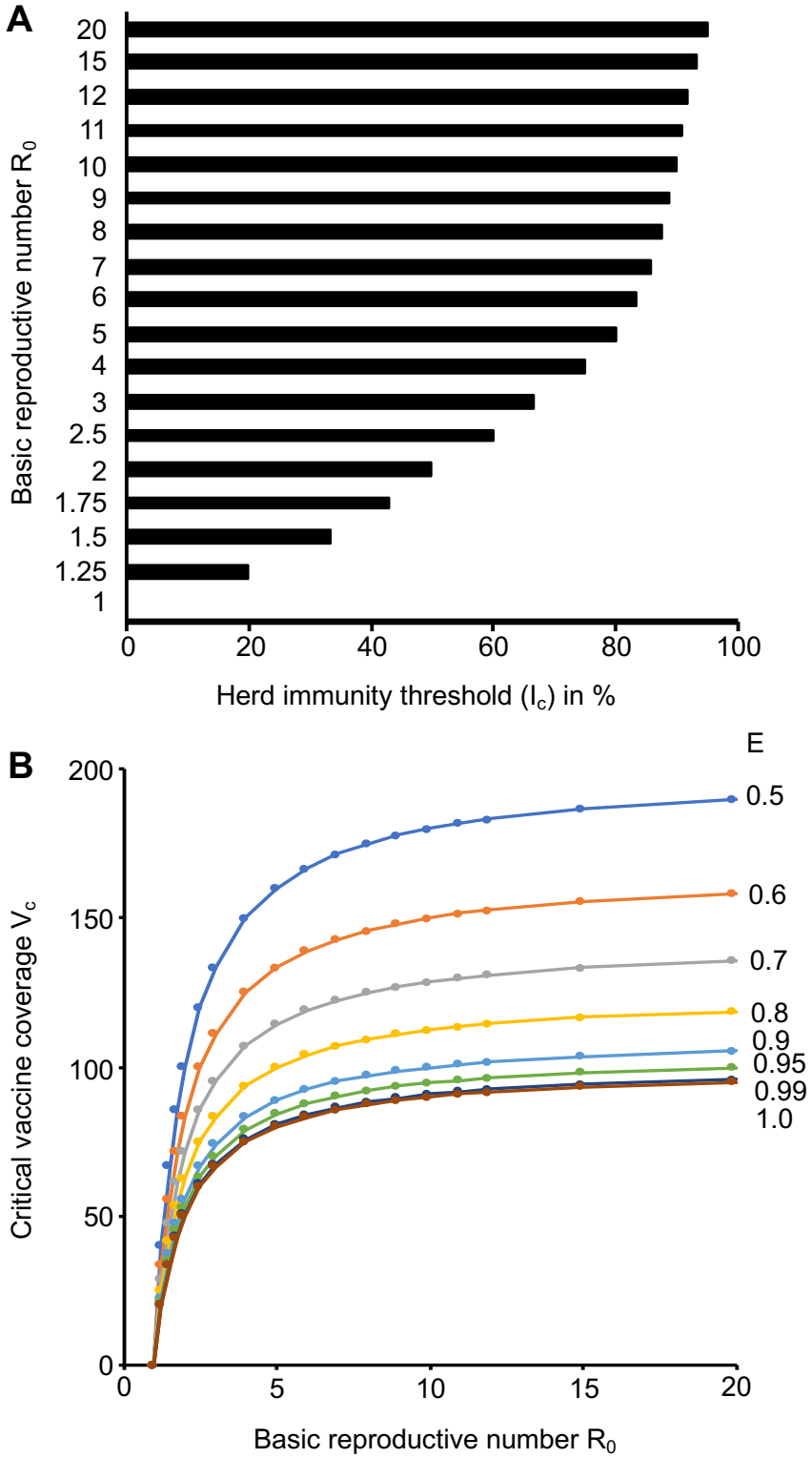


**Figure 2**. Herd immunity thresholds ($I_c$) and Critical vaccine coverage ($V_c$) values in dependence of the basic reproductive number ($R_0$) and the vaccine efficacy (E). A) $I_c$ values based on a range of $R_0$ values that cover the range reported for Ebolaviruses. B) $V_c$ values based on $R_0$ values that cover the range reported for Ebolaviruses and E values that are in the range of those reported for approved vaccines. The respective numerical data are presented in Data Sheet 3.