1    **Rigorous surveillance is necessary for high confidence in end-of-outbreak**

2    **declarations for Ebola and other infectious diseases**

3    Robin N. Thompson, Oliver W. Morgan, Katri Jalava

4    Author affiliations: University of Oxford, Oxford, UK (RNT); World Health Organization,

5    Geneva, Switzerland (OWM); University of Helsinki, Helsinki, Finland (KJ)

6    Address for correspondence: Robin N. Thompson, Christ Church, University of Oxford, St

7    Aldates, Oxford, OX1 1DP; email: robin.thompson@chch.ox.ac.uk; tel: +44 1865 615 162.

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9    **<u>Abstract</u>**

10    The World Health Organization considers an Ebola outbreak to have ended once 42 days have

11    passed since the last possible exposure to a confirmed case. Benefits of a quick end-of-outbreak

12    declaration, such as reductions in trade/travel restrictions, must be balanced against the chance of

13    flare-ups from undetected residual cases. We show how epidemiological modelling can be used

14    to estimate the surveillance level required for decision-makers to be confident that an outbreak is

15    over. Results from a simple model characterising an Ebola outbreak suggest that a surveillance

16    sensitivity (i.e. case reporting percentage) of 79% is necessary for 95% confidence that an

17    outbreak is over after 42 days without symptomatic cases. With weaker surveillance,

18    unrecognised transmission may still occur: if the surveillance sensitivity is only 40%, then 62

19    days must be waited for 95% certainty.  By quantifying the certainty in end-of-outbreak

20    declarations, public health decision-makers can plan and communicate more effectively.

21

22    **<u>Keywords</u>**

23    Ebola virus disease; End-of-outbreak declarations; World Health Organization; Outbreak

24    forecasting; Surveillance

25

## **Main Text**

### **Introduction**

28    The 2018 Ebola outbreak in Equateur Province, Democratic Republic of the Congo (DRC), was

29    brought under control following 54 cases between $5^{th}$ April and $2^{nd}$ June (*1*). Another

30    unconnected outbreak was declared in DRC on $1^{st}$ August 2018, and that outbreak is still in

31    progress. It is about to become the second largest in history, with 421 probable and confirmed

32    cases as of $26^{th}$ November 2018 (*2*). Increasingly, decision-makers use forecasts generated using

33    mathematical models to guide control measures when outbreaks are ongoing (*3,4*). However, less

34    attention has been directed towards using mathematical modelling to inform decision-making at

35    the ends of outbreaks (*5*).

36

37    Determining when an outbreak of any infectious disease is over is important for decision-makers,

38    as they need to choose when to relax control measures, scale-back the deployment of personnel

39    and resources, adjust communication messages to the public, and re-establish confidence in

40    commercial sectors such as agriculture and tourism. However, the difficulty of end-of-outbreak

41    decision-making was illustrated during the 2013-16 Ebola epidemic, when the World Health

42    Organization (WHO) declared Liberia disease-free four times only to have new cases detected

43    after the first three declarations (Fig 1A). This raises an important question: how confident can

44    public health decision-makers be when declaring an outbreak over?

45

46    The proportion of cases identified by public health authorities through passive or active case

47    finding, otherwise called the sensitivity of a surveillance system (*6,7*), is a critical parameter that

48    underlies how confident a decision-maker can be when declaring the end to an outbreak (*8*). The

49    surveillance sensitivity is the ratio of the number of infectious cases detected to the total number

50    of cases (including both cases that are detected and those that go unnoticed), and should not be

51    confused with the sensitivity of a diagnostic test (i.e. the probability that the diagnostic test

52    correctly identifies an infected host). Intuitively, there will be a lower confidence that an

53    outbreak is over if the surveillance system has low sensitivity. However, decision-makers do not

54    typically make quantitative assessments about the confidence in their end-of-outbreak decisions.

55    A retrospective modelling study of the MERS-CoV outbreak in South Korea in 2015 concluded

56    that, with no quantitative end-of-outbreak assessment, decision-makers took longer than

57    epidemiologically necessary to declare the outbreak over (*9*), although we note that the

58    sensitivity of the surveillance system was assumed to be 100% in that study.

59

60    To illustrate how the confidence that an outbreak is over can be estimated, and that the

61    confidence level can be increased by improving surveillance, we consider the situation of

62    declaring the end of an Ebola outbreak. The WHO considers an Ebola outbreak to be over once

63    42 days have passed since the last possible exposure to a confirmed case without any new cases

64    being detected (*10*), with this rule most often deployed at the scale of a single country. The

65    incubation period (the time between an individual becoming infected and displaying

66    recognisable symptoms) for Ebola has been estimated to be in the range of 2-21 days (*11*), and so

67    the period of 42 days is based on two maximal incubation periods. For a disease that is

68    transmitted directly from person-to-person, the passing of two incubation periods is

69    epidemiologically relevant because additional between-person transmission is then unlikely. We

70    use mathematical modelling to show that, if the surveillance sensitivity is 100%, then it is likely

71   that an Ebola outbreak is over after 42 days without symptomatic cases. However, we also

72   demonstrate that, if the surveillance sensitivity is lower, there is an increased chance of

73   undetected infected cases remaining after 42 days. This leads to a lower confidence that the

74   outbreak is over after this time period.

75

76   Although we focus on Ebola virus disease here, we note that the question of whether or not an

77   infectious disease outbreak is over is not only important for diseases of humans, but also those of

78   animals and plants. Declaring an outbreak over allows disease management interventions to be

79   lifted, including restrictions on travel (*12*) and plant trade quarantine (*13*). The idea that

80   improved surveillance may lead to increased confidence in an end-of-outbreak declaration is

81   related to well-established theory regarding conducting surveys to ascertain the absence of a

82   pathogen (see e.g. (*14-19*)). In that context, the more hosts are tested and found to be disease-

83   free, the higher the confidence that the entire population is disease-free. This can in turn be used

84   to generate sample-size requirements to establish freedom from disease to pre-specified

85   confidence levels. While initial studies in this area – motivated by the desire to limit pathogen

86   transmission via the animal trade – assumed that the level of disease in the host population was

87   static, more recent elaborations have included incorporation of dynamic models describing

88   parasite/pathogen transmission in the host population (see e.g. (*20,21*)). Statistical disease

89   freedom studies have not only been applied to animal disease epidemics, but the theory has also

90   been used in the context of epidemics in populations of plants (*22, 23*) and humans (*24*).

91

92   In this paper, rather than considering surveys of the host population at the apparent end of an

93   outbreak, we show how the confidence in end-of-outbreak assessments can be estimated using

94 epidemiological models once the surveillance system sensitivity has been approximated. Our

95 approach, which can be used when the outbreak in question is still ongoing, provides decision-

96 makers with a practical way to gauge whether current surveillance efforts will be sufficient to

97 declare the outbreak over with conviction, or whether an intensification of surveillance is

98 necessary instead.

99

100 **Methods**

101 We extended an epidemiological model commonly used for Ebola (the SEIR model, see e.g.

102 (*25,26*)) to include imperfect surveillance (Fig 1B). In the resulting model (the SEICR model)

103 individuals were classified according to whether they were (*S*)usceptible, (*E*)xposed, (*I*)nfectious

104 and reporting disease, (*C*)ryptically infectious (i.e. infectious but not reporting disease), or

105 (*R*)emoved. The parameters of the model and the baseline values used in our analyses to

106 illustrate the model behaviour are given in Table 1, although we also tested the robustness of our

107 results to these values (Fig S1). We ran stochastic simulations of the model, thereby including

108 randomness in whether or not each outbreak was over when the number of symptomatic

109 individuals (*I*) reached zero (for additional details, see the Supplementary Material).

110

111 The surveillance sensitivity was implemented in the model via the proportion, *d,* of infectious

112 individuals that reported disease (*I*) as opposed to remained cryptically infectious (*C*). When an

113 individual left the exposed class, they either transitioned into the *I* class (with probability *d*) or

114 into the *C* class (with probability $1 - d$). The parameter *d* represents a proportion/probability and

115 therefore lies between zero and one, whereas the surveillance sensitivity is reported as a

116 percentage. As an example, the value $d = 0.1$ corresponds to a surveillance sensitivity of 10%.

5

117     For simplicity, we assumed that whether or not an infectious individual reported disease did not

118     alter their infectiousness or duration of infection, although this simplification could be relaxed

119     straightforwardly. As described above, the cryptically infectious class represents individuals that

120     are infectious but do not report disease – this could include asymptomatic carriers that are

121     infectious (27) or symptomatic individuals not reporting for reasons including a lack of access to

122     healthcare (8).

123

124     By continuing to run simulations after the number of symptomatic infectious individuals (*I*)

125     reached zero, the confidence that an outbreak will be over, defined as the probability that no

126     undetected infected hosts (*E* or *C*) remained in the population, was estimated at different time

127     periods beyond the removal of the last detected case.

128

129     **Results**

130     We inferred the expected number of undetected infected cases once the number of symptomatic

131     cases reached zero (Fig 1C), considering only outbreaks that successfully invaded the host

132     population (outbreaks in which more than 20 individuals were ever infected). We estimated the

133     confidence that the outbreak is over for different time periods beyond the removal of the last

134     detected case (Fig 1D). For additional results with different model parameters, see the

135     Supplementary Material.

136

137     Since a period of 42 days has been estimated as twice the maximal incubation period for Ebola, it

138     is unsurprising that, when the sensitivity of the surveillance system was perfect so that 100% of

139     infectious cases were detected accurately, the model suggested a high confidence (more than

140    97%) that an Ebola outbreak is over after 42 days without symptomatic cases. Additional new

141    cases could only occur if existing infected individuals remained pre-symptomatic, and this was

142    very unlikely after this time period. However, when we assumed that the surveillance sensitivity

143    was only 40%, an estimate made for Ebola surveillance in Liberia (*28*), the probability that Ebola

144    cases remained in the population was 16%, leading to only an 84% confidence that the outbreak

145    was finished (red line in Fig 1D). With such a low surveillance sensitivity, a period of 62 days

146    with no cases would need to elapse to be 95% confident that an outbreak is over (light green line

147    in Fig 1D), or 88 days to be 99% confident (dark green line in Fig 1D).

148

149    Most Ebola cases in outbreak areas are reported via infected individuals presenting to a health

150    facility or Ebola Treatment Unit. Close contacts of confirmed cases are also identified and

151    usually followed for 21 days, to permit rapid identification if symptoms develop (*29*). Other case

152    finding strategies may take place, for example visitations to identify and test suspect cases in

153    disease hotspot regions or in rural areas where access to healthcare systems might be limited

154    (*30*). Since surveillance can potentially be improved, for example by intensifying active case

155    finding, the quantity of most practical value is the sensitivity of surveillance required for

156    decision-makers to be confident that Ebola outbreaks are over after 42 days. We therefore

157    considered the end-of-outbreak confidence for varying levels of the surveillance sensitivity (Fig

158    1E). To be at least 95% confident that an Ebola outbreak is over after 42 days, surveillance

159    needed to be at least 79% sensitive (light green line in Fig 1E). For lower surveillance levels,

160    there is a significant chance ($> 5\%$) of residual infectious cases remaining in the population, and

161    these might generate outbreak flare-ups.

162

163     **Discussion**

164     We have proposed an approach for decision-makers to estimate their confidence that an Ebola

165     outbreak is over after 42 days (two maximal incubation periods) have passed with no new cases.

166     In scenarios with a low surveillance sensitivity, decision-makers may either choose to wait

167     longer than two incubation periods before declaring the end of an outbreak, take measures to

168     increase the surveillance sensitivity, or adopt both of these approaches. Communicating that an

169     outbreak is over following two incubation periods is epidemiologically coherent when the

170     surveillance level is high, and so decision-makers may prefer to focus efforts on achieving a high

171     surveillance sensitivity rather than adjusting the guideline period before declaring the end of an

172     outbreak. However, in contexts that prevent strengthening of disease surveillance, for example if

173     there is poor security due to armed conflict or other factors, extending the period with no cases

174     before declaring an outbreak over may be the more pragmatic option.

175

176     Sensitivity measurements are sometimes carried out for evaluation of surveillance systems (*31*).

177     Analysis of the percentage of cases being recorded can be conducted using serological surveys

178     (*32*) or by comparing multiple data sources (*33*). When an outbreak is ongoing, however,

179     measuring the surveillance sensitivity might not be the first priority. For assessing the confidence

180     in a potential end-of-outbreak declaration, it is most important to measure the surveillance

181     sensitivity towards the apparent end of the outbreak, and so resources can be directed to this task

182     after the acute outbreak period has passed. In scenarios in which the surveillance sensitivity is

183     insufficient for declaring an outbreak over with confidence, remedial actions can be taken such

184     as strengthening case finding for example via contact tracing (*34*), closer working with

8

185    community leaderships to establish a case finding and reporting network (*35*), and/or providing

186    incentives for successful case reporting (*36*), among other approaches.

187

188    In this paper, we sought to use a simple approach to demonstrate how the confidence in end-of-

189    outbreak declarations could be assessed, and to show that rigorous surveillance is extremely

190    important. While accurate case reporting will minimise the chance of incorrect declarations that

191    Ebola outbreaks are over in future, we note that surveillance during the outbreak alone is not

192    always sufficient. In the 2013-16 Ebola epidemic in West Africa, additional cases occurred after

193    regions were declared disease-free due to factors including persistently infected sources (*37*) and

194    importation of the virus from other geographical regions (*38*).  There were suspicions of a flare-

195    up arising from a female survivor, who became infectious after her immune system was

196    weakened due to pregnancy (*39*), although this remains unproven (*40*). There is also evidence

197    that Ebola survivors might have the potential to drive new cases after long periods following

198    apparent recovery (*41*), for example reports of the virus being detected in semen up to 18 months

199    after symptom onset or isolated in cell culture up to 82 days after symptom onset (*42,43*). Here,

200    we only considered potential flare-ups due to unreported cases, and did not explicitly model the

201    possibility that Ebola survivors, who were assumed to have fully recovered, might drive

202    additional cases. Recrudescence from survivors could, in theory, be included in assessments of

203    the risk of outbreak flare-ups after outbreaks are declared over, however this would require

204    sufficient understanding of the epidemiology of these rare events. While this understanding is

205    developed, targeted monitoring of survivors beyond the WHO guideline period of 42 days that

206    we consider here is also important.  This should be supplemented with advice for survivors on

207    safe practices that will help to avoid additional flare-ups (*44*).

208

209    Extending our approach to other disease outbreaks might require elaborations to the underlying

210    model.  To illustrate the principle that the surveillance sensitivity affects the confidence in end-

211    of-outbreak declarations, we modelled surveillance as simply as possible – by assuming that a

212    proportion of infectious hosts report disease, but that reporting did not impact on the underlying

213    transmission process. In practice, individuals that report disease are more likely to be subject to

214    interventions that reduce infectiousness or shorten their infectious period, such as isolation or

215    treatment. This could straightforwardly be built into the framework that we have presented. We

216    also use a single parameter to denote the surveillance sensitivity, whereas in practice a

217    surveillance program is likely to encompass many aspects, including both passive and active case

218    finding strategies, that could be built explicitly into an epidemiological model. One of the

219    benefits of our approach is that, in contrast to methods relying on surveys to prove disease

220    absence, our analysis can be conducted in advance of the apparent end of the outbreak to see

221    whether or not surveillance needs to be intensified. However, it might be possible to combine our

222    approach with surveys to establish the end of an outbreak, and to make use of statistical methods

223    for estimating the number of hosts to survey so that the probability of the population being

224    disease-free exceeds a pre-specified threshold (*14-24*).

225

226    Other extensions could include modelling the risk of importation of disease from other

227    geographical locations (*13*), accounting for temporal or spatial variation in the surveillance

228    sensitivity (*8*), or allowing for the possibility of introductions of immunologically naïve hosts

229    resulting from population displacement (*45*).  Additional refinement would be needed to estimate

230    the confidence in end-of-outbreak declarations when diseases that persist at low endemic levels

10

231 in a population have returned below an outbreak threshold prevalence, an important

232 consideration for outbreaks of diseases such as cholera and yellow fever. Nonetheless, we have

233 demonstrated that measurement of the sensitivity of surveillance can help decision-makers

234 estimate their confidence that an outbreak has ended.  Moreover, after measuring the

235 performance of disease surveillance systems, the confidence that an outbreak has ended can be

236 increased by optimising the surveillance system.

237

238 Communicating the confidence in end-of-outbreak decisions, as our framework permits, is

239 helpful for decision-makers and the public, and it will increase trust in public health

240 organisations such as WHO. Measurements of the surveillance sensitivity during outbreaks are

241 not always routinely taken, but we think that by providing a useful way to use measures of

242 surveillance system performance, decision-makers will be motivated to implement what should

243 be considered as good practice. We encourage the use of quantitative approaches, such as the one

244 we describe here, to inform decisions regarding the continuation of disease control measures,

245 appropriate use of resources, and communication of public health messages to the public towards

246 the end of an outbreak.

247

248 **<u>Figure caption</u>**

249 **Fig. 1.** The confidence in end-of-outbreak declarations following the apparent end of an Ebola outbreak.
250 A) Schematic showing the sequence of events in Liberia at the end of the 2013-16 Ebola epidemic, in
251 which the outbreak was incorrectly declared over three times. B) Schematic of the compartmental model
252 used in our analyses. C) The number of hidden cases ($E$ or $C$) remaining in simulated Ebola outbreaks at
253 the first timepoint at which the number of symptomatic cases ($I$) reaches zero. D) The confidence in end-
254 of-outbreak declarations (i.e. the probability that no undetected infections ($E$ or $C$) remain in the
255 population), for different time periods after removal of the "final" symptomatic case (blue) at the ends of
256 major outbreaks (outbreaks in which more than 20 individuals are ever infected). The current WHO
257 guideline period of 42 days leads to a confidence of 0.84 that the outbreak is over (red), whereas periods
258 of 62 or 88 days correspond to confidences of 0.95 (light green) and 0.99 (dark green), respectively. E)
259 The confidence in end-of-outbreak declarations made 42 days after removal of the "final" symptomatic

260 case, for different values of the surveillance sensitivity (blue). For an end-of-outbreak confidence of 0.95
261 after 42 days without symptomatic cases, a surveillance sensitivity of 79% is required (light green). The
262 results in panels C and D were obtained using 10,000 simulations of the model, and the results in panel E
263 were obtained using 10,000 simulations of the model for each possible value of the surveillance
264 sensitivity.

265

266 **Table 1**

| Epidemiological parameter | Meaning | Baseline value (used except where stated) | Justification |
|---|---|---|---|
| $\beta$ | Infection rate | $2.7 \times 10^{-6}$ day$^{-1}$ | Chosen such that $R_0 = 2$ (see e.g. (*46,47*)) |
| $1/\gamma$ | Incubation period | 12.27 days | (*48*) |
| $1/\mu$ | Infectious period | 7.37 days | (*48*) |
| $N$ | Effective population size | 100,000 | For consistency of mean final size of simulated epidemics with 2013-16 Ebola epidemic |
| $d$ | Proportion of infectious hosts reporting disease | 0.4 | (*28*) |

267
268 Table 1. Epidemiological parameters of the SEICR model, along with the default values used in our analyses (except
269 where stated in the relevant figure captions) and references supporting the values used. We also tested the robustness
270 of our results to the values of *N*, *d* and $\beta$ (Fig S1). For more details about the model and its parameterisation, see
271 Supplementary Material.

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273

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401

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## **Competing interests**

407 We have no competing interests.

## **Authors' contributions**

409 RNT conceived the research; All authors designed the study; RNT carried out the research; RNT

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18

**A**

28/3/15
Final
burial

9/5/15
WHO
declaration

Additional
cases

3/9/15
WHO
declaration

Additional
cases

14/1/16
WHO
declaration

Additional
cases

9/6/16
WHO
declaration

LIBERIA
EBOLA
FREE

**B**

$\beta S(I+C)$

$\gamma(1-d)E$

$\gamma dE$

$\mu C$

$\mu I$

$S$  $E$  $C$  $I$  $R$

**C**

Probability

Number of hidden infections

**D**

Confidence

Time after final symptomatic case (days)

**E**

Confidence

Surveillance sensitivity (%)