

1 Protective Population Behavior Change in Outbreaks of Emerging Infectious Disease

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12 **ABSTRACT:**

13 During outbreaks of emerging infections, the lack of effective drugs and vaccines increases
14 reliance on non-pharmacologic public health interventions and behavior change to limit human-
15 to-human transmission. Interventions that increase the speed with which infected individuals
16 remove themselves from the susceptible population are paramount, particularly isolation and
17 hospitalization. Ebola virus disease (EVD), Severe Acute Respiratory Syndrome (SARS), and
18 Middle East Respiratory Syndrome (MERS) are zoonotic viruses that have caused significant
19 recent outbreaks with sustained human-to-human transmission. This investigation quantified
20 changing mean removal rates (MRR) and days from symptom onset to hospitalization (DSOH) of
21 infected individuals from the population in seven different outbreaks of EVD, SARS, and MERS,
22 to test for statistically significant differences in these metrics between outbreaks. We found
23 that epidemic week and viral serial interval were correlated with the speed with which
24 populations developed and maintained health behaviors in each outbreak.

25

26 **KEYWORDS:**

27 Ebola, MERS, SARS, outbreak, public health, behavior change

28

29 **INTRODUCTION:**

30 One of the most important factors in assessing the danger posed by an epidemic of infectious
31 disease is pathogen transmissibility. Widespread public anxiety during the 2013-2016 West
32 African Ebola epidemic, while driven by an extremely high fatality rate during the early stages,
33 was fueled in part by the speed with which Ebola Virus Disease (EVD) spread throughout the
34 populations of Liberia, Sierra Leone, and Guinea.¹⁻³ Similarly, concerns over annual influenza
35 epidemics in the United States center on densely inhabited areas with multiple opportunities
36 for viral transmission due to physical proximity between susceptible individuals.⁴ Regardless of
37 geographic setting, understanding how to slow and control pathogen dissemination is a high
38 priority in forecasting and preventing epidemics of infectious disease.

39

40 Epidemic modelers frequently employ compartmental models of disease outbreaks, such as
41 Susceptible-Infected-Recovered (SIR) models as in Keeling and Rohani,⁵ Susceptible-Infected-
42 Susceptible (SIS) models as in Gray *et al*,⁶ and Susceptible-Exposed-Infected-Recovered (SEIR)
43 models as in LeGrand *et al*.⁷ Accurately estimating and modeling the number of infected and
44 susceptible individuals in at-risk populations is of crucial importance in these models. Such

45 estimation is complicated, however, by efforts to isolate infected individuals in hospitals or
46 other settings to decrease contact with the susceptible population. While the isolation of
47 infected individuals is beneficial and should be encouraged, it challenges data analysts because
48 it is time-varying and reflects dynamic and often unpredictable human behavior. Moreover, the
49 rate at which infected individuals are removed from the population typically accelerates
50 throughout an epidemic as awareness of the infectious threat increases,⁸ a process Drake *et al*
51 referred to as “societal learning.”⁹ Obtaining accurate estimates of this time-varying removal of
52 infected persons, while difficult, improves the quality of compartmental models for epidemics
53 of infectious disease.^{9,10} To our knowledge, however, no work has directly compared the rate of
54 behavioral adaptation across multiple epidemics, societies, and geographic settings.

55
56 Many factors can affect how quickly effective isolation practices are implemented, such as
57 access to health care, local public health funding, international aid, and the efficacy of
58 information campaigns.¹¹ Local health care practices and non-formal healthcare systems also
59 provide care to patients during epidemics and can play a part in quarantining infected
60 individuals.¹² Previous work in Liberia has shown that a combination of these approaches
61 through simultaneous community engagement and clinical intervention is more effective than
62 any single intervention, with both health care access and utilization increasing hand-in-hand to
63 decrease EVD transmission during the 2013-2016 Ebola epidemic.¹³ While infection prevention
64 often includes vaccination, progress to develop effective vaccines for emerging infections is
65 slow and not necessarily more effective than isolation of infected individuals.¹⁴ Ring vaccination
66 with the rVSV-ZEBOV-GP Ebola vaccine¹⁵ in the Democratic Republic of the Congo is
67 promising,¹⁶ but previous work has suggested that ring vaccination may only provide a marginal
68 benefit to rigorous contact tracing and patient isolation.¹⁷

69
70 The focus of this paper is the identification of key similarities and differences in the behavioral
71 response to outbreaks of three emerging zoonotic infections. We sought to determine how the
72 mean removal rate of infected individuals changed over the course of each outbreak as
73 measured by epidemic week and viral serial interval. Individuals often experience zoonotic and
74 emerging infections as innately more frightening than “familiar” diseases, leading to rapid
75 behavioral adaptations due to high perceived risk.¹⁸ Behavior modification, while crucial for
76 epidemic containment,¹⁹⁻²¹ is context dependent and difficult to predict due to social network,
77 socioeconomic, and behavioral differences between populations.²² Thus, we chose seven
78 different outbreaks of disease that stoked significant local and international fear due to the risk
79 of global pandemic: the 2013-2016 Liberian Ebola epidemic, subsets of the 2013-2016 Liberian
80 outbreak from Lofa and Montserrado Counties,²³ the 2003 Hong Kong SARS epidemic,²⁴⁻²⁶ the
81 2014 Saudi Arabia MERS outbreaks in Riyadh and Jeddah,²⁷ and the 2015 South Korea MERS
82 outbreak.²⁸ We examined whether epidemic week and serial interval successfully predicted
83 days from disease onset to hospitalization (DSOH) and mean removal rate (MRR) throughout
84 each epidemic.

85 86 **MATERIALS AND METHODS:**

87 **DATA:**

88 We obtained patient-level data for Ebola and MERS, and daily aggregated data for SARS. We
89 added new columns to each epidemic dataset to track the number of days from symptom onset
90 to hospitalization (calculated as hospitalization date - date of symptom onset; abbreviated
91 DSOH) and the mean removal rate (calculated as $1 / \text{DSOH}$; abbreviated MRR). In calculating
92 MRR, we considered only positive DSOH values in order to focus on community transmission
93 rather than nosocomial transmission. Additionally, we converted symptom onset dates to
94 weekly onset dates by replacing each date with that of the closest previous Sunday.

95

96 **BINNED DATA:**

97 We compiled data for each outbreak location binned by epidemic week, to produce comparable
98 data for regression analysis. Epidemic weeks came from weekly onset dates described above.
99 We also binned the same data by serial interval, using 12 days as the estimated serial interval
100 for Ebola,²³ 8 days for SARS,²⁴ and 7 days for MERS;²⁷ this was calculated as epidemic
101 week/(serial interval/7). Each dataset included, per week, the number of new cases, the
102 cumulative number of cases, mean DSOH and associated standard deviation, and MRR and
103 associated standard deviation. We removed epidemic weeks from the beginning of each
104 outbreak so that the first three epidemic weeks had greater than 0 cases of disease each in
105 order to focus on population-level behavioral adaptation to large-scale disease outbreaks
106 instead of adaptations to individual disease events early in an epidemic. We performed all
107 regression analyses using this binned data.

108

109 **REGRESSION ANALYSES:**

110 Initial regression analyses fit linear models to predict DSOH and MRR (Table 1, Eqs. 1-2). As
111 before, data for DSOH excluded negative values (individuals who become symptomatic after
112 being hospitalized for other reasons) to focus on community disease transmission and behavior
113 change instead of nosocomial infection.

114

115 Outlying points in
116 the Liberian Ebola
117 epidemic skewed
118 our initial linear
119 regression models.
120 We compared
121 manual removal of
122 outliers, quantile
123 regression, and
124 robust linear
125 regression to find

Eq.	Regression Type	Response	Predictor	Interaction Term
1	linear	DSOH	epidemic week	none
2	linear	MRR	epidemic week	none
3	robust linear	DSOH	epidemic week	none
4	robust linear	MRR	epidemic week	none
5	robust linear	MRR	epidemic week	outbreak location
6	robust linear	MRR	serial interval	outbreak location

126 **Table 1. Regression equations.**

127 DSOH stands for days from symptom onset to hospitalization; MRR stands for mean removal
128 rate, calculated as $(1 / \text{DSOH})$. Epidemic weeks were weighted by cases per week. Outbreak
129 location for DSOH and MRR included seven levels (Liberia, [Lofa County](#), [Montserrado County](#),
130 South Korea, Riyadh, Jeddah, and Hong Kong).

126 the most appropriate method for handling such points. The three methods produced almost
127 identical results. We used robust regression to re-fit all initial linear regression models to avoid
128 the influence of outliers (Table 1, Eqs. 3-4). In addition, we performed robust linear regressions
129 of MRR with an interaction term accounting for outbreak location (Table 1, Eq. 5-6) to examine
130 predicted mean change in the MRR in each epidemic. We used the Bonferroni correction²⁹ for
131 multiple comparisons to compute confidence intervals, utilizing a 99% confidence interval in

132 our model comparisons. The size of the smaller epidemics (MERS and SARS) played a large part
133 in determining confidence interval size and significance. All data management, modeling, and
134 visualization was performed in R.³⁰

135

136 RESULTS:

137 **DAYS TO HOSPITALIZATION (DSOH) AND MEAN REMOVAL RATE (MRR):**

138 DSOH consistently declined over time in each epidemic. Robust regressions for DSOH and MRR
139 (Table 1, Eqs. 3 and 4) showed negative and positive slopes, respectively, which corroborated
140 the observations made on non-binned data (Fig. 1).

141

142 From robust
143 regression analyses
144 accounting for
145 outbreak location
146 (Table 1, Eqs. 5 and 6),
147 we calculated the
148 mean change in the
149 MRR for each
150 outbreak location
151 using the
152 *interactionMeans*
153 function from the R
154 package *phia* for post-
155 hoc interaction
156 analysis. This analysis
157 showed that the mean
158 change in the MRR of
159 the Hong Kong SARS
160 epidemic was
161 approximately five
162 times (per serial
163 interval) to seven
164 times (per epidemic
165 week) more than the
166 mean change in the
167 MRR of the Liberian
168 Ebola epidemic (Fig.
169 2). The mean change
170 of the MRR in the
171 Ebola epidemic in Lofa
172 County, Liberia, was
173 significantly higher than the mean change of the MRR for the overall Liberian epidemic and the

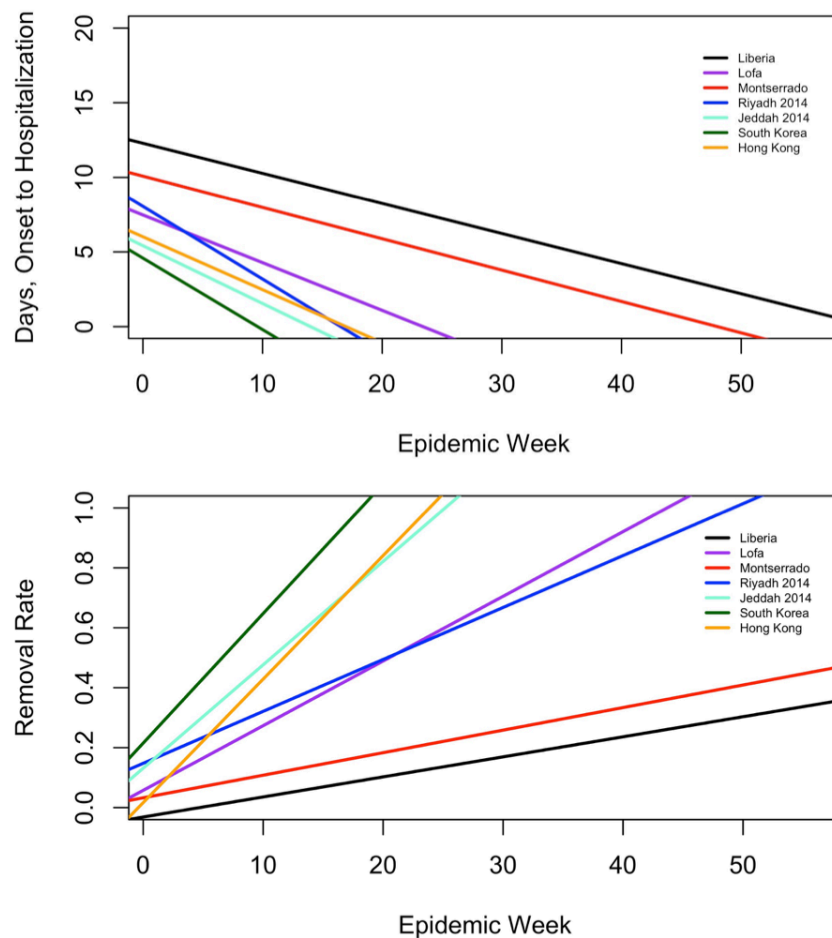
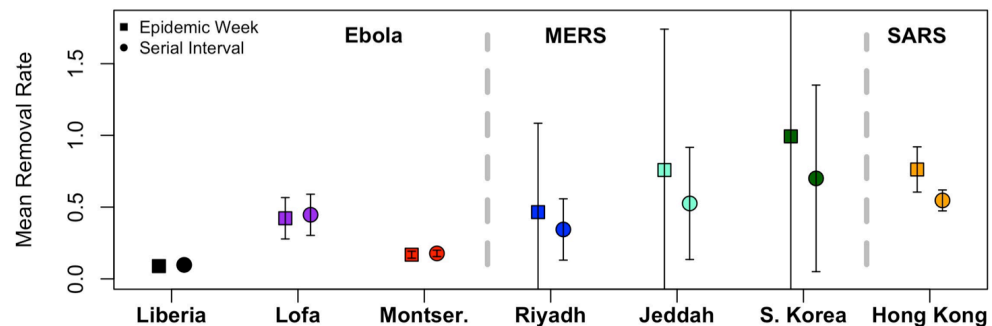


Figure 1. Regression: DSOH and MRR.

The public health response to epidemic infection varied widely between the outbreaks studied. These graphs depict model lines from regressions of each of the 2 response variables (DSOH (Table 1, Eq. 4) and MRR (Table 1, Eq. 5)) on epidemic week for the 7 outbreaks indicated in the legend. South Korea and Liberia exhibited the most extreme slopes in both analyses. As an illustration of the observed difference between outbreaks, the graphs show South Korea achieving an almost complete removal of infected individuals from the population and a sharp decline in days till hospitalization within 20 weeks, while Liberia only achieved a roughly 20% removal rate by 50 weeks.

174 outbreak in Montserrado County, Liberia, regardless of predictor (epidemic week or serial
175 interval) (Fig. 2). The three MERS outbreaks (Riyadh, Jeddah, and South Korea) did not differ
176 significantly from one another and had limited precision (Fig. 2).

177
178 We found that
179 predicting mean
180 change of the MRR
181 by epidemic week
182 (Table 1, Eq. 5) led
183 to higher mean
184 estimates and
185 wider confidence
186 intervals in the
187 MERS and SARS
188 outbreaks;
189 conversely,
190 predicting with
191 serial interval
192 (Table 1, Eq. 6)
193 lowered mean
194 estimates and
195 narrowed the



186
187 **Figure 2. Adjusted MRR.**

188 The average change in the mean removal rate (MRR) differed based on the type of outbreak,
189 the location, and the independent variable (epidemic week or serial interval) used to predict
190 changes in MRR. The error bars plotted around the estimated MRR values represent the
191 normalized 99% confidence intervals calculated using the *interactionMeans* function in R. The
192 most precise estimates were observed for the Ebola outbreak, and the largest for the outbreaks
193 of MERS. Predicting the mean change of the MRR with serial interval generally led to tighter
194 confidence intervals than predictions using epidemic week. These results indicate that an
195 outbreak's type and location are important determinants of the mean change in the MRR per
196 epidemic week or serial interval.

196 associated confidence intervals (Fig. 2). We identified little difference in the mean change of
197 the MRR for the Ebola outbreak depending on predictor (Fig. 2). This indicates that, at least in
198 the case of MERS and SARS, both the passage of time and the serial interval of each virus may
199 affect the speed with which populations develop and maintain health behaviors.

200
201

202 **DISCUSSION:**

203 The primary finding of this study was that removal of infected individuals from the susceptible
204 population, measured as DSOH and MRR, increases over time and varies significantly based on
205 outbreak duration and location. While DSOH improved (decreased) in every epidemic over
206 time, extreme disparities in starting values (approximately 13 days from symptom onset to
207 hospitalization at the beginning of the 2013-2016 Ebola outbreak in Liberia, versus
208 approximately 5 days in the 2015 MERS outbreak in South Korea) highlight the intrinsic
209 disadvantage that low-income countries may experience due to the interrelated concerns of
210 poverty, limited access to health care, and low investment in public health. DSOH and MRR
211 regressed against epidemic week differed across all observed outbreaks, and MRR likewise
212 differed markedly based on the virus in question (Ebola, MERS, or SARS), the location, and at
213 times both. Both DSOH and MRR are useful measurements of public health behavior during
214 outbreaks, and are useful tools to compare outbreak response effectiveness in distinct
215 geographic, economic, and social settings. Of course, DSOH and MRR are intrinsically and simply
216 related since one is simply the reciprocal of the other. The main advantage of DSOH is that it is

217 expressed in intuitive units (days elapsed), whereas MRR reflects the theoretical “removal rate”
218 of standard compartmental models.⁵

219

220 Figure 2 highlights differences in mean change of the MRR due to outbreak type (Ebola, MERS,
221 or SARS) and location. Mean change of the MRR was similar when calculated using epidemic
222 week versus serial interval for Ebola, but demonstrated a lower estimate and lower standard
223 error when calculated using serial interval in all three outbreaks of MERS and the outbreak of
224 SARS in Hong Kong. This suggests that the relevance of various predictors (epidemic week
225 versus serial interval) may vary based upon the type and location of an outbreak, although the
226 comparative relevance of epidemic type versus location cannot be disentangled with the data
227 available in this study. We recommend similar analyses of MRR be conducted across a wide
228 range of geographies as outbreaks of emerging pathogens arise, providing important data on
229 the range of MRR, and its expected rate of change, in different settings.

230

231 While our findings demonstrate large and statistically significant differences in MRR, it is
232 notable that the calculated rates of change in the MRRs are within a factor of ten (when
233 calculated using epidemic week) to seven (when calculated using serial interval) of each other
234 (Fig. 2), with the mean change being the lowest in the EVD outbreak in Liberia and the highest
235 in the MERS outbreak in South Korea. For modelers seeking to understand the epidemiology of
236 emerging infectious diseases with limited or no data from previous outbreaks, this study
237 provides a range of acceptable values for the MRR based on seven geographically distinct
238 outbreaks of three emerging diseases. Similarly, while large disparities in DSOH are obvious (Fig.
239 1), these data highlight that all societies quickly adapt to outbreaks of emerging infections.
240 Drake *et al* previously demonstrated the positive impact of behavior change in infectious
241 outbreaks, noting that doubling the rate of “societal learning” in a model of the 2003 SARS
242 outbreak in Singapore approximately halved the estimated number of infected patients.⁹ While
243 there is a theoretical upper limit to the speed with which newly-infected individuals can be
244 removed from the susceptible population,⁹ public health strategies aimed at fostering
245 behavioral adaptations and accelerating isolation should form a cornerstone of interventions
246 tasked with limiting the spread of highly contagious and deadly emerging pathogens.³¹

247

248 **CONCLUSION:**

249 We have shown that public health practices for isolating infected individuals from the
250 susceptible population vary significantly by pathogen and location, but can in some cases be
251 predicted by the timing and serial interval of the epidemic. This study detected variation in
252 DSOH and MRR based on epidemic location and outbreak type, indicating that it may be
253 possible to estimate a general range of the rate of change in these variables over time. Due to
254 location-specific differences in DSOH and MRR, modelers who seek to develop forecasts early in
255 an outbreak would benefit from estimating an expected range for removal of infected
256 individuals using data from past outbreaks of the same pathogen in a similar setting.
257 Furthermore, the quality of these estimates will be impacted by the metric chosen, as seen by
258 the notable, but distinct, trends detected in DSOH and MRR. As seen in this study, utilizing a
259 well-chosen response variable with a relatively small amount of data can provide material for
260 making effective forecasts about public health behavior.

261

262 **DATA, CODE, AND MATERIALS:**

263 We studied seven outbreaks: the 2013-2016 Liberian Ebola epidemic on a country-wide level,
264 subsets of the same epidemic in Lofa and Montserrado Counties, the 2003 Hong Kong SARS
265 epidemic, the 2014 Saudi Arabia MERS outbreaks in Riyadh and Jeddah, and the 2015 South
266 Korea MERS outbreak. The Ebola data was originally obtained by the World Health Organization
267 and provided by Christopher Dye (dyec@who.int). The Hong Kong SARS data was provided by
268 Gabriel Leung (gmleung@hku.hk) of Hong Kong University. Please contact Christopher and
269 Gabriel for data regarding Ebola and SARS, respectively, due to concerns regarding potentially
270 identifiable health information. Finally, the MERS data for Saudi Arabia and South Korea were
271 obtained from data compiled by Andrew Rambaut (a.rambaut@ed.ac.uk) of the University of
272 Edinburgh, and is publicly available at [https://github.com/rambaut/MERS-Cases/blob/gh-](https://github.com/rambaut/MERS-Cases/blob/gh-pages/data/cases.csv)
273 [pages/data/cases.csv](https://github.com/rambaut/MERS-Cases/blob/gh-pages/data/cases.csv).

274

275 **COMPETING INTERESTS:**

276 We have no competing interests.

277

278 **AUTHOR'S CONTRIBUTIONS:**

279 Evans Lodge helped develop the project and conduct initial data analysis with John Drake as
280 part of the University of Georgia Population Biology of Infectious Diseases REU Site. Annakate
281 Schatz updated Lodge's analyses with finalized Ebola data and wrote an initial paper draft from
282 that work. Lodge and Drake finalized the manuscript for submission.

283

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