



Kent Academic Repository

Masterson, Stuart G., Lobel, Leslie, Carroll, Miles W., Wass, Mark N. and Michaelis, Martin (2018) *Herd Immunity to Ebolaviruses Is Not a Realistic Target for Current Vaccination Strategies*. *Frontiers in Immunology*, 9 . ISSN 1664-3224.

Downloaded from

<https://kar.kent.ac.uk/66962/> The University of Kent's Academic Repository KAR

The version of record is available from

<https://doi.org/10.3389/fimmu.2018.01025>

This document version

Author's Accepted Manuscript

DOI for this version

Licence for this version

CC BY (Attribution)

Additional information

Versions of research works

Versions of Record

If this version is the version of record, it is the same as the published version available on the publisher's web site. Cite as the published version.

Author Accepted Manuscripts

If this document is identified as the Author Accepted Manuscript it is the version after peer review but before type setting, copy editing or publisher branding. Cite as Surname, Initial. (Year) 'Title of article'. To be published in **Title of Journal** , Volume and issue numbers [peer-reviewed accepted version]. Available at: DOI or URL (Accessed: date).

Enquiries

If you have questions about this document contact ResearchSupport@kent.ac.uk. Please include the URL of the record in KAR. If you believe that your, or a third party's rights have been compromised through this document please see our [Take Down policy](https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies) (available from <https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies>).

Kent Academic Repository

Full text document (pdf)

Citation for published version

Masterson, Stuart G. and Lobel, Leslie and Carroll, Miles W. and Wass, Mark N. and Michaelis, Martin (2018) Herd Immunity to Ebolaviruses Is Not a Realistic Target for Current Vaccination Strategies. *Frontiers in Immunology*, 9 . ISSN 1664-3224.

DOI

<https://doi.org/10.3389/fimmu.2018.01025>

Link to record in KAR

<http://kar.kent.ac.uk/66962/>

Document Version

Author's Accepted Manuscript

Copyright & reuse

Content in the Kent Academic Repository is made available for research purposes. Unless otherwise stated all content is protected by copyright and in the absence of an open licence (eg Creative Commons), permissions for further reuse of content should be sought from the publisher, author or other copyright holder.

Versions of research

The version in the Kent Academic Repository may differ from the final published version.

Users are advised to check <http://kar.kent.ac.uk> for the status of the paper. **Users should always cite the published version of record.**

Enquiries

For any further enquiries regarding the licence status of this document, please contact:

researchsupport@kent.ac.uk

If you believe this document infringes copyright then please contact the KAR admin team with the take-down information provided at <http://kar.kent.ac.uk/contact.html>

1 **HERD IMMUNITY TO EBOLAVIRUSES IS NOT A**
2 **REALISTIC TARGET FOR CURRENT VACCINATION**
3 **STRATEGIES**

4
5 Stuart G. Masterson¹, Leslie Lobel^{2,3}, Miles W. Carroll⁴, Mark N. Wass^{1*}, Martin
6 Michaelis^{1*}

7
8 ¹ Industrial Biotechnology Centre and School of Biosciences, University of Kent, Canterbury,
9 UK

10 ² Department of Microbiology, Immunology and Genetics, Faculty of Health Sciences, Ben-
11 Gurion University of the Negev, Beer-Sheva, Israel

12 ³ Department of Emerging and Re-emerging Diseases and Special Pathogens Uganda Virus
13 Research Institute (UVRI), Entebbe, Uganda

14 ⁴ Public Health England, Porton Down, Salisbury, United Kingdom

15
16 * Correspondence: Mark N. Wass, M.N.Wass@kent.ac.uk; Martin Michaelis,
17 M.Michaelis@kent.ac.uk

18
19 **Word count:** 1998

20 **Figures:** 2

21 **Tables:** 0

22 **Abstract**

23 The recent West African Ebola virus pandemic, which affected >28,000 individuals increased
24 interest in anti-Ebolavirus vaccination programs. Here, we systematically analyzed the
25 requirements for a prophylactic vaccination program based on the basic reproductive number
26 (R_0 , i.e. the number of secondary cases that result from an individual infection). Published R_0
27 values were determined by systematic literature research and ranged from 0.37 to 20. $R_0s \geq 4$
28 realistically reflected the critical early outbreak phases and superspreading events. Based on
29 the R_0 , the herd immunity threshold (I_c) was calculated using the equation $I_c = 1 - (1/R_0)$. The
30 critical vaccination coverage (V_c) needed to provide herd immunity was determined by
31 including the vaccine effectiveness (E) using the equation $V_c = I_c / E$. At an R_0 of 4, the I_c is
32 75% and at an E of 90%, more than 80% of a population need to be vaccinated to establish
33 herd immunity. Such vaccination rates are currently unrealistic because of resistance against
34 vaccinations, financial/ logistical challenges, and a lack of vaccines that provide long-term
35 protection against all human-pathogenic Ebolaviruses. Hence, outbreak management will for
36 the foreseeable future depend on surveillance and case isolation. Clinical vaccine candidates
37 are only available for Ebola viruses. Their use will need to be focused on health care workers,
38 potentially in combination with ring vaccination approaches.

39

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

41 **Introduction**

42 The genus *Ebolavirus* contains five species: *Zaire ebolavirus* (type virus: Ebola virus), *Sudan*
43 *ebolavirus* (type virus: Sudan virus), *Bundibugyo ebolavirus* (type virus: Bundibugyo virus),
44 *Tai Forest ebolavirus* (type virus: Tai Forest virus, previously also referred to by names such
45 as Côte d'Ivoire ebolavirus or Ivory Coast ebolavirus), *Reston ebolavirus* (type virus: Reston
46 virus) (1). Four Ebolaviruses (Ebola virus, Sudan virus, Bundibugyo virus, Tai Forrest virus)
47 are endemic to Africa and can cause severe disease in humans (2). Reston viruses are
48 endemic to Asia and considered to be non-pathogenic in humans (2). However, very few
49 genetic changes may result in human-pathogenic Reston viruses (2-4). Since the discovery of
50 the first two members of the *Ebolavirus* family in 1976 in Sudan (today South Sudan) and
51 Zaïre (today Democratic Republic of Congo), Ebolaviruses had until 2013 only caused small
52 outbreaks in humans affecting up to a few hundred individuals (5,6). The recent Ebola virus
53 outbreak in West Africa (2013-2016) resulted in 28,616 confirmed, probable, and suspected
54 cases of Ebola virus disease and 11,310 deaths (6), which may still underestimate the actual
55 numbers (7). It was the first Ebolavirus outbreak that affected multiple countries, was
56 introduced to another country via air travel, and resulted in a significant number of human
57 disease cases outside of Africa (5,6). Prior to this outbreak, only isolated human cases were
58 treated outside of Africa. A scientist who had become infected by Tai Forest virus after an
59 autopsy of a Chimpanzee was treated in Switzerland (8), and two laboratory infections were
60 reported in Russia (9,10). In addition, Reston virus-infected non-human primates were
61 exported from the Philippines to the US and Italy (11). Finally, Marburg virus (which belongs
62 like the Ebolaviruses to the Filoviruses) was exported out of Africa (12,13) and was
63 associated with laboratory infections (14,15). Due to its unique size, the West African Ebola
64 virus outbreak emphasized the health threats posed by Ebolaviruses and the importance of
65 protection strategies (6,7).

66
67 Vaccination programs are effective in controlling infectious diseases, as demonstrated by the
68 WHO-driven smallpox eradication (16). However, eradication is likely to be more difficult
69 for zoonotic viruses like the Ebolaviruses that circulate in animal reservoirs (17). Only herd
70 immunity could prevent future outbreaks and protect individuals that cannot be vaccinated
71 due to health issues (16). The herd immunity threshold (I_c) describes the number of society
72 members that need to be protected (18) to prevent outbreaks. It is based on the basic
73 reproductive number R_0 (number of secondary cases caused per primary case) of a pathogen
74 (18-22).

75
76 Here, we performed a systematic analysis to determine the critical vaccine coverage (V_c)
77 required to prevent Ebolavirus outbreaks by a prophylactic mass vaccination program based
78 on the R_0 associated with Ebolavirus infection in humans. The results were further critically
79 considered in the context of 1) the status of current Ebolavirus vaccine candidates and 2) the
80 feasibility of a large-scale prophylactic Ebolavirus vaccination program taking into account
81 a) the preparedness to participate in vaccination programs in the affected societies, b) logistic
82 challenges, and c) costs.

83 **Methods**

84

85 **Identification of studies that report on the basic reproductive number (R_0) of**
86 **Ebolaviruses**

87 To identify scientific articles that have calculated the basic reproductive number (R_0) for
88 Ebolaviruses, we performed a literature search using PubMed
89 (www.ncbi.nlm.nih.gov/pubmed) for the search term combinations “Ebola R_0 ”, “Ebola basic
90 reproductive number”, and “Ebola basic reproduction number” (retrieved on 29th September
91 2017).

92

93 **Determination of herd immunity thresholds and their implications for Ebolavirus**
94 **diseases prevention strategies**

95 Based on the basic reproductive number R_0 , i.e. the number of secondary cases that result
96 from an individual infection, the herd immunity threshold (I_c) was calculated using equation
97 1

98

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

99

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

103

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

104

(18-22).

105 **Results**

106

107 **Basic reproductive number (R_0) values for Ebolaviruses**

108 The PubMed search for “Ebola R_0 ” provided 18 hits, the search for “Ebola basic
109 reproductive number” provided 42 hits, and the search for “Ebola basic reproduction
110 number” provided 35 hits (Figure 1; Data Sheet 1). After removal of the overlaps and
111 inclusion of an additional article (identified from the reference list of (21)) this resulted in 51
112 articles, 35 of which provided relevant information on Ebolavirus R_0 values (Figure 1; Data
113 Sheet 1).

114

115 R_0 data were only available for Ebola virus and Sudan virus outbreaks. (Data Sheet 1). 29/35
116 studies analyzed data from the recent West African Ebola virus outbreak (Data Sheet 1). The
117 others reported on Ebola virus outbreaks in the Democratic Republic of Congo. Four studies
118 also included data from the Sudan virus outbreak 2000/2001 in Gulu, Uganda. We also
119 considered a review that summarized all available data until February 2015 (5) (Data Sheet
120 1).

121

122 R_0 indicates the number of new infections caused by an infected individual, and when greater
123 than 1 an outbreak will spread. Different approaches to calculate R_0 s lead to varying results
124 (22). Accordantly, R_0 values calculated for the Sudan virus outbreak 2000/ 2001 in Gulu
125 using identical data ranged from 1.34 to 3.54 (Data Sheet 1, Data Sheet 2). Small outbreak
126 sizes may also limit the accuracy of the calculated R_0 values. Additionally, virus transmission
127 is influenced by socio-economic and behavioral factors including the health care response,
128 society perceptions, religious practices, population density, and/ or infrastructure (22,23).
129 Concordantly, R_0 s that were determined by the same methodology in different districts of
130 Guinea, Liberia, and Sierra Leone during the West African Ebola virus epidemic ranged from
131 0.36 to 3.37 (24). Three studies directly compared the Ebola virus outbreak in Kikwit (1995,
132 DR Congo) and the Sudan virus outbreak in Gulu (2000/ 2001, Uganda) (25-27), but did not
133 reveal fundamental differences between the R_0 s of the viruses (Data Sheet 1, Data Sheet 2).
134 Across all relevant studies, R_0 s ranged from 0.36 to 12 for Ebola virus and from 1.34 to 3.54
135 for Sudan virus (Data Sheet 1). 9 of the 35 studies that provided R_0 values showed that
136 Ebolaviruses can spread with an $R_0 >3$, and 5 studies suggested that Ebolaviruses can spread
137 with R_0 values >4 . High reproductive numbers (≥ 4) are typically observed at the beginning of
138 Ebolavirus outbreaks, prior to the implementation of control measures (28-31). Also, the
139 spread of Ebolaviruses may be substantially driven by “superspreaders” who infect a high
140 number (up to 15-20) of individuals (23,32-35). Studies from the West African Ebola virus
141 outbreak suggested that relatively small numbers of superspreaders may have been
142 responsible for the majority of cases (35,36). Since the available data suggest that Ebolavirus
143 transmission can occur with R_0 values of 3, 4, or even higher, a prophylactic vaccination
144 program should establish herd immunity against Ebolaviruses that spread at such levels.

145

146 **Herd immunity threshold (I_c)**

147 At an R_0 of 3, the I_c (eqn 1) is 67%, which means that 67% of a population need to be
148 immune to provide herd immunity (Figure 2A, Data Sheet 3). The I_c further rises to 75% at
149 an R_0 of 4, 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
150 Sheet 3). This shows that high proportions of a population need to be immune to establish
151 effective herd immunity.

152

153 **Critical vaccine coverage (V_c)**

154 As there is currently no approved vaccine for the prevention of Ebolavirus disease, we
155 calculated a range of V_c (eqn 2) scenarios that reflect the efficacy range covered by approved
156 vaccines. Attenuated replication-competent measles virus vaccines have been reported to
157 protect up to 95% of individuals from disease after one dose, which increased to up to 99%
158 after a second dose (37). The efficacy of varicella zoster virus vaccines, another attenuated
159 replication-competent vaccine, was recently calculated to be 81.9% after one dose and 94.4%
160 after two doses (38). Inactivated seasonal influenza virus split vaccines have been reported to
161 have a substantially lower efficiency of 50-60% (39-41). Hence, we considered a V_c range
162 between 50% and 100% (Figure 2B, Data Sheet 3). Vaccines, which provide high protection
163 (ideally after a single vaccination), and high vaccination rates are required for prophylactic
164 vaccination programs that establish a level of herd immunity that prevents Ebolavirus
165 outbreaks. If we assume an R_0 of 3 and a vaccination efficacy E of 90%, more than 70% of a
166 population need to be vaccinated to establish herd immunity. At an R_0 of 4 and a vaccination
167 efficacy E of 90%, more than 80% of a population need to be vaccinated. If the R_0 rises to 5 a
168 vaccine coverage of 80% would be required, even if a vaccine with 100% efficacy was
169 available (Figure 2B, Data Sheet 3).

170

171 Discussion

172
173 We performed an analysis of the Ebolavirus vaccine requirements to achieve the V_c needed
174 for prophylactic mass vaccination programs. A number of studies suggested that Ebolavirus
175 transmission can occur with R_0 values of 3, 4, or even higher, in particular during early
176 outbreak stages (prior to the implementation of control measures) and/ or as consequence of
177 superspreading events (23,24,28-36). Therefore, a prophylactic vaccination program should
178 establish herd immunity against Ebolaviruses that spread at such levels. At an R_0 of 3, >70%
179 of individuals and at an R_0 of 4, >80% of individuals need to be vaccinated with a
180 vaccination efficacy of 90% to achieve herd immunity. Hence, highly effective vaccines and
181 a high vaccination coverage are essential for successful prophylactic mass vaccination
182 programs against Ebolaviruses.

183
184 Clinical vaccine candidates providing protection against all three to four human-pathogenic
185 Ebolaviruses (Ebola virus, Sudan virus, Bundibugyo virus, potentially Tai Forest virus) do
186 not currently exist (Data Sheet 4), although pre-clinical data suggest that the development of
187 such vaccines may be feasible (6). Current vaccine candidates may also not provide the long-
188 term protective immunity (≥ 10 years) necessary for sustainable protection against spillover
189 events from animal reservoirs. Two studies reported immune responses 12 months after
190 vaccination with different Ebola virus vaccine candidates (42,43). One of them described
191 seroconversion in >90% of individuals after a single injection of rVSV-ZEBOV, a vesicular
192 stomatitis virus-based Ebola virus vaccine. No or only a minor drop in antibody titers and
193 neutralization capacity was reported 360 days after vaccination (42). A study investigating
194 rVSV-ZEBOV and ChAd3-EBO-Z, a chimpanzee adenovirus type-3 vector-based Ebola
195 virus vaccine, found lower seroconversion rates (rVSV-ZEBOV: 83.7%; ChAd3-EBO-Z:
196 70.8%) and reported the highest antibody response after one month and a decline afterwards
197 (43). Thus, it is not clear, whether the vaccine-induced immunity covers the time frame of
198 two years (or perhaps even longer) that Ebolavirus survivors may remain contagious for
199 (6,42,43-52). It is also not clear whether (and if yes, to which extent) immunity to
200 Ebolaviruses is mediated by cell-mediated and/ or humoral immune responses (53). A
201 challenge study using non-human primates suggested that protection by adenovirus-based
202 vaccines is cell-mediated (54). This means that antigen binding and/ or neutralization titers
203 may not always correlate with protection from disease. Consequently, the efficacy levels of
204 vaccines cannot be determined with certainty based on antibody responses at various time
205 points post vaccination. Thus, it remains unknown whether current vaccine candidates offer
206 the long-term protection necessary for mass vaccination programs that effectively prevent
207 zoonotic Ebolavirus outbreaks. Ebola virus recurrences and reinfections indicate that,
208 although natural Ebolavirus infections are generally assumed to provide long-term protection,
209 natural infections may not always result in sustained protective immunity in every survivor,
210 which may further complicate the development of vaccines that provide long-term protection
211 (55,56). In this context, the establishment of long-term immunity may be influenced by the
212 disease treatment. In a case of relapse nine months after discharge, it was speculated whether
213 the treatment of the initial disease with convalescent plasma and monoclonal antibodies
214 might have contributed to the recurrence (55).

215
216 Limited acceptance of vaccinations may also limit Ebolavirus vaccination programs. In a
217 rVSV-ZEBOV ring vaccination trial, only 5,837/ 11,841 patient contacts could be vaccinated.
218 34% of the contacts refused the vaccination (57). In a survey in Sierra Leone during the West
219 African Ebola epidemic, 106/ 400 respondents (26.6%) were prepared to pay for a
220 vaccination, while 290 respondents (72.5%) would have accepted a free vaccination (58).

221 Since 74% of the population need to be vaccinated by a vaccine with a 90% efficacy to
222 prevent an outbreak that spreads with an R_0 of 3 and 83% of the population to prevent an
223 outbreak that spreads with an R_0 of 4 (Data Sheet 3), such levels of vaccine coverage seem
224 currently unachievable, even under the threat of an ongoing epidemic, although attitudes may
225 change in the future if more (clinical) data becomes available. Therefore, more differentiated
226 vaccination strategies with a focus on healthcare workers and patient contacts appear more
227 feasible.

228
229 The median maximum fee that survey participants in Sierra Leone during the West African
230 Ebola epidemic were prepared to pay for a vaccine was about 5,000 leones (\$0.65 as of 11th
231 January 2018) (58). The international organization GAVI (www.gavi.org) is providing \$5
232 million for the development of rVSV-ZEBOV, which is expected to pay for 300,000 vaccine
233 doses (about \$16.70/ dose) (59). Within a rVSV-ZEBOV ring vaccination trial, 11,841
234 contacts requiring vaccination from 117 clusters were identified over a ten-month period, i.e.
235 about 101 individuals per confirmed Ebola virus disease patient (57). Hence, 300,000 doses
236 will enable vaccination of the contacts of approximately 2,970 Ebola virus disease patients. If
237 an effective vaccine (which provided protection against all human-pathogenic Ebolaviruses)
238 was available, a vaccination program would comprise about 462 million individuals in the
239 countries that have been affected by Ebolavirus outbreaks (Data Sheet 5). Notably, the
240 countries, which have been affected by Ebolavirus outbreaks so far, have large rural
241 populations ranging from 13% (Gabon) to 84% (Uganda) (Data Sheet 5). Vaccination
242 programs in rural areas are associated with logistical issues including transport difficulties,
243 lack of equipment and trained medical specialists, and cultural and language barriers (60,61).

244
245 In conclusion, the achievement of a V_c of 75% that is necessary to prevent an outbreak that
246 spreads with an R_0 of 4 with a vaccine that has an efficacy of 100% is currently unrealistic
247 because of limited vaccine acceptance in the affected populations and because of financial
248 and logistical challenges. In addition, concurrent diseases such as HIV and cancer, along with
249 potential side effects of vaccination, may remove significant numbers of potential vaccinees
250 (6,62). Alternative vaccination strategies will be required for such patients. Replication-
251 deficient vaccines such as DNA vaccines, virus-like particles, nanoparticle-based vaccines,
252 and viral vectors (e.g. Modified Vaccinia Ankara (MVA), which was already demonstrated to
253 be safe in immunocompromised individuals) may be safer alternatives (6,63). Moreover,
254 vaccines that provide long-term immunity against all three (or including Taï Forest virus,
255 four) human-pathogenic Ebolaviruses, which would be needed to protect populations
256 effectively from large Ebolavirus outbreaks in endemic areas, do not exist. Therefore,
257 outbreak control of Ebolaviruses will for the foreseeable future depend on surveillance and
258 the isolation of cases. Clinical vaccine candidates are only available for Ebola viruses and
259 will need to be focused on health care workers, who are often involved in disease
260 transmission (30), potentially in combination with the vaccination of patient contacts. Hence,
261 our findings support the conclusions of the WHO Strategic Advisory Group of Experts on
262 immunization (SAGE) at the WHO SAGE meeting on 25th to 27th April 2017 (64). SAGE
263 acknowledged the need for further research on Ebolavirus vaccines, including the generation
264 of conclusive data on the duration of protection provided by Ebolavirus vaccine candidates.
265 In case of future Ebolavirus outbreaks, SAGE recommended the use of rVSV-ZEBOV ring
266 vaccination strategies (64).

267 **Author Contributions Statement**

268 SGM performed the calculations. MM performed the literature search. All authors analyzed
269 the data. SGM, MM, and MNW wrote the manuscript. All authors gave their final approval
270 of the version to be published.

271

272 **Conflict of Interest Statement**

273 There is no conflict of interest.

274 **References**

- 275 1. Kuhn JH, Becker S, Ebihara H, Geisbert TW, Johnson KM, Kawaoka Y, et al. Proposal for
276 a revised taxonomy of the family Filoviridae: classification, names of taxa and viruses, and
277 virus abbreviations. *Arch Virol* (2010) 155:2083-103.
- 278 2. Michaelis M, Rossman JS, Wass, M.N. Computational analysis of Ebolavirus data:
279 prospects, promises and challenges. *Biochem Soc Trans* (2016) 44:973-8.
- 280 3. Pappalardo M, Juliá M, Howard MJ, Rossman JS, Michaelis M, Wass MN. Conserved
281 differences in protein sequence determine the human pathogenicity of Ebolaviruses. *Sci Rep*
282 (2016) 6:23743. doi:10.1038/srep23743
- 283 4. Pappalardo M, Reddin IG, Cantoni D, Rossman JS, Michaelis M, Wass MN. Changes
284 associated with Ebola virus adaptation to novel species. *Bioinformatics* (2017) 33:1911-5.
- 285 5. Van Kerkhove MD, Bento AI, Mills HL, Ferguson NM, Donnelly CA. A review of
286 epidemiological parameters from Ebola outbreaks to inform early public health decision-
287 making. *Sci Data* (2015) 2:150019. doi: 10.1038/sdata.2015.19
- 288 6. Keshwara R, Johnson RF, Schnell MJ. Toward an Effective Ebola Virus Vaccine. *Annu*
289 *Rev Med* (2017) 68:371-86.
- 290 7. Rojek A, Horby P, Dunning J. Insights from clinical research completed during the west
291 Africa Ebola virus disease epidemic. *Lancet Infect Dis* (2017) 17:e280-e292.
- 292 8. Le Guenno B, Formenty P, Wyers M, Gounon P, Walker F, Boesch C. Isolation and partial
293 characterisation of a new strain of Ebola virus. *Lancet* (1995) 345:1271-4.
- 294 9. Akinfeyeva LA, Aksyonova OI, Vasilyevich IV, Ginko ZI, Zarkov KA, Zubavichene NM,
295 et al. A case of Ebola hemorrhagic fever. *Infektsionnye Bolezni (Moscow)* (2005) 3:85–8.
- 296 10. Borisevich IV, Markin VA, Firsova IV, Evseev AA, Khamitov RA, Maksimov VA.
297 Hemorrhagic (Marburg, Ebola, Lassa, and Bolivian) fevers: epidemiology, clinical pictures,
298 and treatment. *Vopr Virusol* (2006) 51:8-16.
- 299 11. Cantoni D, Hamlet A, Michaelis M, Wass MN, Rossman JS. Risks Posed by Reston, the
300 Forgotten Ebolavirus. *mSphere* (2016) 1:pil: e00322-16.
- 301 12. Timen A, Koopmans MP, Vossen AC, van Doornum GJ, Günther S, van den Berkmortel
302 F, et al. Response to imported case of Marburg hemorrhagic fever, the Netherland. *Emerg*
303 *Infect Dis* (2009) 15:1171-5.
- 304 13. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM. Ebola and Marburg
305 haemorrhagic fever. *J Clin Virol* (2015) 64:111-9.
- 306 14. Nikiforov VV, Turovskii Iul, Kalinin PP, Akinfeeva LA, Katkova LR, Barmin VS, et al.
307 A case of a laboratory infection with Marburg fever. *Zh Mikrobiol Epidemiol Immunobiol*
308 (1994) 3:104-6.
- 309 15. Beer B, Kurth R, Bukreyev A. Characteristics of Filoviridae: Marburg and Ebola viruses.
310 *Naturwissenschaften* (1999) 86:8-17.
- 311 16. Bonanni P, Sacco C, Donato R, Capei R. Lifelong vaccination as a key disease-
312 prevention strategy. *Clin Microbiol Infect* (2014) 20(Suppl 5):32-6.
- 313 17. Judson SD, Fischer R, Judson A, Munster VJ. Ecological Contexts of Index Cases and
314 Spillover Events of Different Ebolaviruses. *PLoS Pathog* (2016) 12:e1005780.
315 doi:10.1371/journal.ppat.1005780
- 316 18. Anderson RM. The concept of herd immunity and the design of community based
317 immunization programs. *Vaccine* (1992): 10:928-35.
- 318 19. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. *Clin Infect Dis* (2011)
319 52:911-6.
- 320 20. Plans-Rubió P. The vaccination coverage required to establish herd immunity against
321 influenza viruses. *Prev Med* (2012) 55:72-7.
- 322 21. Gittings K, Matson KL. Establishing herd immunity against Ebola through vaccination.
323 *Vaccine* (2016) 34:2644-7.

324 22. Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, et al. The basic reproduction
325 number (R0) of measles: a systematic review. *Lancet Infect Dis* (2017) 17:e420-e428.

326 23. Skrip LA, Fallah MP, Gaffney SG, Yaari R, Yamin D, Huppert A, et al. Characterizing
327 risk of Ebola transmission based on frequency and type of case-contact exposures. *Philos*
328 *Trans R Soc Lond B Biol Sci* (2017) 372(1721). pii: 20160301. doi:10.1098/rstb.2016.0301

329 24. Krauer F, Gsteiger S, Low N, Hansen CH, Althaus CL. Heterogeneity in District-Level
330 Transmission of Ebola Virus Disease during the 2013-2015 Epidemic in West Africa. *PLoS*
331 *Negl Trop Dis* (2016); 10:e0004867. doi:10.1371/journal.pntd.0004867

332 25. Chowell G, Hengartner NW, Castillo-Chavez C, Fenimore PW, Hyman JM. The basic
333 reproductive number of Ebola and the effects of public health measures: the cases of Congo
334 and Uganda. *J Theor Biol* (2004) 229:119-26.

335 26. Legrand J, Grais RF, Boelle PY, Valleron AJ, Flahault A. Understanding the dynamics of
336 Ebola epidemics. *Epidemiol Infect* (2007) 135:610-21.

337 27. Chen T, Ka-Kit Leung R, Liu R, Chen F, Zhang X, Zhao J, et al. Risk of imported Ebola
338 virus disease in China. *Travel Med Infect Dis* (2014) 12:650-8.

339 28. Althaus CL. Rapid drop in the reproduction number during the Ebola outbreak in the
340 Democratic Republic of Congo. *PeerJ* (2015) 3:e1418. doi:10.7717/peerj.1418

341 29. Althaus CL, Low N, Musa EO, Shuaib F, Gsteiger S. Ebola virus disease outbreak in
342 Nigeria: Transmission dynamics and rapid control. *Epidemics* (2015) 11:80-4.

343 30. Rosello A, Mossoko M, Flasche S, Van Hoek AJ, Mbala P, Camacho A, et al. Ebola virus
344 disease in the Democratic Republic of the Congo, 1976-2014. *Elife* (2015) 4. pii: e09015.
345 doi:10.7554/eLife.09015

346 31. Kucharski AJ, Eggo RM, Watson CH, Camacho A, Funk S, Edmunds WJ. Effectiveness
347 of Ring Vaccination as Control Strategy for Ebola Virus Disease. *Emerg Infect Dis* (2016)
348 22:105-8.

349 32. Volz E, Pong S. Phylodynamic analysis of ebola virus in the 2014 sierra leone epidemic.
350 *PLoS Curr.* 2014;6. pii: ecurrents.outbreaks.6f7025f1271821d4c815385b08f5f80e.
351 doi:10.1371/currents.outbreaks.6f7025f1271821d4c815385b08f5f80e

352 33. Osterholm MT, Moore KA, Kelley NS, Brosseau LM, Wong G, Murphy FA, et al.
353 Transmission of Ebola viruses: what we know and what we do not know. *MBio* (2015)
354 6:e00137. doi:10.1128/mBio.00137-15

355 34. Althaus CL. Ebola superspreading. *Lancet Infect Dis.* (2015) 15:507-8.

356 35. Lau MS, Dalziel BD, Funk S, McClelland A, Tiffany A, Riley S, et al. Spatial and
357 temporal dynamics of superspreading events in the 2014-2015 West Africa Ebola epidemic.
358 *Proc Natl Acad Sci U S A* (2017) 114:2337-42.

359 36. International Ebola Response Team, Agua-Agum J, Ariyaratnam A, Aylward B, Bawo L,
360 Bilivogui P, et al. Exposure Patterns Driving Ebola Transmission in West Africa: A
361 Retrospective Observational Study. *PLoS Med* (2016) 13:e1002170.
362 doi:10.1371/journal.pmed.1002170

363 37. Holzmann H, Hengel H, Tenbusch M, Doerr HW. Eradication of measles: remaining
364 challenges. *Med Microbiol Immunol* (2016) 205:201-8.

365 38. Rieck T, Feig M, An der Heiden M, Siedler A, Wichmann O. Assessing varicella vaccine
366 effectiveness and its influencing factors using health insurance claims data, Germany, 2006 to
367 2015. *Euro Surveill* (2017) 22. pii: 30521. doi:10.2807/1560-7917.ES.2017.22.17.30521

368 39. Beyer WE, Nauta JJ, Palache AM, Giezenan KM, Osterhaus AD. Immunogenicity and
369 safety of inactivated influenza vaccines in primed populations: a systematic literature review
370 and meta-analysis. *Vaccine.* (2011) 29:5785-92.

371 40. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of
372 influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* (2012) 12:36-
373 44.

374 41. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza
375 vaccine efficacy against mismatched and matched strains: a systematic review and meta-
376 analysis. *BMC Med* (2013) 11:153. doi:10.1186/1741-7015-11-153

377 42. Heppner DG Jr, Kemp TL, Martin BK, Ramsey WJ, Nichols R, Dasen EJ, et al. Safety
378 and immunogenicity of the rVSVΔG-ZEBOV-GP Ebola virus vaccine candidate in healthy
379 adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response
380 study. *Lancet Infect Dis* (2017) 17:854-66.

381 43. Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 Placebo-
382 Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. *N Engl J Med* (2017)
383 377:1438-47.

384 44. Diallo B, Sissoko D, Loman NJ, Bah HA, Bah H, Worrell MC, et al. Resurgence of Ebola
385 Virus Disease in Guinea Linked to a Survivor With Virus Persistence in Seminal Fluid for
386 More Than 500 Days. *Clin Infect Dis* (2016) 63:1353-6.

387 45. Sissoko D, Duraffour S, Kerber R, Kolie JS, Beavogui AH, Camara AM, et al.
388 Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease
389 survivors: a longitudinal analysis and modelling study. *Lancet Glob Health* (2017) 5:e80-e88.

390 46. Li JX, Hou LH, Meng FY, Wu SP, Hu YM, Liang Q, et al. Immunity duration of a
391 recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost
392 immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-
393 controlled, phase 1 trial. *Lancet Glob Health* (2017) 5:e324-34.

394 47. Winslow RL, Milligan ID, Voysey M, Luhn K, Shukarev G, Douoguih M, et al. Immune
395 Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored
396 Ebola Vaccines at 1 Year. *JAMA* (2017) 317:1075-7.

397 48. Zhu FC, Wurie AH, Hou LH, Liang Q, Li YH, Russell JB, et al. Safety and
398 immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy
399 adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2
400 trial. *Lancet* (2017) 389:621-8.

401 49. Soka MJ, Choi MJ, Baller A, White S, Rogers E, Purpura LJ, et al. Prevention of sexual
402 transmission of Ebola in Liberia through a national semen testing and counselling programme
403 for survivors: an analysis of Ebola virus RNA results and behavioural data. *Lancet Glob
404 Health* (2016) 4:e736-43. doi:10.1016/S2214-109X(16)30175-9

405 50. Uyeki TM, Erickson BR, Brown S, McElroy AK, Cannon D, Gibbons A, et al. Ebola
406 Virus Persistence in Semen of Male Survivors. *Clin Infect Dis* (2016) 62:1552-5.

407 51. Barnes KG, Kindrachuk J, Lin AE, Wohl S, Qu J, Tostenson SD, et al. Evidence of Ebola
408 Virus Replication and High Concentration in Semen of a Patient During Recovery. *Clin
409 Infect Dis* (2017) 65:1400-3.

410 52. Deen GF, Broutet N, Xu W, Knust B, Sesay FR, McDonald SLR, et al. Ebola RNA
411 Persistence in Semen of Ebola Virus Disease Survivors - Final Report. *N Engl J Med* (2017)
412 377:1428-37.

413 53. Lambe T, Bowyer G, Ewer KJ. A review of Phase I trials of Ebola virus vaccines: what
414 can we learn from the race to develop novel vaccines? *Philos Trans R Soc Lond B Biol Sci*
415 (2017) 372:pri: 20160295. doi:10.1098/rstb.2016.0295

416 54. Stanley DA, Honko AN, Asiedu C, Trefry JC, Lau-Kilby AW, Johnson JC, et al.
417 Chimpanzee adenovirus vaccine generates acute and durable protective immunity against
418 ebolavirus challenge. *Nat Med* (2014) 20:1126-9.

419 55. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus
420 relapse causing meningoencephalitis: a case report. *Lancet* (2016) 388:498-503.

421 56. MacIntyre CR, Chughtai AA. Recurrence and reinfection--a new paradigm for the
422 management of Ebola virus disease. *Int J Infect Dis* (2016) 43:58-61.

- 423 57. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et
424 al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease:
425 final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça
426 Suffit!). *Lancet* (2017) 389:505-18.
- 427 58. Huo X, Shi G, Li X, Lai X, Deng L, Xu F, et al. Knowledge and attitudes about Ebola
428 vaccine among the general population in Sierra Leone. *Vaccine* (2016) 34:1767-72.
- 429 59. Henao-Restrepo AM, Preziosi MP, Wood D, Moorthy V, Kieny MP; WHO Ebola
430 Research, Development Team. On a path to accelerate access to Ebola vaccines: The WHO's
431 research and development efforts during the 2014-2016 Ebola epidemic in West Africa. *Curr*
432 *Opin Virol* (2016) 17:138-44.
- 433 60. Alexander KA, Sanderson CE, Marathe M, Lewis BL, Rivers CM, Shaman J, et al. What
434 factors might have led to the emergence of Ebola in West Africa? *PLoS Negl Trop Dis*
435 (2015) 9:e0003652. doi:10.1371/journal.pntd.0003652
- 436 61. Moon S, Sridhar D, Pate MA, Jha AK, Clinton C, Delaunay S, et al. Will Ebola change
437 the game? Ten essential reforms before the next pandemic. The report of the Harvard-
438 LSHTM Independent Panel on the Global Response to Ebola. *Lancet* (2015) 386:2204-21.
- 439 62. Kagina BM, Wiysonge CS, Lesosky M, Madhi SA, Hussey GD. Safety of licensed
440 vaccines in HIV-infected persons: a systematic review protocol. *Syst Rev* (2014) 3:101. doi:
441 10.1186/2046-4053-3-101
- 442 63. Volz A, Sutter G. Modified Vaccinia Virus Ankara: History, Value in Basic Research,
443 and Current Perspectives for Vaccine Development. *Adv Virus Res* (2017) 97:187-243.
- 444 64. [No authors listed]. Meeting of the Strategic Advisory Group of Experts on
445 immunization, April 2017 – conclusions and recommendations. *Wkly Epidemiol Rec* (2017)
446 92(3):301-20.
- 447 65. Ledgerwood JE, Costner P, Desai N, Holman L, Enama ME, Yamshchikov G, et al. A
448 replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and
449 immunogenic in healthy adults. *Vaccine* (2010) 29:304-13.

450 **Figure legends**

451

452 **Figure 1.** Summary of the literature search using PubMed (www.ncbi.nlm.nih.gov/pubmed)
453 to identify articles that report on the basic reproductive number (R_0) of Ebolaviruses.

454

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