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Title Page

Forecasting and Control Policy Assessment for the Ebola Virus Disease (EVD)

Epidemic in Sierra Leone Using Small-World Networked Model Simulations

Constantinos I. Siettos¹, Cleo Anastassopoulou², Lucia Russo³, Christos Grigoras^{1,4},
Eleftherios Mylonakis⁴

Authors' affiliations:

¹ School of Applied Mathematics and Physical Sciences, National Technical University of Athens, Athens, Greece.

² Division of Genetics, Cell and Developmental Biology, Department of Biology, University of Patras, Patras, Greece.

³ Consiglio Nazionale di Ricerca, Napoli, Italy.

⁴ Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA.

Corresponding author:

Constantinos I. Siettos: Associate Professor Computational Science & Engineering, School of Applied Mathematics and Physical Sciences, National Technical University of Athens, 9, Heron Polytechniou Str., GR-157 80 Athens, Greece. Tel.: +30 210-772-3950; E-mail: ksiet@mail.ntua.gr

Eleftherios Mylonakis, M.D., Ph.D., FIDSA, Dean's Professor of Medical Science (Medicine, and Molecular Microbiology and Immunology), Chief, Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, Tel: 401-444-7856 / Fax: 401-444-8179.

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2
3 35 **Abstract**

4 36
5 37 **Objectives:** As the Ebola Virus Disease (EVD) still ravages Sierra Leone, we aimed at
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7 38 analyzing the epidemic for the latest period (December 21, 2014 -April 17, 2015) using a
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9 39 small-world networked model and forecast its evolution. Different policy-control scenarios
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11 40 that could lead to the containment of the epidemic were also examined.

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14 41 **Methods:** We developed a stochastic model with 6.0 million individuals (the population of
15
16 42 Sierra Leone) interacting through a small-world social network with adjustable density. The
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18 43 model incorporates the main epidemiologic factors, including the effect of burial practices to
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20 44 virus transmission. The effective reproductive number (Re) was also evaluated directly from
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22 45 the individual-based simulations. Estimates of the epidemiologic variables were computed on
23
24 46 the basis of the time series of the official cases as reported by the Centers for Disease Control
25
26 47 and Prevention (CDC).

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28
29 48 **Results:** From December 21, 2014 to February 18, 2015 the epidemic was in recession
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31 49 compared to previous months, as indicated by the estimated effective reproductive number
32
33 50 (Re) of ~ 0.77 (95% CI: 0.76-0.78). From February 18 to April 17, 2015 Re rose above
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35 51 criticality (~ 1.98 , 95% CI: 1.93-2.02), flashing a note of caution for the situation. Projecting
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37 52 until mid June, we predicted that the epidemic will continue through July. Assessment of
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39 53 different policy-control scenarios showed that the current density of the social network
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41 54 should be reduced by more than 50% to obtain $Re < 1$ and contain the epidemic soon.

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44 55 **Conclusions:** Our results call for an immediate implementation of drastic control measures to
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46 56 contain the epidemic in Sierra Leone.

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52 58 **Keywords:** EBOV, Sierra Leone, Effective reproductive number, Forecasting,
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54 59 Communicable Disease Control

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3 61 **Article summary**
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5 63 **Strengths and limitations of this study**
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- 7 64
- 8 65 - The worst Ebola Virus Disease (EVD) epidemic in history continues to ravage West
 - 9 66 Africa.
 - 10 67 - The mounting concern regarding the continuation of the Ebola Virus Disease (EVD)
 - 11 68 epidemic in Sierra Leone prompted us to investigate the most recent transmission
 - 12 69 dynamics of the epidemic in the country.
 - 13 70 - While the number of new cases in Sierra Leone seems to decline and schools have
 - 14 71 reopened for the first time in months, we flash a note of caution for the situation.
 - 15 72 - Our analysis reveals that unless drastic control measures are taken immediately, the
 - 16 73 epidemic is not expected to fade out, but it will continue through July.
 - 17 74 - The validity of the analysis depends on the accuracy of the publicly available data. As
 - 18 75 it has been reported there might be a potential underreporting of the estimated cases
 - 19 76 and deaths. However even so, the outcome the analysis calls for immediate action.
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89 Introduction

90 The worst Ebola Virus Disease (EVD) epidemic in history continues to ravage West
91 Africa. The epidemic began with the report of 49 cases and 29 deaths in Guinea on March 22,
92 2014 (1). Liberia reported its first laboratory-confirmed cases on March 30, 2014, while the
93 first cases in Sierra Leone were reported on May 28, 2014 (2). Following regular daily
94 population movements for trade and family visitation, the virus crossed the local porous
95 international borders, establishing chains of transmission not just in small villages, where it
96 would have been easier to contain it, but also in large urban centers. Insufficient public health
97 infrastructure, poor sanitation conditions, lack of education about the disease and unsafe
98 traditional burial practices have also contributed to the spread of the epidemic in the region
99 (2).

100 In Liberia, one of the most affected countries, as of April 20, 2015, a total of 10,042
101 cases have been recorded, while the toll of death has exceeded 4,480 (3). In early March a
102 halt of the epidemic was announced, and even though a new case was confirmed on March
103 20, 2015, the epidemic is considered to have ceased, while the situation in Sierra Leone is
104 notably different. With more than 12,360 cases and 3,900 deaths until now, Sierra Leone
105 experienced a drop in new cases in January 2015 and authorities loosened mobilization
106 restriction measures to support economic activity (4). However, recent WHO updates on the
107 status of the EVD epidemic in this West African nation report a flare up (3), with a
108 significant increase among the community of fishermen living in the coastal area of Aberdeen
109 in Freetown (5). The synchronous occurrence of over 20 cases suggested they had been
110 infected by a single source, possibly an unsafe burial (5).

111 In light of these recent developments, we analyzed the EVD epidemic dynamics in
112 Sierra Leone for the period between December 21, 2014 and April 17, 2015, using an agent-
113 based, social network model that we reported recently and that proved to provide accurate

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3 114 predictions for the case of Liberia (6). For this purpose, the latest official case counts from
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5 115 WHO were fitted to the model, following the so-called Equation-Free approach (7). The
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7 116 estimation of key epidemiologic parameters, such as the case fatality rate, the per-contact
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9 117 transmission probability and the mean time from symptoms onset to recovery or to death,
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11 118 allowed us to study the evolving dynamics through the social transmission network whose
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13 119 structure and density are also examined. Through agent-based simulations, we found that the
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15 120 indicative of secondary infections, effective reproductive number (Re) was raised above
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17 121 criticality (~ 1.97 , 95% CI: 1.92-2.01) from February 18 to April 17. We thus explored
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19 122 different policy-control scenarios that could lead to reduced Re values, and, thereby, to the
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21 123 containment of the epidemic.
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28 125 **Methods**

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31 126 We developed an individual-based model for the study of the Ebola epidemic (6) with
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33 127 N individuals that interact through a Watts & Strogatz (WS) (8) small-world network that
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35 128 approximates some attributes of the real social interactions, which are characterized by
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37 129 relatively high clustering and short social distances between them. Here, the network was
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39 130 constructed with the Newman-Watts (9) algorithm, in which short-cut edges are added
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41 131 between pairs of nodes with a probability, in the same way as in a WS network, but without
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43 132 removing edges from the underlying lattice. The algorithm starts with a one-dimensional ring
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45 133 network with k local-nearest neighbors per node and with a probability p_{rw} that a link is
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47 134 added between two nodes. Hence, the mean number of additional shortcuts is $p_{rw} k N$, and
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49 135 the mean total degree of the network is $2 k N (1 + p_{rw})$. In the constructed small-world
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51 136 network we can adjust the density of the network, say α , at will, by randomly adding or
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53 137 subtracting the required number of links.
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3 138 Agents are categorized in five discrete states: *Susceptible* (S), *Exposed* (E), *Infected*
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5 139 (I), *Dead of the disease but not yet buried* (D_I), and *Dead of the disease and safely buried*
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8 140 (D_b). The D_I infectious state includes agents who die, but whose burial entails risk for
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11 141 onward virus transmission. The transition between states is modeled as a discrete-time,
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13 142 discrete state *non-Markov random process*. Within this framework, the state space over the
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15 143 set of the network links is represented by $Y(\mathbf{V})$, where $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_I, R\}$ is
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18 144 the set of the states of individual v_k .

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21 145 The agent-based rules that govern the dynamics of the epidemic on a daily basis read as
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23 146 follows:

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26 147 $p(Y_{v_k}(t+1) = D_b | Y_{v_k}(t) = D_I) = 1$ (1)
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29 148 $p(Y_{v_k}(t+1) = E | Y_{v_l}(t) = I, Y_{v_l}(t) = D_I) = p_{s \rightarrow E}, v_l \in \mathfrak{R}_{v_k}$ (2)
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31
32 149 $p(Y_{v_k}(t+1) = I | Y_{v_k}(t) = E) = p_{E \rightarrow I}$ (3)
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35 150 $p(Y_{v_k}(t+1) = D_I | Y_{v_k}(t) = I) = p_{I \rightarrow D}$ (4)
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38 151 $p(Y_{v_k}(t+1) = R | Y_{v_k}(t) = I) = p_{I \rightarrow R}$ (5)
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43 153 where $p_{s \rightarrow E}$ is the per infected contact transmission probability (still alive or dead, but not
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46 154 yet buried), $p_{E \rightarrow I}$, is the inverse of the incubation period, $p_{I \rightarrow D}$ is the inverse of the time
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49 155 from symptoms onset to death, $p_{I \rightarrow R}$ is the inverse of the recovery period, and, p_{D_I} , is the
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51 156 ratio of deaths to the infected population. The rate of the incubation period is taken to be
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54 157 constant, set at $p_{E \rightarrow I} = \frac{1}{9}$, as reported by the Who Ebola Response Team (10). \mathfrak{R}_{v_k} denotes the
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57 158 neighborhood of an individual v_k . This first rule sets the time period from death to burial to

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2 159 two days, during which family members and loved ones may be infected due to physical
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4 160 contact with the dead, still-contagious body. Long-range links of a dead, yet potentially
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6 161 infectious, agent are cut, reflecting the fact that only relatives and close community members
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9 162 can be infected during unsafe funeral practices and rites. The second rule implies that a
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11 163 susceptible agent gets exposed to the disease with a rate determined by the probability $p_{s \rightarrow E}$
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13 164 per infected contact (still alive or dead, but not yet buried). The third rule implies that an
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15 165 exposed agent becomes infectious with a rate determined by the probability $p_{E \rightarrow I}$, whose
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17 166 inverse corresponds to the incubation period, i.e. the time from exposure to symptoms onset.
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20 167 Rules (4) and (5) define the case fatality rate, $p_{D/I}$: an agent dies of the disease with a rate
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22 168 determined by the probability $p_{I \rightarrow D}$ (whose inverse is the time from symptoms onset to
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24 169 death) (Rule (4)); alternatively, an agent could recover with a rate determined by the
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26 170 probability $p_{I \rightarrow R}$ (Rule (5)).
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31 171 The effective reproductive ratio R_e , defined as the average number of secondary
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33 172 infections produced by a typical infective person, is also computed directly from the agent-
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35 173 based simulations.
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37 174 Based on the demographics reported by the United Nations (UN), the population of
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39 175 Sierra Leone is 6 million (11). Time series of the official case counts from the Centers for
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41 176 Disease Control and Prevention (CDC) were used for model fitting (3). Case data, which
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43 177 included cumulative incidence and cumulative deaths by date of report for Sierra Leone
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45 178 retrieved on March 19, 2015 were found on (12) and compiled from WHO case reports.
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49 179 Simulations were performed using December 21, 2014 as an initial date and a time
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51 180 horizon of 60 days with an equal sliding window time interval; the last date was April 18,
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53 181 2015. Thus, fitted values of the network and model parameters, as well as estimates of the
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55 182 effective reproductive ratio, were computed in sequences of succeeded time intervals of 6
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57 183 weeks corresponding to 2 periods (December 21, 2014 – February 18, 2015 and February 18,
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3 184 2015 – April 17, 2015). The initial conditions for the starting date of December 21, 2014
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5 185 were calculated on the basis of agent-based simulations from May 27, 2014, i.e. the date on
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7 186 which the first cases were officially reported from WHO (2), following the procedure
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9 187 described in detail elsewhere (6). In particular, we obtained the following (expected) numbers
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11 188 for December 21, 2014: $E_0 = 450$, $I_0 = 901$, $D_{b0} = 2390$, $D_{I0} = 28$, $R_0 = 5579$; the estimated
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14 189 cumulative number of cases then was 8,828.

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16 190 The expected (averaged) values of the agents' states $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_I, R\}$
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19 191 were computed over $N_r = 8$ network realizations and $N_s = 100$ simulations for each one of the
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21 192 network realizations. The model parameters were fitted to the reported data using a trust-
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23 193 region-reflective approach for nonlinear minimization, implemented for parameter estimation
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25 194 (13) exploiting the Equation-Free approach (7,14-18). Matlab (19) was the simulation
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27 195 environment of choice, while the model was programmed in Fortran 90 and linked to Matlab
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29 196 through mex files.

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32 197 To forecast the evolution of the Ebola virus epidemic in Sierra Leone, we used the
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34 198 values of the model parameters as estimated in the last period; the resulting parameter values
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36 199 were then fed to the simulator using as coarse initial conditions the values of
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38 200 $\{S, E, I, D_b, D_I, R\}$ as computed on April 17, 2015. We tested the effect of control policy
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40 201 scenarios by reducing the density of the network structure as estimated in the second period.
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42 202 Sparser network densities could reflect partial isolation of the population, restriction of social
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44 203 mobilization combined with an expanded public campaign for increased awareness.
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53 206 **Results and Discussion**

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55 207 The cumulative numbers of infected and dead obtained by the model compared to the
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57 208 reported cases in Sierra Leone are shown in Figure 1. As shown, our framework succeeds in
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2 209 approximating the actual data for total cases and deaths (3). For example, on December 21,
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4 210 2014 the number of total cases, as reported by the WHO, was 9,004 and the number of deaths
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6 211 was 2,582, while our simulations resulted in 8,828 cases and ~2,400 deaths. On February 18,
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8 212 2015, the total cases and deaths were 11,103 and 3,408, respectively, and our simulations
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10 213 resulted in 11,049 total cases and 3,394 deaths. Finally, on April 17, 2015, the reported total
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12 214 cases and deaths were 12,244 and 3,865, respectively; our simulations resulted in 12,299 total
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14 215 cases and 3,919 deaths.

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18 216 The epidemiologic parameters that were obtained through the optimization approach
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20 217 are illustrated in Figure 2 and a summary of the estimated epidemic parameters for the period
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22 218 under study, together with their 95% confidence intervals, is presented in Table 1. Panel (a)
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24 219 depicts the evolution of the estimated network characteristics, p_{rw} and a , while panels (b-e)
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26 220 illustrate the model parameters $p_{D/I}$, $p_{I \rightarrow R}$, $p_{I \rightarrow D}$, and $p_{S \rightarrow E}$ that fit best to the reported EVD
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28 221 epidemic dynamics in the country. The evolution of the estimated effective reproductive
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30 222 number R_e in Sierra Leone is shown in panel (f). More specifically, the contact network of
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32 223 Sierra Leone exhibits a rather random structure with a rewiring switching probability (p_{rw}) of
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34 224 ~0.37 (95% CI: ~0.33-0.41) that falls down to ~0.22 (95% CI: 0.20-0.24) during the study
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36 225 period (Figure 2a). A slight increase is shown in the density ratio of the network as
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38 226 represented by a , which was ~0.54 (95% CI: ~0.51-0.58) during the first period (December
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40 227 21, 2014 – February 18, 2015) and ~0.63 (95% CI: 0.59-0.68) during the second period of the
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42 228 study (February 18, 2015 – April 17, 2015) (Figure 2a). The differences of the network
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44 229 characteristics between the 2 periods indicate a more clustered, yet denser contact network
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46 230 during the second period that could partially reflect a relaxation of awareness in the first
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48 231 period, when the epidemic seemed to decline.

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55 232 The case fatality rate ($p_{D/I}$) that was estimated to be ~32% (95% CI: 31-33%) for the
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57 233 period extending from late December 2014 to February 18 2015, increased to ~39% (95% CI:
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3 234 38-40%) from February 18 to April 17 (Figure 2b). The expected period from the onset of
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5 235 symptoms to recovery (i.e., the inverse of $P_{I \rightarrow R}$) was ~9.5 days (95% CI: 8.6-10.7 days)
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7 236 during the first period and ~8 days (95% CI: 6.5-10.5 days) for the second period of study
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9 237 (Figure 2c). The expected period from the onset of symptoms to death (i.e., the inverse
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11 238 of $P_{I \rightarrow D}$) was constant at ~3.6 days (95% CI: 3.3-4.0 days) during the period of study (Figure
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13 239 2d).

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17 240 Regarding the epidemic parameters, our estimates are quite close to the ones reported
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19 241 by the WHO Ebola Response Team and other groups. For example, Ansumana et al. (20)
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21 242 reported a 31% CFR at Hastings center, while the National Institute of Communicable
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23 243 diseases (NICD) reports a CFR of 32% for Sierra Leone on April 5, 2015 (21); a mean of
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25 244 31.6% CFR was reported for Sierra Leone from the WHO Ebola response team as of
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27 245 September 14, 2014 (10). Gomes et al. (22) reported an ~8 day-period from the onset of
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29 246 symptoms to recovery, while in a recent study by the WHO Ebola response team (23) a
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31 247 period of 10.6 days (with a SD of 8.2 days) was reported from symptoms onset to hospital
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33 248 discharge for individuals of older than 45 years old. In the same paper, a period of ~6 days
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35 249 (with equal SD) is reported from symptoms onset to death for the same age group. The same
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37 250 delay period from symptoms onset to death was also reported in Ansumana et al. (20).

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41 251 The per-contact transmission probability $P_{S \rightarrow E}$ values were estimated at ~0.03 (95%
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43 252 CI: 0.028-0.033) in the first period and ~0.08 (95% CI: 0.067-0.09) in the second period
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45 253 (Figure 2e). Finally, the effective reproductive number R_e , as computed using the agent-
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47 254 based simulator, was ~0.77 (95% CI: 0.76-0.78) from December 21, 2014 to February 18,
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49 255 2015, rising up to ~1.98 (95% 1.93-2.02) from February 18, 2015 to April 17, 2015 (Figure
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51 256 2f).

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55 257 Simulations show that the expected cumulative number of infected cases may reach as
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57 258 high as 13,400 by mid of June, while the cumulative number of dead may reach 4,380, if no

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2 259 further action is undertaken. Hence, we decided to perform an assessment of the impact of
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4 260 potential control strategies. Based on the recently announced isolation policy (24), we
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7 261 simulated the influence on the epidemic dynamics of sparser, with respect to the estimated
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9 262 network density of the second period, network densities, by 10%, 20%, 30%, 40% and 50%.
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11 263 We tested these scenarios by reducing analogously the expected density of the contact
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13 264 network as estimated during the second period and running the agent-based simulation from
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15 265 April 18 until mid of June 2015, keeping all other values of the model parameters fixed.

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18 266 The results of the exploration of these different scenarios are summarized in Table 2
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20 267 and portrayed graphically in Figure 3. The “no further action” case, with respect to the
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22 268 estimated current network structure is also depicted in Figure 3 for comparison. By applying
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24 269 a 10% reduction in the network density (yielding an a of ~ 0.57), the expected reproductive
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26 270 number R_e was estimated to be ~ 1.7 . Accordingly, for a 20% reduction in the network density
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28 271 (yielding an a of ~ 0.51), R_e was estimated to be ~ 1.51 . Reductions of 30%, 40% and 50%
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30 272 yielding network densities of ~ 0.44 , ~ 0.38 and ~ 0.32 respectively, resulted in R_e values of
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32 273 ~ 1.42 , ~ 1.23 and ~ 1.05 correspondingly (Table 2). As is shown even large reductions in the
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34 274 density of the network will not lower the R_e below unity soon.

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37 275 In reality, the reduction in the network density could potentially reflect analogous
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39 276 reductions in social interactions further to the current restrictions of community mobilization.
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41 277 Examples would include raising public awareness and/or strengthening medical care. The
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43 278 country's National Ebola Response Centre has already announced a 3-day lockdown that will
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45 279 affect around 2.5 million people (20). Nevertheless, it is worth noticing that even with a 30%
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47 280 reduction in the social network density, the epidemic shows no signs of fading out until the
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49 281 mid of June and we estimate that new cases will continue to be recorded.

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51 282 In conclusion, we found that the EVD epidemic in Sierra Leone was in recession in
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53 283 the period between December 21, 2014 through mid of February, 2015, as reflected by the
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3 284 <1 value of the reproductive number for this period. However, during the last period (i.e.,
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5 285 from February 18 to April 17, 2015), the epidemic has spiked and the reproductive number
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7 286 was estimated to be well above criticality, with the potential to persist at this level beyond the
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9 287 end of June and through July. Control measures associated with mobilization restrictions
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11 288 were also evaluated. Our findings, supported by real epidemiologic data and the projection of
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13 289 a spilling over of the epidemic to mid of June, indicate that the measures implemented so far
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15 290 are inadequate. Taken in their totality, these findings indicate that the epidemic, even with
16
17 291 strict control isolation policies in effect, will go on through July with a probability of fading
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19 292 out thereafter if policies are implemented and consistently kept in place. Immediate, more
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21 293 intense efforts are needed before further complications emerge. Reducing the effective
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23 294 density of the derived contact small-world-like network, through limited social interactions,
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25 295 has the potential to improve the current situation.
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2 308 **Contributorship statement**
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5 309 Constantinos Siettos, Lucia Russo and Christos Grigoras contributed to the development of
6
7 310 the model. Constantinos Siettos and Cleo Anastassopoulou contributed to the data collection,
8
9 311 interpretation of the data and drafting the paper. Eleftherios Mylonakis contributed to the
10
11 312 interpretation of the data and substantially revised the paper. All authors approved the final
12
13 313 manuscript and accepted accountability for all aspects of the work.
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17 314
18 315 **Competing interests**

19 316 There are no competing interests.
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21 317

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23
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26 320 This research received no specific grant from any funding agency in the public, commercial
27
28 321 or not-for-profit sectors.
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30 322

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33 323 **Data Sharing Statement**

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35 324 The data used in this study are publicly available from CDC at
36
37 325 <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/>
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 417 **Table 1.** Key epidemiologic features of the Ebola Virus Disease (EVD) epidemic in Sierra
 418 Leone estimated by the model during the first and second study period (December 21, 2014 -
 419 April 17, 2015).

		Sierra Leone	
Period	Variable	Mean	95% CI
First (Dec. 21- Feb. 18, 2015)	p_{rw}	0.37	0.33-0.41
	Network density (α)	0.55	0.51-0.58
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	9.5	8.6-10.7
	CFR (%)	32	31-33
	R_e	0.77	0.76-0.78
Second (Feb. 18-April. 17, 2015)	p_{rw}	0.22	0.20-0.24
	Network density (α)	0.63	0.59-0.68
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	8.0	6.5-10.5
	CFR (%)	39	38-40
	R_e	1.98	1.93-2.02

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 421 p_{rw} , Rewiring switching probability; CFR, Case fatality rate ($p_{D/I}$); R_e , Effective

422 reproductive number

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424 **Table 2.** Outcomes of isolation control policy scenarios on the basis of the expected
425 reproductive number R_e , as computed by running the agent-based simulation from April 17
426 to the mid of June 2015 (keeping fixed all other values of the model parameters). Sparser
427 density refers to a percent reduction of the expected density of the contact network compared
428 to the 0.63 value that was estimated for the second period (February 18 – April 17, 2015).

429

Period	% Sparser density	Network density (α)	R_e
(April 7- June, 17, 2015)	10%	~0.57	~1.7
	20%	~0.51	~1.5
	30%	~0.44	~1.4
	40%	~0.38	~1.2
	50%	~0.32	~1.0

430

431 **FIGURE LEGENDS**

432

433 **Figure 1. Simulation Results for Sierra Leone from December 21, 2014 to April 17,**
434 **2015.** Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data
435 are depicted by solid lines. The period under study has been tessellated into two windows
436 with a length of 60 days each. For each window, the model parameters are estimated based on
437 the data reported from WHO.

438

439 **Figure 2. Estimated model parameters for Sierra Leone from December 21, 2014 to**
440 **April 17, 2015. (a)** Evolution of contact network characteristics: switching probability (p_{rw})
441 and density ratio of the transmission network (a). **(b)** Case fatality rate (p_{DI}). **(c)**
442 $1/\{\text{recovery period}\}$ ($p_{I \rightarrow R}$). **(d)** $1/\{\text{period from onset of symptoms to death}\}$ ($p_{I \rightarrow D}$). **(e)** Per-
443 contact transmission probability ($p_{s \rightarrow E}$). **(f)** Effective reproductive number (R_e). 95%
444 Confidence intervals are also shown.

445

446 **Figure 3. Forecasting of the evolution of the epidemic from April, 17 to June 17, 2015**
447 **under different control scenarios.** Network density values were compared to the density of
448 the social network estimated for the period February 18-April 17, 2015. **(a)** Total Cases, **(b)**
449 Deaths. The “no further action” scenario is also depicted.

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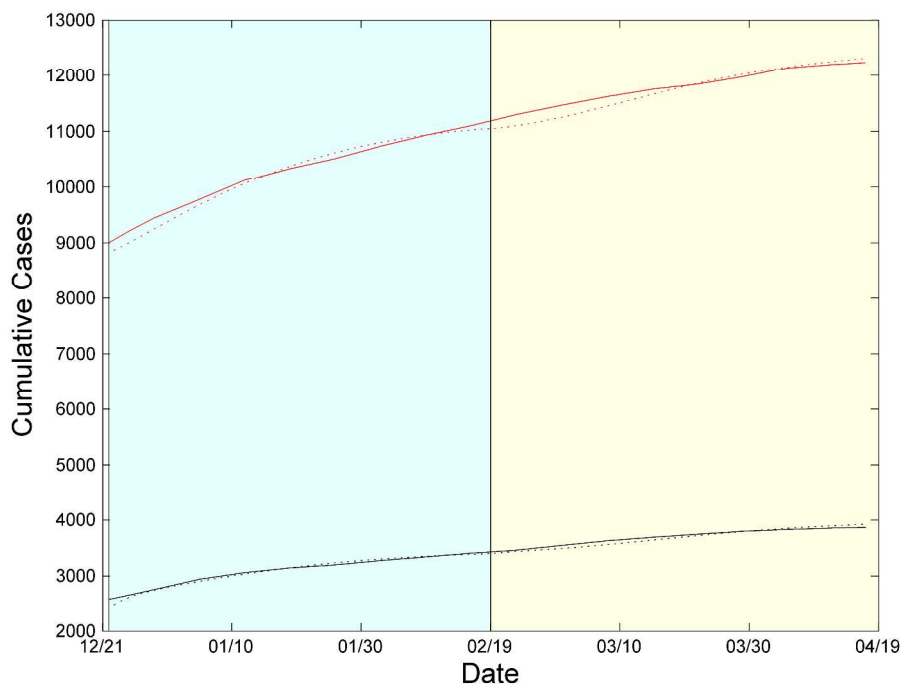


Figure 1. Simulation Results for Sierra Leone from December 21, 2014 to April 17, 2015. Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data are depicted by solid lines. The period under study has been tessellated into two windows with a length of 60 days each. For each window, the model parameters are estimated based on the data reported from WHO.

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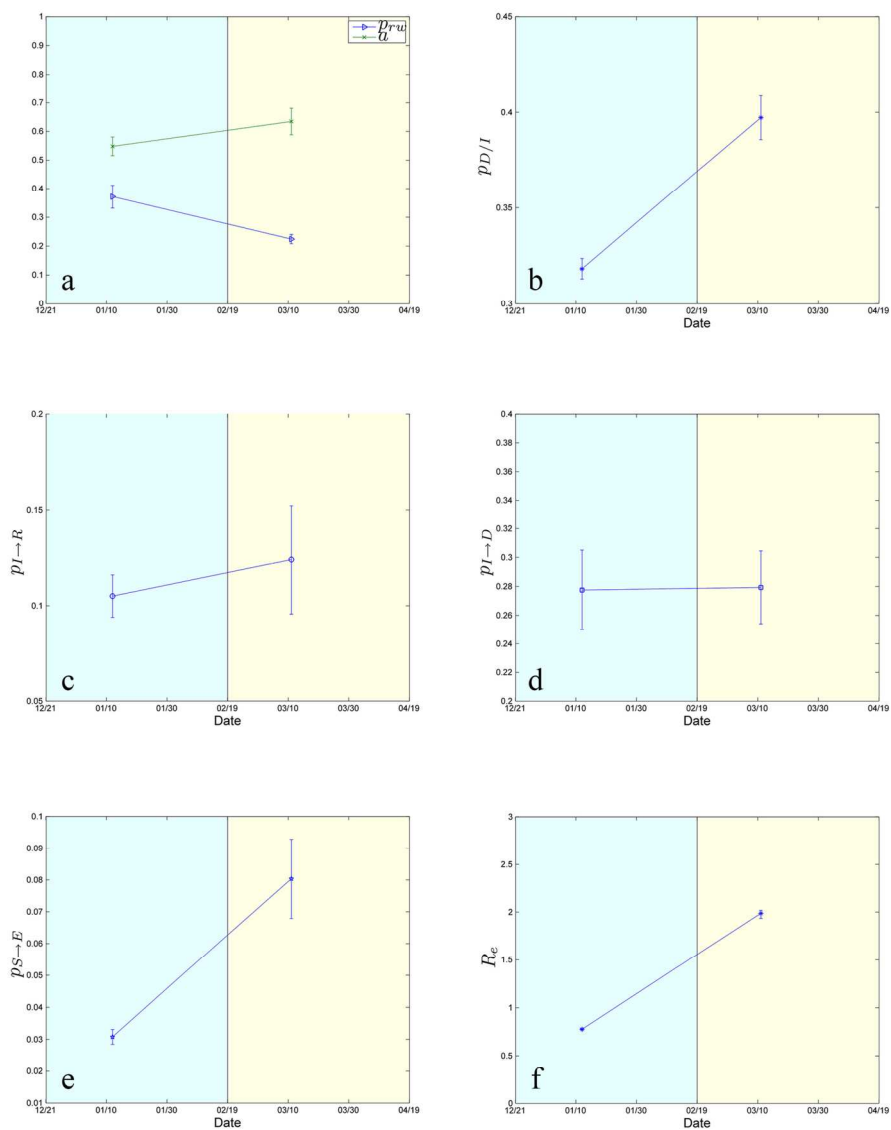


Figure 2. Estimated model parameters for Sierra Leone from December 21, 2014, to April 17, 2015. (a) Evolution of contact network characteristics: switching probability and density ratio of the transmission network. (b) Case fatality rate. (c) $1/\{\text{recovery period}\}$. (d) $1/\{\text{period from onset of symptoms to death}\}$. (e) Per-contact transmission probability. (f) Effective reproductive number. 95% Confidence intervals are also shown.
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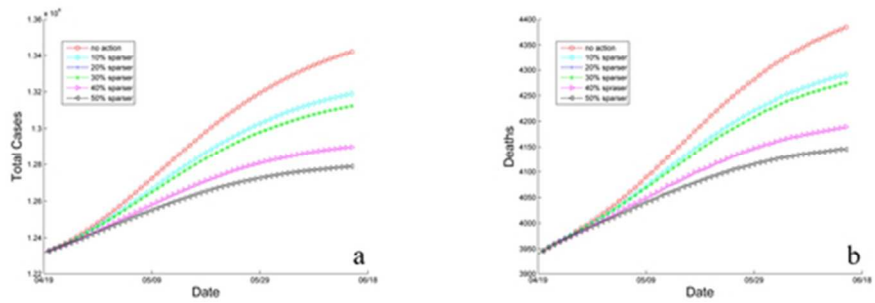


Figure 3. Forecasting of the evolution of the epidemic from April, 17 to June 17, 2015 under different control scenarios. Network density values were compared to the density of the social network estimated for the period February 18-April 17, 2015. (a) Total Cases, (b) Deaths. The "no further action" scenario is also depicted.

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Forecasting and Control Policy Assessment for the Ebola Virus Disease (EVD) Epidemic in Sierra Leone Using Small-World Networked Model Simulations

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Title Page

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2 **Forecasting and Control Policy Assessment for the Ebola Virus Disease (EVD)**3 **Epidemic in Sierra Leone Using Small-World Networked Model Simulations**4
5 Constantinos I. Siettos¹, Cleo Anastassopoulou², Lucia Russo³, Christos Grigoras^{1,4},
6 Eleftherios Mylonakis⁴7
8 **Authors' affiliations:**9 ¹ School of Applied Mathematics and Physical Sciences, National Technical University of
10 Athens, Athens, Greece.11 ² Division of Genetics, Cell and Developmental Biology, Department of Biology, University
12 of Patras, Patras, Greece.13 ³ Consiglio Nazionale di Ricerca, Napoli, Italy.14 ⁴ Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of
15 Brown University, Providence, RI, USA.16
17 **Corresponding author:**18 Constantinos I. Siettos: Associate Professor Computational Science & Engineering, School of
19 Applied Mathematics and Physical Sciences, National Technical University of Athens, 9,
20 Heron Polytechniou Str., GR-157 80 Athens, Greece. Tel.: +30 210-772-3950; E-mail:
21 ksiet@mail.ntua.gr22
23 Eleftherios Mylonakis, M.D., Ph.D., FIDSA, Dean's Professor of Medical Science (Medicine,
24 and Molecular Microbiology and Immunology), Chief, Infectious Diseases Division, Warren
25 Alpert Medical School of Brown University, Rhode Island Hospital 593 Eddy Street, POB,
26 3rd Floor, Suite 328/330, Providence, RI 02903, Tel: 401-444-7856 / Fax: 401-444-8179.27
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35 **Abstract**

36

37 **Objectives:** As the Ebola Virus Disease (EVD) is still sustained in Sierra Leone, we analyzed
38 the epidemic for the latest period (December 21, 2014 -April 17, 2015) using a small-world
39 networked model and forecasted its evolution. Policy-control scenarios for the containment of
40 the epidemic were also examined.

41 **Methods:** We developed an agent-based model with 6 million individuals (the population of
42 Sierra Leone) interacting through a small-world social network. The model incorporates the
43 main epidemiologic factors, including the effect of burial practices to virus transmission. The
44 effective reproductive number (*Re*) was evaluated directly from the agent-based simulations.
45 Estimates of the epidemiologic variables were computed on the basis of the official cases as
46 reported by the Centers for Disease Control and Prevention (CDC).

47 **Results:** From December 21, 2014 to February 18, 2015 the epidemic was in recession
48 compared to previous months, as indicated by the estimated effective reproductive number
49 (*Re*) of ~0.77 (95% CI: 0.72-0.82). From February 18 to April 17, 2015, *Re* rose above
50 criticality (~1.98, 95% CI: 1.33-2.22), flashing a note of caution for the situation. By
51 projecting in time, we predicted that the epidemic would continue through July 2015. Our
52 predictions were close to the cases reported by CDC by the end of June, verifying the
53 criticality of the situation. In light of these developments, while revising our manuscript, we
54 expanded our analysis to include the most recent data (until August 15, 2015). By mid-
55 August, *Re* has fallen below criticality and the epidemic is expected to fade out by early
56 December 2015.

57 **Conclusions:** Our results call for the continuation of drastic control measures, which in the
58 absence of an effective vaccine or therapy at present can only translate to isolation of the
59 infected section of the population, to contain the epidemic.

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61 **Keywords:** EBOV, Sierra Leone, Effective reproductive number, Forecasting,
62 Communicable Disease Control, Agent-Based Modeling, Social Transmission Network

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64 **Article summary**

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66 **Strengths and limitations of this study**

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- 68 - The greatest strength of this study stems from the undertaken mathematical approach
69 of choice, integrating agent-based modeling on complex networks and the so-called
70 Equation-Free approach, which allowed us to assess various important epidemiologic
71 parameters and to obtain accurate short-term forecasts of the evolution of the Ebola
72 Virus Disease (EVD) epidemic in Sierra Leone.
- 73 - Another advantage of the proposed methodology is that it allows for the rapid
74 evaluation of different policy-control scenarios that could lead to the containment of
75 the epidemic.
- 76 - Our predictions were verified by the official case count reported by CDC. An updated
77 analysis considering data until mid August shows that the epidemic is expected to
78 fade out by early December 2015.
- 79 - The validity of a modeling analysis depends on the accuracy of input data. The most
80 important limitation of our study pertains to the quality and accuracy of the outbreak
81 data that were “fed” to the mathematical model compared to the real figures.
82 Underreporting of cases and deaths is certainly to be expected under the particular
83 circumstances of such a severe epidemic evolving in one of the most impoverished
84 countries in the world. However, even so, the outcome the analysis calls for the
85 continuation of control measures to contain the epidemic.

86

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88 Introduction

89 The worst Ebola Virus Disease (EVD) epidemic in history continues to ravage West
90 Africa. The epidemic began with the report of 49 cases and 29 deaths in Guinea on March 22,
91 2014 (1). Liberia reported its first laboratory-confirmed cases on March 30, 2014, while the
92 first cases in Sierra Leone were reported on May 28, 2014 (2). Following regular daily
93 population movements for trade and family visitation, the virus crossed the local porous
94 international borders, establishing chains of transmission not just in small villages, where it
95 would have been easier to contain it, but also in large urban centers. Insufficient public health
96 infrastructure, poor sanitation conditions, lack of education about the disease and unsafe
97 traditional burial practices have also contributed to the spread of the epidemic in the region
98 (2).

99 In Liberia, one of the most affected countries, as of April 20, 2015, a total of 10,042
100 cases have been recorded, while the toll of death has exceeded 4,480 (3). In early March a
101 halt of the epidemic was announced, and even though a new case was confirmed on March
102 20, 2015, the epidemic is considered to have ceased, while the situation in Sierra Leone is
103 notably different. With more than 12,360 cases and 3,900 deaths until now, Sierra Leone
104 experienced a drop in new cases in January 2015 and authorities loosened mobilization
105 restriction measures to support economic activity (4). However, recent World Health
106 Organization WHO updates on the status of the EVD epidemic in this West African nation
107 report a flare up (3), with a significant increase among the community of fishermen living in
108 the coastal area of Aberdeen in Freetown (5). The synchronous occurrence of over 20 cases
109 suggested they had been infected by a single source, possibly an unsafe burial (5).

110 In light of these recent developments, we analyzed the EVD epidemic dynamics in
111 Sierra Leone for the period between December 21, 2014 and April 17, 2015, using an agent-
112 based, social network model that we reported recently and that proved to provide accurate
113 predictions for the case of Liberia (6). For this purpose, the latest official case counts from
114 WHO were fitted to the model, following the so-called Equation-Free approach (7). Our
115 objective was to obtain estimates of key epidemiologic parameters, such as the case fatality
116 rate, the per-contact transmission probability and the mean time from symptoms onset to
117 recovery or to death, in order to study the evolving dynamics through the social transmission
118 network whose structure and density are also examined. Through agent-based simulations,
119 we found that the indicative of secondary infections, effective reproductive number (Re) was
120 raised above criticality (~ 1.97 , 95% CI: 1.92-2.01) from February 18 to April 17, 2015. We

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3 121 thus explored different policy-control scenarios that could lead to reduced R_e values, and,
4 122 thereby, to the containment of the epidemic. While revising our manuscript, we also
5 123 processed the reported data from CDC of the very last period (April 18-August 15, 2015),
6 124 obtaining more optimistic estimates indicative of a remission of the epidemic in Sierra Leone,
7 125 as reflected by the derived R_e for the period June 17-August 15, 2015 (~0.68, 95% CI: 0.49-
8 126 1.01). Projecting from August 15, we estimate that the epidemic will fade out in early
9 127 December.
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130 Methods

131 We developed an agent-based model for the study of the Ebola epidemic (6) with N
 132 individuals that interact through a Watts & Strogatz (WS) (8) small-world network that
 133 approximates some attributes of the real social interactions, which are characterized by
 134 relatively high clustering and short social distances between them. Here, the network was
 135 constructed with the Newman-Watts (9) algorithm, in which short-cut edges are added
 136 between pairs of nodes with a probability, in the same way as in a WS network, but without
 137 removing edges from the underlying lattice. The algorithm starts with a one-dimensional ring
 138 network with k local-nearest neighbors per node and with a probability p_{rw} that a link is
 139 added between two nodes. Hence, the mean number of additional shortcuts is $p_{rw} k N$, and
 140 the mean total degree of the network is $2 k N (1 + p_{rw})$. In the constructed small-world
 141 network we can adjust the density of the network, say α , at will, by randomly adding or
 142 subtracting the required number of links.

143 Agents are categorized in five discrete states: *Susceptible* (S), *Exposed* (E), *Infected*
 144 (I), *Dead of the disease but not yet buried* (D_I), *Dead of the disease and safely buried*
 145 (D_b), and *Recovered* (R) (6). The D_I infectious state includes agents who die, but whose
 146 burial entails risk for onward virus transmission. The transition between states is modeled as
 147 a discrete-time, discrete state *non-Markov random process*. Within this framework, the state
 148 space over the set of the network links is represented by $Y(\mathbf{V})$, where

149 $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_I, R\}$ is the set of the states of individual v_k .

150 The agent-based rules that govern the dynamics of the epidemic on a daily basis read as
 151 follows:

$$152 \quad p(Y_{v_k}(t+1) = D_b | Y_{v_k}(t) = D_I) = 1 \quad (1)$$

$$153 \quad p(Y_{v_k}(t+1) = E | Y_{v_l}(t) = I, Y_{v_l}(t) = D_I) = p_{S \rightarrow E}, \quad v_l \in \mathfrak{R}_{v_k} \quad (2)$$

$$154 \quad p(Y_{v_k}(t+1) = I | Y_{v_k}(t) = E) = p_{E \rightarrow I} \quad (3)$$

$$155 \quad p(Y_{v_k}(t+1) = D_I | Y_{v_k}(t) = I) = p_{I \rightarrow D} \quad (4)$$

$$156 \quad p(Y_{v_k}(t+1) = R | Y_{v_k}(t) = I) = p_{I \rightarrow R} \quad (5)$$

157

158 where $p_{s \rightarrow E}$ is the per infected contact transmission probability (still alive or dead, but not
 159 yet buried), $p_{E \rightarrow I}$, is the inverse of the incubation period, $p_{I \rightarrow D}$ is the inverse of the time
 160 from symptoms onset to death, $p_{I \rightarrow R}$ is the inverse of the recovery period, and, $p_{D/I}$, is the
 161 ratio of deaths to the infected population (6). The rate of the incubation period is taken to be
 162 constant, set at $p_{E \rightarrow I} = \frac{1}{9}$, as reported by the Who Ebola Response Team (10). \mathfrak{R}_{v_k} denotes the
 163 neighborhood of an individual v_k . This first rule sets the time period from death to burial to
 164 two days, during which family members and loved ones may be infected due to physical
 165 contact with the dead, still-contagious body. Long-range links of a dead, yet potentially
 166 infectious, agent are cut, reflecting the fact that only relatives and close community members
 167 can be infected during unsafe funeral practices and rites. The second rule implies that a
 168 susceptible agent gets exposed to the disease with a rate determined by the probability $p_{s \rightarrow E}$
 169 per infected contact (still alive or dead, but not yet buried). The third rule implies that an
 170 exposed agent becomes infectious with a rate determined by the probability $p_{E \rightarrow I}$, whose
 171 inverse corresponds to the incubation period, i.e. the time from exposure to symptoms onset.
 172 Rules (4) and (5) define the case fatality rate, $p_{D/I}$: an agent dies of the disease with a rate
 173 determined by the probability $p_{I \rightarrow D}$ (whose inverse is the time from symptoms onset to
 174 death) (Rule (4)); alternatively, an agent could recover with a rate determined by the
 175 probability $p_{I \rightarrow R}$ (Rule (5)).

176 The effective reproductive ratio R_e , defined as the average number of secondary
 177 infections produced by a typical infective person, is also computed directly from the agent-
 178 based simulations.

179 Based on the demographics reported by the United Nations (UN), the population of
 180 Sierra Leone is 6 million (11). Time series of the official Ebola case counts from the Centers
 181 for Disease Control and Prevention (CDC) were used for model fitting (3). These case counts
 182 were collected from public data released by the World Health Organization (WHO) (12) and
 183 CDC (3). Even though these data sets do not distinguish between suspect, probable and
 184 laboratory-confirmed case counts, they are considered to represent the best available
 185 estimates of the current state of the epidemic in the severely afflicted West African countries.
 186 Case data, which included cumulative incidence and cumulative deaths by date of report for
 187 Sierra Leone, were retrieved on April 24, 2015.

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3 188 Simulations were performed using December 21, 2014 as an initial date and a time
4 189 horizon of 60 days with an equal sliding window time interval; the last date was April 17,
5 190 2015. Thus, fitted values of the network and model parameters, as well as estimates of the
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7 191 effective reproductive ratio, were computed in sequences of succeeded time intervals of 60
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9 192 days corresponding to 2 periods (December 21, 2014 – February 18, 2015 and February 18,
10 193 2015 – April 17, 2015). The initial conditions for the starting date of December 21, 2014
11 194 were calculated on the basis of agent-based simulations from May 27, 2014, i.e. the date on
12 195 which the first cases were officially reported from WHO (2), following the procedure
13 196 described in detail elsewhere (6). In particular, we obtained the following (expected) numbers
14 197 for December 21, 2014: $E_0 = 450$, $I_0 = 901$, $D_{b0} = 2390$, $D_{l0} = 28$, $R_0 = 5579$; the estimated
15 198 cumulative number of cases then was 8,828.

19 199 The expected (averaged) values of the agents' states $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_l, R\}$
20 200 were computed over $N_r = 8$ network realizations and $N_s = 100$ simulations for each one of the
21 201 network realizations. The model parameters were fitted to the reported data using a trust-
22 202 region-reflective approach for nonlinear minimization, implemented for parameter estimation
23 203 (13) exploiting the Equation-Free approach (7,14-18). Matlab (19) was the simulation
24 204 environment of choice, while the model was programmed in Fortran 90 and linked to Matlab
25 205 through mex files.

26 206 To forecast the evolution of the Ebola virus epidemic in Sierra Leone, we used the
27 207 values of the model parameters as estimated in the last period; the resulting parameter values
28 208 were then fed to the simulator using as coarse initial conditions the values of
29 209 $\{S, E, I, D_b, D_l, R\}$ as computed on April 17, 2015. We tested the effect of control policy
30 210 scenarios by reducing the density of the network structure as estimated in the second period.
31 211 Sparser network densities could reflect partial isolation of the population, restriction of social
32 212 mobilization combined with an expanded public campaign for increased awareness.
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214 Results and Discussion

215 The cumulative numbers of infected and dead obtained by the model compared to the
 216 reported cases in Sierra Leone are shown in Figure 1. Our framework succeeds in
 217 approximating the actual data for total cases and deaths (3). For example, on December 21,
 218 2014 the number of total cases, as reported by the WHO, was 9,004 and the number of deaths
 219 was 2,582, while our simulations resulted in 8,828 cases and ~2,400 deaths. On February 18,
 220 2015, the total cases and deaths were 11,103 and 3,408, respectively, and our simulations
 221 resulted in 11,049 total cases and 3,394 deaths. Finally, on April 17, 2015, the reported total
 222 cases and deaths were 12,244 and 3,865, respectively; our simulations resulted in 12,299 total
 223 cases and 3,919 deaths.

224 The epidemiologic parameters that were obtained through the optimization approach
 225 are illustrated in Figure 2 and a summary of the estimated epidemic parameters for the period
 226 under study, together with their 95% confidence intervals, is presented in Table 1. Panel (a)
 227 depicts the evolution of the estimated network characteristics, p_{rw} and a , while panels (b-e)
 228 illustrate the model parameters $p_{S \rightarrow E}$, $p_{D/I}$, $p_{I \rightarrow R}$ and $p_{I \rightarrow D}$ that fit best to the reported EVD
 229 epidemic dynamics in the country. The evolution of the estimated effective reproductive
 230 number R_e in Sierra Leone is shown in panel (f). More specifically, the contact network of
 231 Sierra Leone exhibits a rather random structure with a rewiring switching probability (p_{rw}) of
 232 ~0.37 (95% CI: ~0.33-0.41) that falls down to ~0.22 (95% CI: 0.20-0.24) during the study
 233 period (Figure 2a). A slight increase is shown in the density ratio of the network as
 234 represented by a , which was ~0.54 (95% CI: ~0.51-0.58) during the first period (December
 235 21, 2014 – February 18, 2015) and ~0.63 (95% CI: 0.59-0.68) during the second period of the
 236 study (February 18, 2015 – April 17, 2015) (Figure 2a). The differences of the network
 237 characteristics between the two periods indicate a more clustered, yet denser contact network
 238 during the second period that could partially reflect a relaxation of awareness in the first
 239 period, when the epidemic seemed to decline.

240 The case fatality rate ($p_{D/I}$) that was estimated to be ~32% (95% CI: 31-33%) for the
 241 period extending from late December 2014 to February 18 2015, increased to ~39% (95% CI:
 242 38-40%) from February 18 to April 17 (Figure 2e). The expected period from the onset of
 243 symptoms to recovery (i.e., the inverse of $p_{I \rightarrow R}$) was ~9.5 days (95% CI: 8.6-10.7 days)
 244 during the first period and ~8 days (95% CI: 6.5-10.5 days) for the second period of study
 245 (Figure 2c). The expected time interval from the onset of symptoms to death (i.e., the inverse

of $P_{I \rightarrow D}$) was constant at ~ 3.6 days (95% CI: 3.3-4.0 days) during the period of study (Figure 2d).

Regarding the epidemic parameters, our estimates are quite close to the ones reported by the WHO Ebola Response Team and other groups. For example, Ansumana *et al.* (20) reported a 31% CFR at Hastings center, while the National Institute of Communicable diseases (NICD) reports a CFR of 32% for Sierra Leone on April 5, 2015 (21); a mean of 31.6% CFR was reported for Sierra Leone from the WHO Ebola response team as of September 14, 2014 (10). Gomes *et al.* (22) reported an ~ 8 day-period from the onset of symptoms to recovery, while in a recent study by the WHO Ebola response team (23) a period of 10.6 days (with a SD of 8.2 days) was reported from symptoms onset to hospital discharge for individuals of older than 45 years old. In the same paper, a period of ~ 6 days (with equal SD) is reported from symptoms onset to death for the same age group. The same delay period from symptoms onset to death was also reported in Ansumana *et al.* (20).

The per-contact transmission probability $P_{s \rightarrow E}$ values were estimated at ~ 0.03 (95% CI: 0.028-0.033) in the first period and ~ 0.08 (95% CI: 0.067-0.09) in the second period (Figure 2b). Finally, the effective reproductive number R_e , as computed using the agent-based simulator, was ~ 0.77 (95% CI: 0.72-0.82) from December 21, 2014 to February 18, 2015, rising up to ~ 1.98 (95% 1.33-2.22) from February 18, 2015 to April 17, 2015 (Figure 2f).

Simulations show that the expected cumulative number of infected cases may reach as high as 13,400 by June 17, while the cumulative number of dead may exceed 4,300, if no further action is undertaken. Hence, we decided to perform an assessment of the impact of potential control strategies. Based on the recently announced isolation policy (24), we simulated the influence on the epidemic dynamics of sparser, with respect to the estimated network density of the second period, network densities, by 10%, 20%, 30%, 40% and 50%. We tested these scenarios by reducing analogously the expected density of the contact network as estimated during the second period and running the agent-based simulation from April 18 until June 17, 2015, keeping all other values of the model parameters fixed.

The results of the exploration of these different scenarios are summarized in Table 2 and portrayed graphically in Figure 3. The “no further action” case, with respect to the estimated current network structure is also depicted in Figure 3 for comparison. By applying a 10% reduction in the network density (yielding an a of ~ 0.57), the expected reproductive number R_e was estimated to be ~ 1.7 . Accordingly, for a 20% reduction in the network density

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3 279 (yielding an a of ~ 0.51), R_e was estimated to be ~ 1.51 . Reductions of 30%, 40% and 50%
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5 280 yielding network densities of ~ 0.44 , ~ 0.38 and ~ 0.32 respectively, resulted in R_e values of
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7 281 ~ 1.42 , ~ 1.23 and ~ 1.05 correspondingly (Table 2). As shown, even large reductions in the
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9 282 density of the network will not lower the R_e below unity soon.

10 283 A study by Khan *et al.* that obtained robust estimates for the basic reproductive ratio
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12 284 R_0 in both Liberia and Sierra Leone showed that effective isolation is required to bring the
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14 285 value of R_0 to less than 1, and hence control the outbreak (25). Khan *et al.* suggested that the
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16 286 contact rate in isolation should be less than one quarter of that for the infected non-isolated
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18 287 population, and that, the fraction of high-risk individuals should be brought to less than 10%
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20 288 of the overall susceptible population, to halt the epidemic (25).

21 289 In reality, the reduction in the network density could potentially reflect analogous
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23 290 reductions in social interactions further to the current restrictions of community mobilization.
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25 291 Examples would include raising public awareness and/or strengthening medical care. The
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27 292 country's National Ebola Response Centre has already announced a 3-day lockdown that will
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29 293 affect around 2.5 million people (20). Nevertheless, it is worth noticing that even with a 30%
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31 294 reduction in the social network density, the epidemic shows no signs of fading out until June
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33 295 17 and we estimate that new cases will continue to be recorded.

34 296 In conclusion, we found that the EVD epidemic in Sierra Leone was in recession in
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36 297 the period between December 21, 2014 through mid-February, 2015, as reflected by the < 1
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38 298 value of the reproductive number for this period. However, during the second study period
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40 299 (i.e., from February 18 to April 17, 2015), the epidemic has spiked and the reproductive
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42 300 number was estimated to be well above criticality, with the potential to persist at this level
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44 301 beyond the end of June and through July. Control measures associated with mobilization
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46 302 restrictions were also evaluated. Our findings, supported by real epidemiologic data and the
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48 303 projection of a spilling over of the epidemic to mid-June, indicate that the measures
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50 304 implemented so far are inadequate. Taken in their totality, these findings indicate that the
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52 305 epidemic, even with strict control isolation policies in effect, will go on through July with a
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54 306 probability of fading out thereafter if policies are implemented and consistently kept in place.
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56 307 Immediate, more intense efforts are needed before further complications emerge. Reducing
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58 308 the effective density of the derived contact small-world-like network, through limited social
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60 309 interactions, has the potential to improve the current situation. Our results and predictions
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311 310 were verified from the official data reported by CDC for the corresponding period of study.
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313 311 Hence, our approach seems promising to forecast re-emergent outbreaks in other vulnerable
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315 312 regions of Africa, such as Eastern and Central Africa, where Ebola outbreaks have

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3 313 traditionally occurred in the past. Estimations through clinical studies of important factors
4 314 such as the contact transmission probability, mortality and recovery rate, incubation periods
5 315 as well as detailed age-specific data as the epidemic develops in space and time, would
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7 316 enhance our ability to better model, forecast and design efficient control policies.
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9 317 However, the usefulness of mathematical models should not be overestimated.
10 318 Despite the significant technological progress and concentrated wealth, breakdowns and cuts
11 319 in public health infrastructures worldwide are (the) major reasons for boosting epidemics.
12 320 Liberia and Sierra Leone, the two countries that have been worst affected from the Ebola
13 321 epidemic had an almost non-existent health care system: as reported Liberia with a
14 322 population of more than 4 million people had just 51 physicians and Sierra Leone with a
15 323 population exceeding 6 million had just 136 physicians (26).
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22 325 *Update to the case of Sierra Leone (period April 18-August 15, 2015)*

23 326 Since the results we obtained by analyzing the reported data until April 17, 2015
24 327 showed that the epidemic was sustained in Sierra Leone, we decided to investigate further the
25 328 current trends of the epidemic dynamics. Therefore, we expanded our analysis by taking into
26 329 account the reported data for the country for the very last period (April 18-August 15, 2015).
27 330 The results of this expanded analysis indicate a declining trend in the transmission potential
28 331 of the virus, as shown in Table 3. More specifically, (p_{rw}) rose significantly in the period
29 332 April 18-June 16, 2015 to ~ 0.69 (95% CI: ~ 0.67 - 0.72) with a further slight increase in the
30 333 very last period (June 17-August 15, 2015) to ~ 0.75 (95% CI: 0.69 - 0.80). The density ratio of
31 334 the network as represented by a , did not show significant changes: in the period April 18-
32 335 June 16, 2015 it was found to be ~ 0.47 (95% CI: ~ 0.42 - 0.51) and ~ 0.46 (95% CI: 0.37 - 0.53)
33 336 during the period June 17-August 15, 2015. The case fatality rate ($p_{D/I}$) dropped to $\sim 10\%$
34 337 (95% CI: 8-12%) for both last periods. The expected period from the onset of symptoms to
35 338 recovery (i.e., the inverse of $P_{I \rightarrow R}$) was ~ 20 days (95% CI: 16-30 days) during the period
36 339 April 18-June 16, 2015 and ~ 16 days (95% CI: 8-32 days) for the period June 17- August 15,
37 340 2015. The expected period from the onset of symptoms to death (i.e., the inverse of $P_{I \rightarrow D}$)
38 341 was almost constant at ~ 3.0 days (95% CI: 2.8-3.2 days) for both last periods. The per-
39 342 contact transmission probability $P_{S \rightarrow E}$ values were estimated at ~ 0.023 (95% CI: 0.02 - 0.026)
40 343 in the period April 18-June 16 and ~ 0.015 (95% CI: 0.01 - 0.21) in the period June 17- August
41 344 15, 2015. Finally, the Re obtained through the agent-based simulations dropped to ~ 1.38
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2 345 (95% CI: 0.95-1.72) in the period April 18-June 16, 2015 and ~ 0.68 (95% CI: 0.47-1.01)
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4 346 from June 17– August 15, 2015, thus indicating a saturation of the epidemic.

5 347 Our analysis succeeded in approximating the actual data for total cases and deaths (3).
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7 348 For example, on June 16, 2015 the number of total cases, as reported by the CDC, was 12,990
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9 349 and the number of deaths was 3,922, while our simulations resulted in 12,963 cases and
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11 350 ~3,940 deaths. On August 14, 2015, the total cases and deaths were 13,485 and 3,952,
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13 351 respectively, and our simulations resulted in 13,437 total cases and 3,993 deaths.

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354 **Contributorship statement**

355 Constantinos Siettos, Lucia Russo, and Christos Grigoras contributed to the development of
356 the model. Constantinos Siettos and Cleo Anastassopoulou contributed to the data collection,
357 interpretation of the data and drafting the paper. Eleftherios Mylonakis contributed to the
358 interpretation of the data and substantially revised the paper. All authors approved the final
359 manuscript and accepted accountability for all aspects of the work.

360
361 **Competing interests**

362 There are no competing interests.

363
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365
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367 or not-for-profit sectors.

368
369 **Data Sharing Statement**

370 The data used in this study are publicly available from CDC at
371 <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/>

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447 **Table 1.** Key epidemiologic features of the Ebola Virus Disease (EVD) epidemic in Sierra
448 Leone estimated by the model during the first and second study period (December 21, 2014 -
449 April 17, 2015).

Period	Variable	Mean	95% CI
First (Dec. 21- Feb. 18, 2015)	p_{rw}	0.37	0.33-0.41
	Network density (α)	0.55	0.51-0.58
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	9.5	8.6-10.7
	CFR (%)	32	31-33
	R_e	0.77	0.72-0.82
Second (Feb. 18-Apr. 17, 2015)	p_{rw}	0.22	0.20-0.24
	Network density (α)	0.63	0.59-0.68
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	8.0	6.5-10.5
	CFR (%)	39	38-40
	R_e	1.98	1.33-2.22

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451 p_{rw} , Rewiring switching probability; CFR, Case fatality rate (p_{DII}); R_e , Effective
452 reproductive number

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454 **Table 2.** Outcomes of isolation control policy scenarios on the basis of the expected
 455 reproductive number R_e , as computed by running the agent-based simulation from April 17
 456 to the mid-June 2015 (keeping fixed all other values of the model parameters). Sparser
 457 density refers to a percent reduction of the expected density of the contact network compared
 458 to the 0.63 value that was estimated for the second period (February 18 – April 17, 2015).

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Period	% Sparser density	Network density (α)	R_e
(April 18- June 17, 2015)	10%	~0.57	~1.7
	20%	~0.51	~1.5
	30%	~0.44	~1.4
	40%	~0.38	~1.2
	50%	~0.32	~1.0

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4 463 **Table 3.** Up-to-date key epidemiologic features of the Ebola Virus Disease (EVD) epidemic
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6 464 in Sierra Leone estimated by the model during the period (June 18- August 15, 2015).
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Period	Variable	Mean	95% CI
(June 18- July 16, 2015)	p_{rw}	0.69	0.67-0.72
	Network density (α)	0.47	0.42-0.51
	Time to death (Days)	3.0	2.8-3.2
	Time to recovery (Days)	20	16-30
	CFR (%)	10	8-12
	R_e	1.38	0.95-1.72
(July 16- August 15, 2015)	p_{rw}	0.75	0.69-0.80
	Network density (α)	0.46	0.37-0.53
	Time to death (Days)	3.0	2.8-3.2
	Time to recovery (Days)	16	8-32
	CFR (%)	10	8-12
	R_e	0.68	0.47-1.01

28 465
29 466 p_{rw} , Rewiring switching probability; CFR, Case fatality rate ($p_{D/I}$); R_e , Effective
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31 467 reproductive number
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469 **FIGURE LEGENDS**

470

471 **Figure 1. Simulation Results for Sierra Leone from December 21, 2014 to April 17,**
472 **2015.** Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data
473 are depicted by solid lines. The period under study has been tessellated into two windows
474 with a length of 60 days each. For each window, the model parameters are estimated based on
475 the data reported from WHO.

476

477 **Figure 2. Estimated model parameters for Sierra Leone from December 21, 2014 to**
478 **April 17, 2015. (a)** Evolution of contact network characteristics: switching probability (p_{rw})
479 and density ratio of the transmission network (a). **(b)** Per-contact transmission probability
480 ($p_{s \rightarrow E}$). **(c)** $1/\{\text{recovery period}\}$ ($p_{I \rightarrow R}$). **(d)** $1/\{\text{period from onset of symptoms to death}\}$
481 ($p_{I \rightarrow D}$). **(e)** Case fatality rate ($p_{D/I}$). **(f)** Effective reproductive number (R_e). 95%
482 Confidence intervals are also shown.

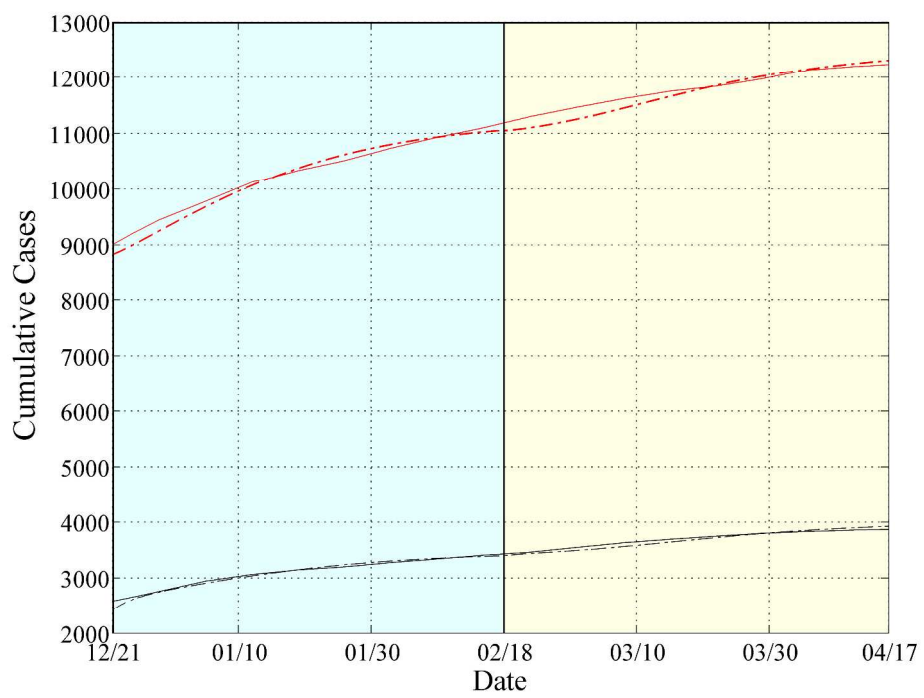
483

484 **Figure 3. Forecasting of the evolution of the epidemic from April 18 to June 17, 2015**
485 **under different control scenarios.** Network density values were compared to the density of
486 the social network estimated for the period February 18-April 17, 2015. **(a)** Total Cases, **(b)**
487 Deaths. The “no further action” scenario is also depicted.

488

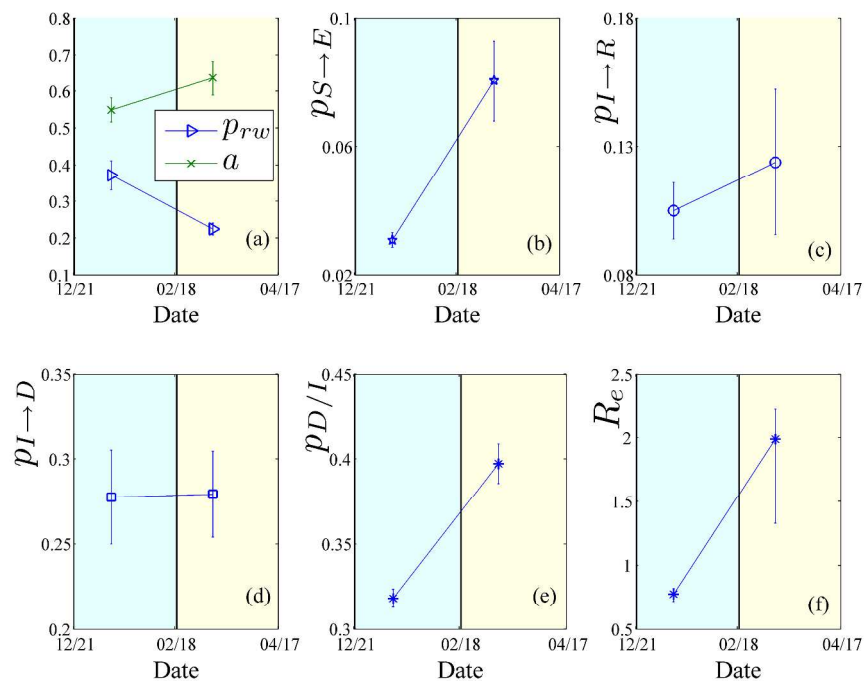
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Simulation Results for Sierra Leone from December 21, 2014 to April 17, 2015. Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data are depicted by solid lines. The period under study has been tessellated into two windows with a length of 60 days each. For each window, the model parameters are estimated based on the data reported from WHO.

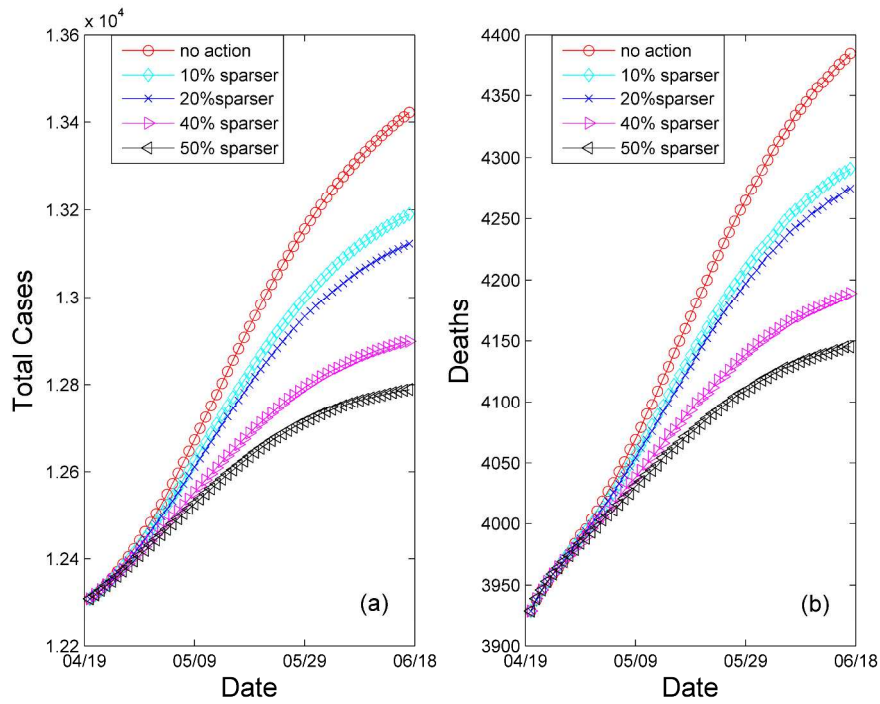
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Estimated model parameters for Sierra Leone from December 21, 2014 to April 17, 2015. (a) Evolution of contact network characteristics: switching probability and density ratio of the transmission network. (b) Per-contact transmission probability. (c) $1/\{\text{recovery period}\}$. (d) $1/\{\text{period from onset of symptoms to death}\}$. (e) Case fatality rate. (f) Effective reproductive number. 95% Confidence intervals are also shown.

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Forecasting of the evolution of the epidemic from April 18 to June 17, 2015 under different control scenarios. Network density values were compared to the density of the social network estimated for the period February 18-April 17, 2015. (a) Total Cases, (b) Deaths. The “no further action” scenario is also depicted.

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Forecasting and Control Policy Assessment for the Ebola Virus Disease (EVD)

Epidemic in Sierra Leone Using Small-World Networked Model Simulations

Constantinos I. Siettos¹, Cleo Anastassopoulou², Lucia Russo³, Christos Grigoras^{1,4},
Eleftherios Mylonakis⁴

Authors' affiliations:

¹ School of Applied Mathematics and Physical Sciences, National Technical University of Athens, Athens, Greece.

² Division of Genetics, Cell and Developmental Biology, Department of Biology, University of Patras, Patras, Greece.

³ Consiglio Nazionale di Ricerca, Napoli, Italy.

⁴ Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA.

Corresponding author:

Constantinos I. Siettos: Associate Professor Computational Science & Engineering, School of Applied Mathematics and Physical Sciences, National Technical University of Athens, 9, Heron Polytechniou Str., GR-157 80 Athens, Greece. Tel.: +30 210-772-3950; E-mail: ksiet@mail.ntua.gr

Eleftherios Mylonakis, M.D., Ph.D., FIDSA, Dean's Professor of Medical Science (Medicine, and Molecular Microbiology and Immunology), Chief, Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, Tel: 401-444-7856 / Fax: 401-444-8179.

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35 **Abstract**

36
37 **Objectives:** As the Ebola Virus Disease (EVD) is still sustained in Sierra Leone, we analyzed
38 the epidemic for the latest period (December 21, 2014 -April 17, 2015) using a small-world
39 networked model and forecasted its evolution. Policy-control scenarios for the containment of
40 the epidemic were also examined.

41 **Methods:** We developed an agent-based model with 6 million individuals (the population of
42 Sierra Leone) interacting through a small-world social network. The model incorporates the
43 main epidemiologic factors, including the effect of burial practices to virus transmission. The
44 effective reproductive number (*Re*) was evaluated directly from the agent-based simulations.
45 Estimates of the epidemiologic variables were computed on the basis of the official cases as
46 reported by the Centers for Disease Control and Prevention (CDC).

47 **Results:** From December 21, 2014 to February 18, 2015 the epidemic was in recession
48 compared to previous months, as indicated by the estimated effective reproductive number
49 (*Re*) of ~0.77 (95% CI: 0.72-0.82). From February 18 to April 17, 2015, *Re* rose above
50 criticality (~1.98, 95% CI: 1.33-2.22), flashing a note of caution for the situation. By
51 projecting in time, we predicted that the epidemic would continue through July 2015. Our
52 predictions were close to the cases reported by CDC by the end of June, verifying the
53 criticality of the situation. In light of these developments, while revising our manuscript, we
54 expanded our analysis to include the most recent data (until August 15, 2015). By mid-
55 August, *Re* has fallen below criticality and the epidemic is expected to fade out by early
56 December 2015.

57 **Conclusions:** Our results call for the continuation of drastic control measures, which in the
58 absence of an effective vaccine or therapy at present can only translate to isolation of the
59 infected section of the population, to contain the epidemic.

60
61 **Keywords:** EBOV, Sierra Leone, Effective reproductive number, Forecasting,
62 Communicable Disease Control, Agent-Based Modeling, Social Transmission Network

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64 **Article summary**

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66 **Strengths and limitations of this study**

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68 - The greatest strength of this study stems from the undertaken mathematical approach
69 of choice, integrating agent-based modeling on complex networks and the so-called
70 Equation-Free approach.

71 - Various important epidemiologic parameters were assessed and accurate short-term
72 forecasts of the evolution of the Ebola Virus Disease (EVD) epidemic in Sierra Leone
73 were obtained.

74 - Another advantage of the proposed methodology is that it allows for the rapid
75 evaluation of different policy-control scenarios that could lead to the containment of
76 the epidemic.

77 - Our predictions were verified by the official case count reported by CDC.

78 - The most important limitation of our study pertains to the quality and accuracy of the
79 outbreak data that were “fed” to the mathematical model compared to the real figures.

80 - Even though underreporting of cases and deaths is to be expected under the particular
81 circumstances of such a severe epidemic, real-life figures agree well with the
82 projections of our analysis.

83

84

85 Introduction

86 The worst Ebola Virus Disease (EVD) epidemic in history continues to ravage West
87 Africa. The epidemic began with the report of 49 cases and 29 deaths in Guinea on March 22,
88 2014 (1). Liberia reported its first laboratory-confirmed cases on March 30, 2014, while the
89 first cases in Sierra Leone were reported on May 28, 2014 (2). Following regular daily
90 population movements for trade and family visitation, the virus crossed the local porous
91 international borders, establishing chains of transmission not just in small villages, where it
92 would have been easier to contain it, but also in large urban centers. Insufficient public health
93 infrastructure, poor sanitation conditions, lack of education about the disease and unsafe
94 traditional burial practices have also contributed to the spread of the epidemic in the region
95 (2).

96 In Liberia, one of the most affected countries, as of April 20, 2015, a total of 10,042
97 cases have been recorded, while the toll of death has exceeded 4,480 (3). In early March a
98 halt of the epidemic was announced, and even though a new case was confirmed on March
99 20, 2015, the epidemic is considered to have ceased, while the situation in Sierra Leone is
100 notably different. With more than 12,360 cases and 3,900 deaths until now, Sierra Leone
101 experienced a drop in new cases in January 2015 and authorities loosened mobilization
102 restriction measures to support economic activity (4). However, recent World Health
103 Organization WHO updates on the status of the EVD epidemic in this West African nation
104 report a flare up (3), with a significant increase among the community of fishermen living in
105 the coastal area of Aberdeen in Freetown (5). The synchronous occurrence of over 20 cases
106 suggested they had been infected by a single source, possibly an unsafe burial (5).

107 In light of these recent developments, we analyzed the EVD epidemic dynamics in
108 Sierra Leone for the period between December 21, 2014 and April 17, 2015, using an agent-
109 based, social network model that we reported recently and that proved to provide accurate
110 predictions for the case of Liberia (6). For this purpose, the latest official case counts from
111 WHO were fitted to the model, following the so-called Equation-Free approach (7). Our main
112 objective was to obtain estimates of key epidemiologic parameters, such as the indicative of
113 secondary infections effective reproductive number (Re), the case fatality rate, the per-contact
114 transmission probability and the mean time from symptoms onset to recovery or to death, in
115 order to study the evolving dynamics through the social transmission network whose
116 structure and density are also examined. Secondary objectives of the study included the

117 exploration of different policy-control scenarios that could lead to reduced Re values, and,
118 thereby, to the containment of the epidemic.

119

120 **Methods**

121 We developed an agent-based model for the study of the Ebola epidemic (6) with N
122 individuals that interact through a Watts & Strogatz (WS) (8) small-world network that
123 approximates some attributes of the real social interactions, which are characterized by
124 relatively high clustering and short social distances between them. Here, the network was
125 constructed with the Newman-Watts (9) algorithm, in which short-cut edges are added
126 between pairs of nodes with a probability, in the same way as in a WS network, but without
127 removing edges from the underlying lattice. The algorithm starts with a one-dimensional ring
128 network with k local-nearest neighbors per node and with a probability p_{rw} that a link is
129 added between two nodes. Hence, the mean number of additional shortcuts is $p_{rw} k N$, and
130 the mean total degree of the network is $2 k N (1 + p_{rw})$. In the constructed small-world
131 network we can adjust the density of the network, say α , at will, by randomly adding or
132 subtracting the required number of links.

133 Agents are categorized in five discrete states: *Susceptible* (S), *Exposed* (E), *Infected*
134 (I), *Dead of the disease but not yet buried* (D_I), *Dead of the disease and safely buried*
135 (D_b), and *Recovered* (R) (6). The D_I infectious state includes agents who die, but whose
136 burial entails risk for onward virus transmission. The transition between states is modeled as
137 a discrete-time, discrete state *non-Markov random process*. Within this framework, the state
138 space over the set of the network links is represented by $Y(\mathbf{V})$, where

139 $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_I, R\}$ is the set of the states of individual v_k .

140 The agent-based rules that govern the dynamics of the epidemic on a daily basis read as
141 follows:

$$142 \quad p(Y_{v_k}(t+1) = D_b \mid Y_{v_k}(t) = D_I) = 1 \quad (1)$$

$$143 \quad p(Y_{v_k}(t+1) = E \mid Y_{v_l}(t) = I, Y_{v_l}(t) = D_I) = p_{S \rightarrow E}, \quad v_l \in \mathfrak{R}_{v_k} \quad (2)$$

$$144 \quad p(Y_{v_k}(t+1) = I \mid Y_{v_k}(t) = E) = p_{E \rightarrow I} \quad (3)$$

$$145 \quad p(Y_{v_k}(t+1) = D_I \mid Y_{v_k}(t) = I) = p_{I \rightarrow D} \quad (4)$$

$$p(Y_{v_k}(t+1) = R | Y_{v_k}(t) = I) = p_{I \rightarrow R} \quad (5)$$

147
 148 where $p_{S \rightarrow E}$ is the per infected contact transmission probability (still alive or dead, but not
 149 yet buried), $p_{E \rightarrow I}$, is the inverse of the incubation period, $p_{I \rightarrow D}$ is the inverse of the time
 150 from symptoms onset to death, $p_{I \rightarrow R}$ is the inverse of the recovery period, and, $p_{D/I}$, is the
 151 ratio of deaths to the infected population (6). The rate of the incubation period is taken to be
 152 constant, set at $p_{E \rightarrow I} = \frac{1}{9}$, as reported by the Who Ebola Response Team (10). \mathfrak{R}_{v_k} denotes the
 153 neighborhood of an individual v_k . This first rule sets the time period from death to burial to
 154 two days, during which family members and loved ones may be infected due to physical
 155 contact with the dead, still-contagious body. Long-range links of a dead, yet potentially
 156 infectious, agent are cut, reflecting the fact that only relatives and close community members
 157 can be infected during unsafe funeral practices and rites. The second rule implies that a
 158 susceptible agent gets exposed to the disease with a rate determined by the probability $p_{S \rightarrow E}$
 159 per infected contact (still alive or dead, but not yet buried). The third rule implies that an
 160 exposed agent becomes infectious with a rate determined by the probability $p_{E \rightarrow I}$, whose
 161 inverse corresponds to the incubation period, i.e. the time from exposure to symptoms onset.
 162 Rules (4) and (5) define the case fatality rate, $p_{D/I}$: an agent dies of the disease with a rate
 163 determined by the probability $p_{I \rightarrow D}$ (whose inverse is the time from symptoms onset to
 164 death) (Rule (4)); alternatively, an agent could recover with a rate determined by the
 165 probability $p_{I \rightarrow R}$ (Rule (5)).

166 The effective reproductive ratio R_e , defined as the average number of secondary
 167 infections produced by a typical infective person, is also computed directly from the agent-
 168 based simulations.

169 Based on the demographics reported by the United Nations (UN), the population of
 170 Sierra Leone is 6 million (11). Time series of the official Ebola case counts from the Centers
 171 for Disease Control and Prevention (CDC) were used for model fitting (3). These case counts
 172 were collected from public data released by the World Health Organization (WHO) (12) and
 173 CDC (3). Even though these data sets do not distinguish between suspect, probable and
 174 laboratory-confirmed case counts, they are considered to represent the best available
 175 estimates of the current state of the epidemic in the severely afflicted West African countries.

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3 176 Case data, which included cumulative incidence and cumulative deaths by date of report for
4 177 Sierra Leone, were retrieved on April 24, 2015.

5 178 Simulations were performed using December 21, 2014 as an initial date and a time
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7 179 horizon of 60 days with an equal sliding window time interval; the last date was April 17,
8
9 180 2015. Thus, fitted values of the network and model parameters, as well as estimates of the
10 181 effective reproductive ratio, were computed in sequences of succeeded time intervals of 60
11 182 days corresponding to 2 periods (December 21, 2014 – February 18, 2015 and February 18,
12 183 2015 – April 17, 2015). The initial conditions for the starting date of December 21, 2014
13 184 were calculated on the basis of agent-based simulations from May 27, 2014, i.e. the date on
14 185 which the first cases were officially reported from WHO (2), following the procedure
15 186 described in detail elsewhere (6). In particular, we obtained the following (expected) numbers
16 187 for December 21, 2014: $E_0 = 450$, $I_0 = 901$, $D_{b0} = 2390$, $D_{t0} = 28$, $R_0 = 5579$; the estimated
17 188 cumulative number of cases then was 8,828.

18 189 The expected (averaged) values of the agents' states $Y(v_k) \equiv Y_{v_k} = \{S, E, I, D_b, D_t, R\}$
19 190 were computed over $N_r = 8$ network realizations and $N_s = 100$ simulations for each one of the
20 191 network realizations. The model parameters were fitted to the reported data using a trust-
21 192 region-reflective approach for nonlinear minimization, implemented for parameter estimation
22 193 (13) exploiting the Equation-Free approach (7,14-18). Matlab (19) was the simulation
23 194 environment of choice, while the model was programmed in Fortran 90 and linked to Matlab
24 195 through mex files.

25 196 To forecast the evolution of the Ebola virus epidemic in Sierra Leone, we used the
26 197 values of the model parameters as estimated in the last period; the resulting parameter values
27 198 were then fed to the simulator using as coarse initial conditions the values of
28 199 $\{S, E, I, D_b, D_t, R\}$ as computed on April 17, 2015. We tested the effect of control policy
29 200 scenarios by reducing the density of the network structure as estimated in the second period.
30 201 Sparser network densities could reflect partial isolation of the population, restriction of social
31 202 mobilization combined with an expanded public campaign for increased awareness.
32 203

204 Results and Discussion

205 The cumulative numbers of infected and dead obtained by the model compared to the
206 reported cases in Sierra Leone are shown in Figure 1. Our framework succeeds in
207 approximating the actual data for total cases and deaths (3). For example, on December 21,
208 2014 the number of total cases, as reported by the WHO, was 9,004 and the number of deaths
209 was 2,582, while our simulations resulted in 8,828 cases and ~2,400 deaths. On February 18,
210 2015, the total cases and deaths were 11,103 and 3,408, respectively, and our simulations
211 resulted in 11,049 total cases and 3,394 deaths. Finally, on April 17, 2015, the reported total
212 cases and deaths were 12,244 and 3,865, respectively; our simulations resulted in 12,299 total
213 cases and 3,919 deaths.

214 The epidemiologic parameters that were obtained through the optimization approach
215 are illustrated in Figure 2 and a summary of the estimated epidemic parameters for the period
216 under study, together with their 95% confidence intervals, is presented in Table 1. Panel (a)
217 depicts the evolution of the estimated network characteristics, p_{rw} and a , while panels (b-e)
218 illustrate the model parameters $p_{S \rightarrow E}$, $p_{D \rightarrow I}$, $p_{I \rightarrow R}$ and $p_{I \rightarrow D}$ that fit best to the reported EVD
219 epidemic dynamics in the country. The evolution of the estimated effective reproductive
220 number R_e in Sierra Leone is shown in panel (f).

221 More specifically, the contact network of Sierra Leone exhibits a rather random
222 structure with a rewiring switching probability (p_{rw}) of ~0.37 (95% CI: ~0.33-0.41) that falls
223 down to ~0.22 (95% CI: 0.20-0.24) during the study period (Figure 2a). A slight increase is
224 shown in the density ratio of the network as represented by a , which was ~0.54 (95% CI:
225 ~0.51-0.58) during the first period (December 21, 2014 – February 18, 2015) and ~0.63 (95%
226 CI: 0.59-0.68) during the second period of the study (February 18, 2015 – April 17, 2015)
227 (Figure 2a). The differences of the network characteristics between the two periods indicate a
228 more clustered, yet denser contact network during the second period that could partially
229 reflect a relaxation of awareness in the first period, when the epidemic seemed to decline.
230 The per-contact transmission probability $p_{S \rightarrow E}$ values were estimated at ~0.03 (95% CI:
231 0.028-0.033) in the first period and ~0.08 (95% CI: 0.067-0.09) in the second period (Figure
232 2b). The expected period from the onset of symptoms to recovery (i.e., the inverse of $p_{I \rightarrow R}$)
233 was ~9.5 days (95% CI: 8.6-10.7 days) during the first period and ~8 days (95% CI: 6.5-10.5
234 days) for the second period of study (Figure 2c). The expected time interval from the onset of
235 symptoms to death (i.e., the inverse of $p_{I \rightarrow D}$) was constant at ~3.6 days (95% CI: 3.3-4.0
236 days) during the period of study (Figure 2d). The case fatality rate ($p_{D \rightarrow I}$) that was estimated

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2 237 to be ~32% (95% CI: 31-33%) for the period extending from late December 2014 to February
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4 238 18 2015, increased to ~39% (95% CI: 38-40%) from February 18 to April 17 (Figure 2e).
5
6 239 Finally, the effective reproductive number R_e , as computed using the agent-based simulator,
7
8 240 was ~0.77 (95% CI: 0.72-0.82) from December 21, 2014 to February 18, 2015, rising up to
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10 241 ~1.98 (95% 1.33-2.22) from February 18, 2015 to April 17, 2015 (Figure 2f).

11
12 242 Regarding the epidemic parameters, our estimates are quite close to the ones reported
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14 243 by the WHO Ebola Response Team and other groups. For example, Ansumana *et al.* (20)
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16 244 reported a 31% CFR at Hastings center, while the National Institute of Communicable
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18 245 diseases (NICD) reports a CFR of 32% for Sierra Leone on April 5, 2015 (21); a mean of
19
20 246 31.6% CFR was reported for Sierra Leone from the WHO Ebola response team as of
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22 247 September 14, 2014 (10). Gomes *et al.* (22) reported an ~8 day-period from the onset of
23
24 248 symptoms to recovery, while in a recent study by the WHO Ebola response team (23) a
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26 249 period of 10.6 days (with a SD of 8.2 days) was reported from symptoms onset to hospital
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28 250 discharge for individuals of older than 45 years old. In the same paper, a period of ~6 days
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30 251 (with equal SD) is reported from symptoms onset to death for the same age group. The same
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32 252 delay period from symptoms onset to death was also reported in Ansumana *et al.* (20).

33
34 253 Simulations show that the expected cumulative number of infected cases may reach as
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36 254 high as 13,400 by June 17, while the cumulative number of dead may exceed 4,300, if no
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38 255 further action is undertaken. Hence, we decided to perform an assessment of the impact of
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40 256 potential control strategies. Based on the recently announced isolation policy (24), we
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42 257 simulated the influence on the epidemic dynamics of sparser, with respect to the estimated
43
44 258 network density of the second period, network densities, by 10%, 20%, 30%, 40% and 50%.
45
46 259 We tested these scenarios by reducing analogously the expected density of the contact
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48 260 network as estimated during the second period and running the agent-based simulation from
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50 261 April 18 until June 17, 2015, keeping all other values of the model parameters fixed.

51
52 262 The results of the exploration of these different scenarios are summarized in Table 2
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54 263 and portrayed graphically in Figure 3. The “no further action” case, with respect to the
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56 264 estimated current network structure is also depicted in Figure 3 for comparison. By applying
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58 265 a 10% reduction in the network density (yielding an a of ~0.57), the expected reproductive
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60 266 number R_e was estimated to be ~1.7. Accordingly, for a 20% reduction in the network density
267 (yielding an a of ~0.51), R_e was estimated to be ~1.51. Reductions of 30%, 40% and 50%
268 yielding network densities of ~0.44, ~0.38 and ~0.32 respectively, resulted in R_e values of

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3 269 ~1.42, ~1.23 and ~1.05 correspondingly (Table 2). As shown, even large reductions in the
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5 270 density of the network will not lower the R_e below unity soon.

6
7 271 A study by Khan *et al.* that obtained robust estimates for the basic reproductive ratio
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9 272 R_0 in both Liberia and Sierra Leone showed that effective isolation is required to bring the
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11 273 value of R_0 to less than 1, and hence control the outbreak (25). Khan *et al.* suggested that the
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13 274 contact rate in isolation should be less than one quarter of that for the infected non-isolated
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15 275 population, and that, the fraction of high-risk individuals should be brought to less than 10%
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17 276 of the overall susceptible population, to halt the epidemic (25).

18
19 277 In reality, the reduction in the network density could potentially reflect analogous
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21 278 reductions in social interactions further to the current restrictions of community mobilization.
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23 279 Examples would include raising public awareness and/or strengthening medical care. The
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25 280 country's National Ebola Response Centre has already announced a 3-day lockdown that will
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27 281 affect around 2.5 million people (20). Nevertheless, it is worth noticing that even with a 30%
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29 282 reduction in the social network density, the epidemic shows no signs of fading out until June
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31 283 17 and we estimate that new cases will continue to be recorded.

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33 284 In conclusion, we found that the EVD epidemic in Sierra Leone was in recession in
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35 285 the period between December 21, 2014 through mid-February, 2015, as reflected by the <1
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37 286 value of the reproductive number for this period. However, during the second study period
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39 287 (i.e., from February 18 to April 17, 2015), the epidemic has spiked and the reproductive
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41 288 number was estimated to be well above criticality, with the potential to persist at this level
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43 289 beyond the end of June and through July. Control measures associated with mobilization
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45 290 restrictions were also evaluated. Our findings, supported by real epidemiologic data and the
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47 291 projection of a spilling over of the epidemic to mid-June, indicate that the measures
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49 292 implemented so far are inadequate. Taken in their totality, these findings indicate that the
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51 293 epidemic, even with strict control isolation policies in effect, will go on through July with a
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53 294 probability of fading out thereafter if policies are implemented and consistently kept in place.
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55 295 Immediate, more intense efforts are needed before further complications emerge. Reducing
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57 296 the effective density of the derived contact small-world-like network, through limited social
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59 297 interactions, has the potential to improve the current situation. Our results and predictions
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298 were verified from the official data reported by CDC for the corresponding period of study.
299 Hence, our approach seems promising to forecast re-emergent outbreaks in other vulnerable
300 regions of Africa, such as Eastern and Central Africa, where Ebola outbreaks have
301 traditionally occurred in the past. Estimations through clinical studies of important factors
302 such as the contact transmission probability, mortality and recovery rate, incubation periods

303 as well as detailed age-specific data as the epidemic develops in space and time, would
304 enhance our ability to better model, forecast and design efficient control policies.

305 However, the usefulness of mathematical models should not be overestimated.

306 Despite the significant technological progress and concentrated wealth, breakdowns and cuts
307 in public health infrastructures worldwide are (the) major reasons for boosting epidemics.
308 Liberia and Sierra Leone, the two countries that have been worst affected from the Ebola
309 epidemic had an almost non-existent health care system: as reported Liberia with a
310 population of more than 4 million people had just 51 physicians and Sierra Leone with a
311 population exceeding 6 million had just 136 physicians (26).

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313 *Update to the case of Sierra Leone (period April 18-August 15, 2015)*

314 Since the results we obtained by analyzing the reported data until April 17, 2015
315 showed that the epidemic was sustained in Sierra Leone, we decided to investigate further the
316 current trends of the epidemic dynamics. Therefore, we expanded our analysis by taking into
317 account the reported data for the country for the very last period (April 18-August 15, 2015).
318 The results of this expanded analysis indicate a declining trend in the transmission potential
319 of the virus, as shown in Table 3. More specifically, (p_{rw}) rose significantly in the period
320 April 18-June 16, 2015 to ~ 0.69 (95% CI: ~ 0.67 - 0.72) with a further slight increase in the
321 very last period (June 17-August 15, 2015) to ~ 0.75 (95% CI: 0.69 - 0.80). The density ratio of
322 the network as represented by a , did not show significant changes: in the period April 18-
323 June 16, 2015 it was found to be ~ 0.47 (95% CI: ~ 0.42 - 0.51) and ~ 0.46 (95% CI: 0.37 - 0.53)
324 during the period June 17-August 15, 2015. The case fatality rate ($p_{D/I}$) dropped to $\sim 10\%$
325 (95% CI: 8 - 12%) for both last periods. The expected period from the onset of symptoms to
326 recovery (i.e., the inverse of $P_{I \rightarrow R}$) was ~ 20 days (95% CI: 16 - 30 days) during the period
327 April 18-June 16, 2015 and ~ 16 days (95% CI: 8 - 32 days) for the period June 17- August 15,
328 2015. The expected period from the onset of symptoms to death (i.e., the inverse of $P_{I \rightarrow D}$)
329 was almost constant at ~ 3.0 days (95% CI: 2.8 - 3.2 days) for both last periods. The per-
330 contact transmission probability $P_{S \rightarrow E}$ values were estimated at ~ 0.023 (95% CI: 0.02 - 0.026)
331 in the period April 18-June 16 and ~ 0.015 (95% CI: 0.01 - 0.21) in the period June 17- August
332 15, 2015. Finally, the Re obtained through the agent-based simulations dropped to ~ 1.38
333 (95% CI: 0.95 - 1.72) in the period April 18-June 16, 2015 and ~ 0.68 (95% CI: 0.47 - 1.01)
334 from June 17- August 15, 2015, thus indicating a saturation of the epidemic.

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3 335 Our analysis succeeded in approximating the actual data for total cases and deaths (3).
4 336 For example, on June 16, 2015 the number of total cases, as reported by the CDC, was 12,990
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6 337 and the number of deaths was 3,922, while our simulations resulted in 12,963 cases and
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8 338 ~3,940 deaths. On August 14, 2015, the total cases and deaths were 13,485 and 3,952,
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10 339 respectively, and our simulations resulted in 13,437 total cases and 3,993 deaths.
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3 342 **Contributorship statement**

4 343 Constantinos Siettos, Lucia Russo, and Christos Grigoras contributed to the development of
5 344 the model. Constantinos Siettos and Cleo Anastassopoulou contributed to the data collection,
6 345 interpretation of the data and drafting the paper. Eleftherios Mylonakis contributed to the
7 346 interpretation of the data and substantially revised the paper. All authors approved the final
8 347 manuscript and accepted accountability for all aspects of the work.

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15 349 **Competing interests**

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18 350 There are no competing interests.

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24
25 353

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27 355 or not-for-profit sectors.

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33 357 **Data Sharing Statement**

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35 358 No additional data available.

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434 **Table 1.** Key epidemiologic features of the Ebola Virus Disease (EVD) epidemic in Sierra
435 Leone estimated by the model during the first and second study period (December 21, 2014 -
436 April 17, 2015).

Period	Variable	Mean	95% CI
First (Dec. 21- Feb. 18, 2015)	p_{rw}	0.37	0.33-0.41
	Network density (α)	0.55	0.51-0.58
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	9.5	8.6-10.7
	CFR (%)	32	31-33
	R_e	0.77	0.72-0.82
Second (Feb. 18-Apr. 17, 2015)	p_{rw}	0.22	0.20-0.24
	Network density (α)	0.63	0.59-0.68
	Time to death (Days)	3.6	3.3-4.0
	Time to recovery (Days)	8.0	6.5-10.5
	CFR (%)	39	38-40
	R_e	1.98	1.33-2.22

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438 p_{rw} , Rewiring switching probability; CFR, Case fatality rate (p_{DII}); R_e , Effective
439 reproductive number

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441 **Table 2.** Outcomes of isolation control policy scenarios on the basis of the expected
442 reproductive number R_e , as computed by running the agent-based simulation from April 17
443 to the mid-June 2015 (keeping fixed all other values of the model parameters). Sparser
444 density refers to a percent reduction of the expected density of the contact network compared
445 to the 0.63 value that was estimated for the second period (February 18 – April 17, 2015).

Period	% Sparser density	Network density (α)	R_e
(April 18- June 17, 2015)	10%	~0.57	~1.7
	20%	~0.51	~1.5
	30%	~0.44	~1.4
	40%	~0.38	~1.2
	50%	~0.32	~1.0

449
 450 **Table 3.** Up-to-date key epidemiologic features of the Ebola Virus Disease (EVD) epidemic
 451 in Sierra Leone estimated by the model during the period (June 18- August 15, 2015).

Period	Variable	Mean	95% CI
(June 18- July 16, 2015)	p_{rw}	0.69	0.67-0.72
	Network density (α)	0.47	0.42-0.51
	Time to death (Days)	3.0	2.8-3.2
	Time to recovery (Days)	20	16-30
	CFR (%)	10	8-12
	R_e	1.38	0.95-1.72
(July 16- August 15, 2015)	p_{rw}	0.75	0.69-0.80
	Network density (α)	0.46	0.37-0.53
	Time to death (Days)	3.0	2.8-3.2
	Time to recovery (Days)	16	8-32
	CFR (%)	10	8-12
	R_e	0.68	0.47-1.01

452
 453 p_{rw} , Rewiring switching probability; CFR, Case fatality rate (p_{DII}); R_e , Effective
 454 reproductive number

455

456 **FIGURE LEGENDS**

457

458 **Figure 1. Simulation Results for Sierra Leone from December 21, 2014 to April 17,**
459 **2015.** Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data
460 are depicted by solid lines. The period under study has been tessellated into two windows
461 with a length of 60 days each. For each window, the model parameters are estimated based on
462 the data reported from WHO.

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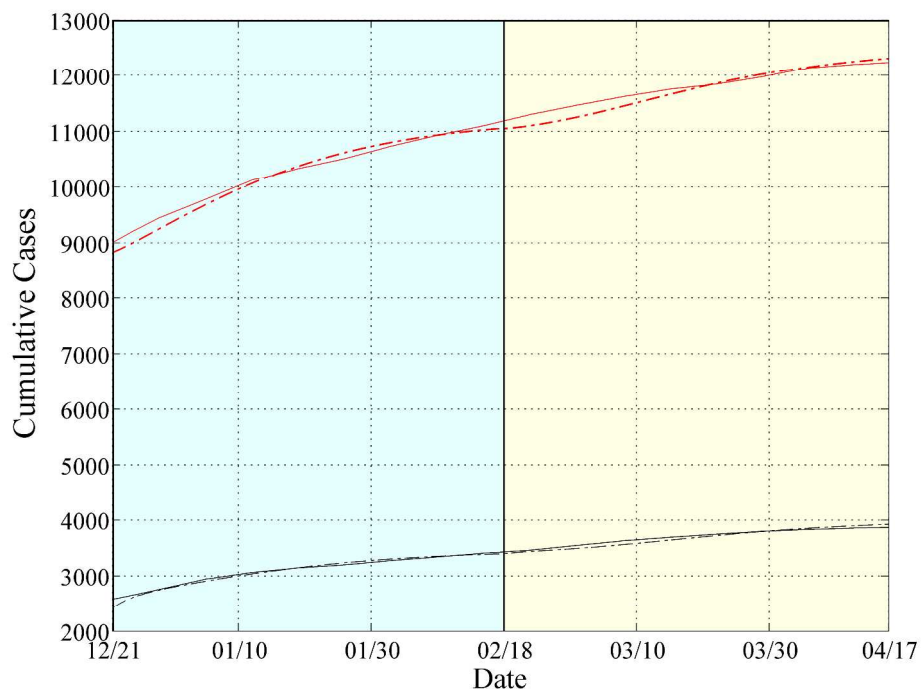
464 **Figure 2. Estimated model parameters for Sierra Leone from December 21, 2014 to**
465 **April 17, 2015. (a)** Evolution of contact network characteristics: switching probability (p_{rw})
466 and density ratio of the transmission network (a). **(b)** Per-contact transmission probability
467 ($p_{s \rightarrow E}$). **(c)** $1/\{\text{recovery period}\}$ ($p_{I \rightarrow R}$). **(d)** $1/\{\text{period from onset of symptoms to death}\}$
468 ($p_{I \rightarrow D}$). **(e)** Case fatality rate (p_{DH}). **(f)** Effective reproductive number (R_e). 95%
469 Confidence intervals are also shown.

470

471 **Figure 3. Forecasting of the evolution of the epidemic from April 18 to June 17, 2015**
472 **under different control scenarios.** Network density values were compared to the density of
473 the social network estimated for the period February 18-April 17, 2015. **(a)** Total Cases, **(b)**
474 Deaths. The “no further action” scenario is also depicted.

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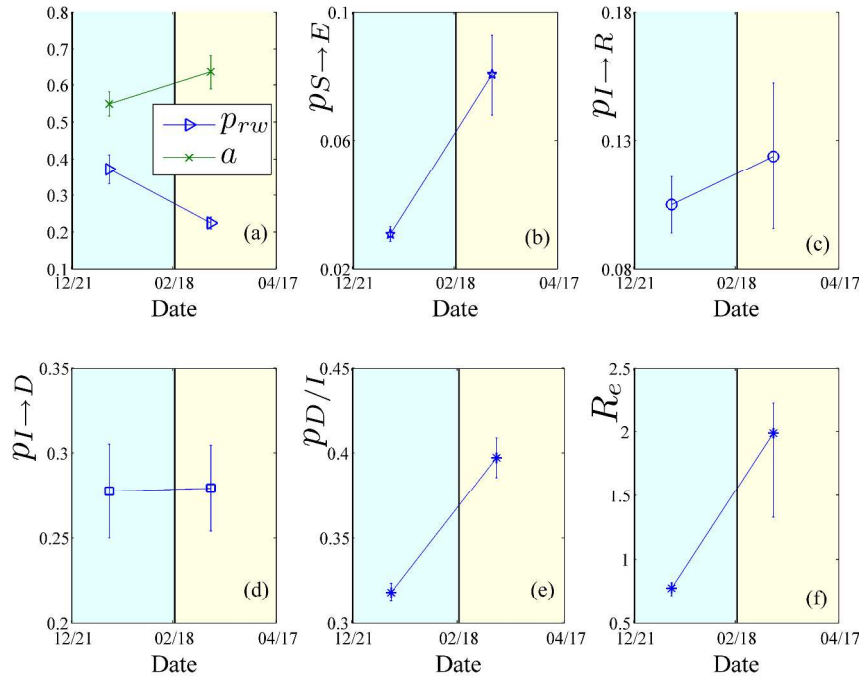
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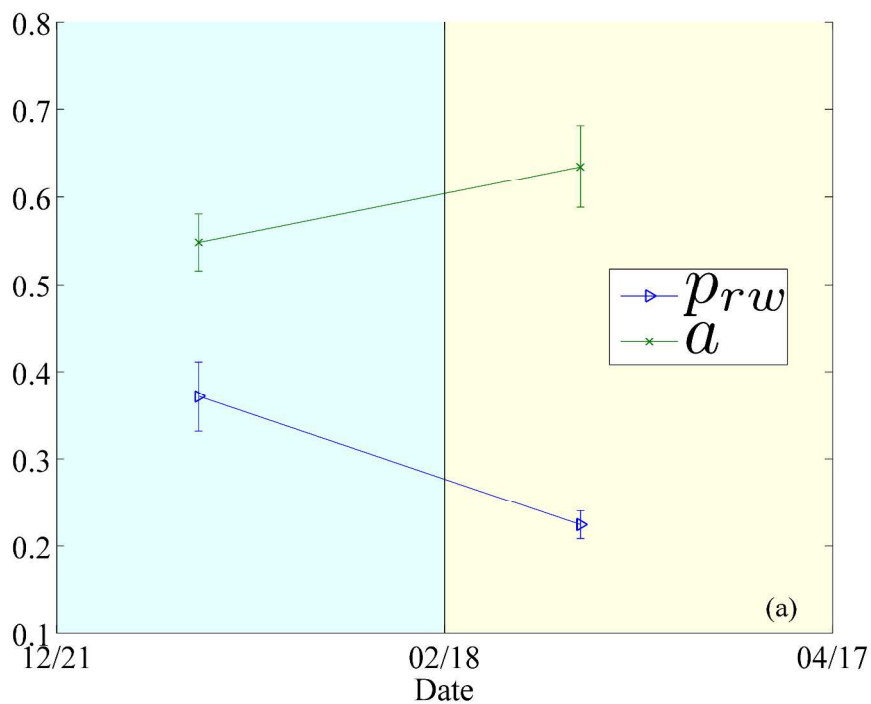
Simulation Results for Sierra Leone from December 21, 2014 to April 17, 2015. Expected cumulative cases of infected (dotted red) and dead (dotted black). WHO data are depicted by solid lines. The period under study has been tessellated into two windows with a length of 60 days each. For each window, the model parameters are estimated based on the data reported from WHO.

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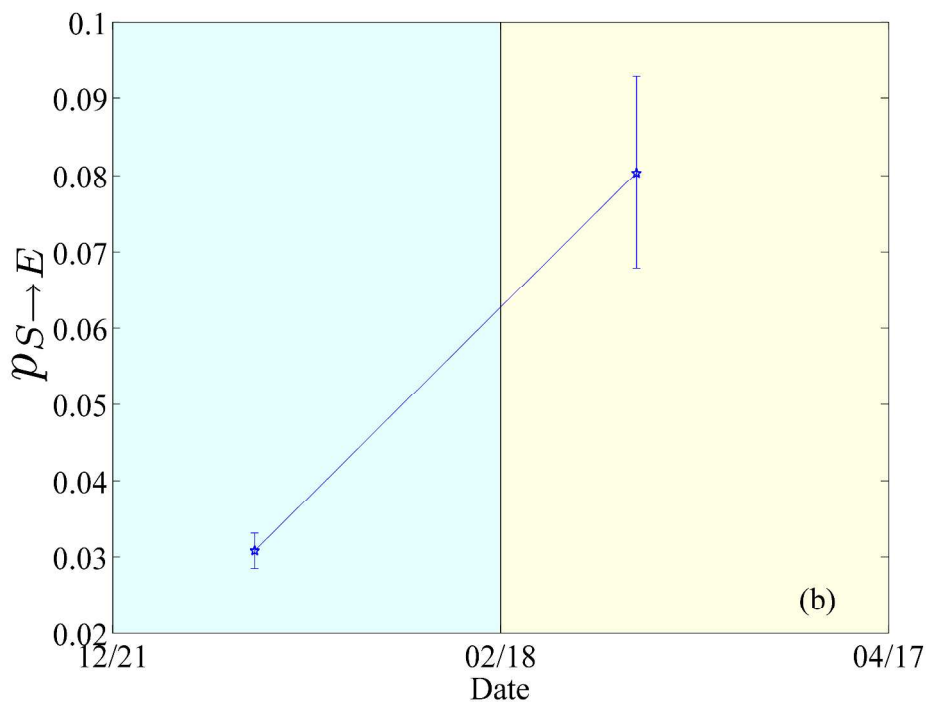
Estimated model parameters for Sierra Leone from December 21, 2014 to April 17, 2015. (a) Evolution of contact network characteristics: switching probability and density ratio of the transmission network. (b) Per-contact transmission probability. (c) $1/\{\text{recovery period}\}$. (d) $1/\{\text{period from onset of symptoms to death}\}$. (e) Case fatality rate. (f) Effective reproductive number. 95% Confidence intervals are also shown.



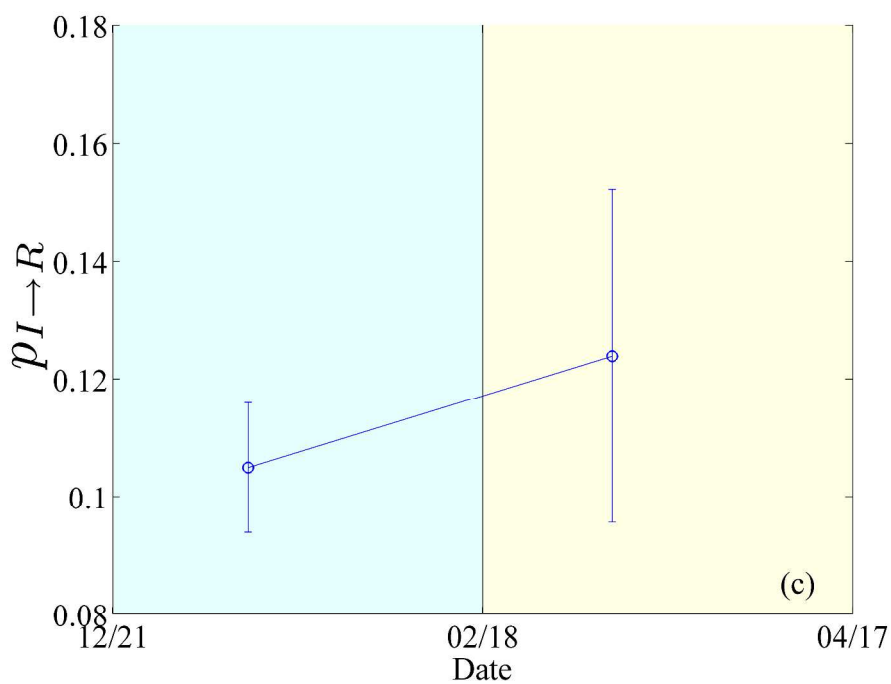
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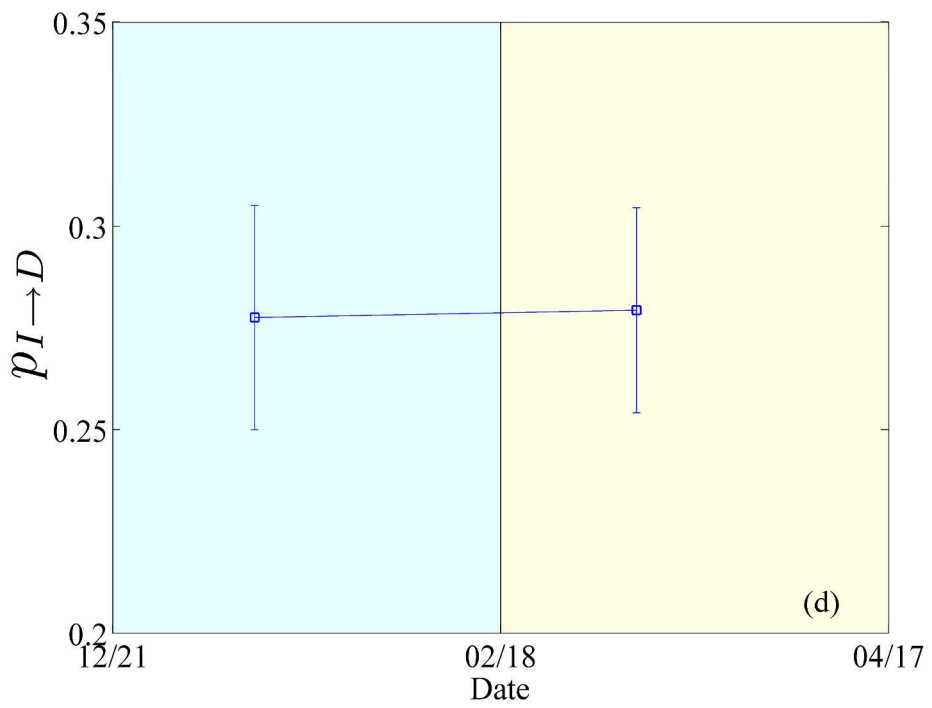
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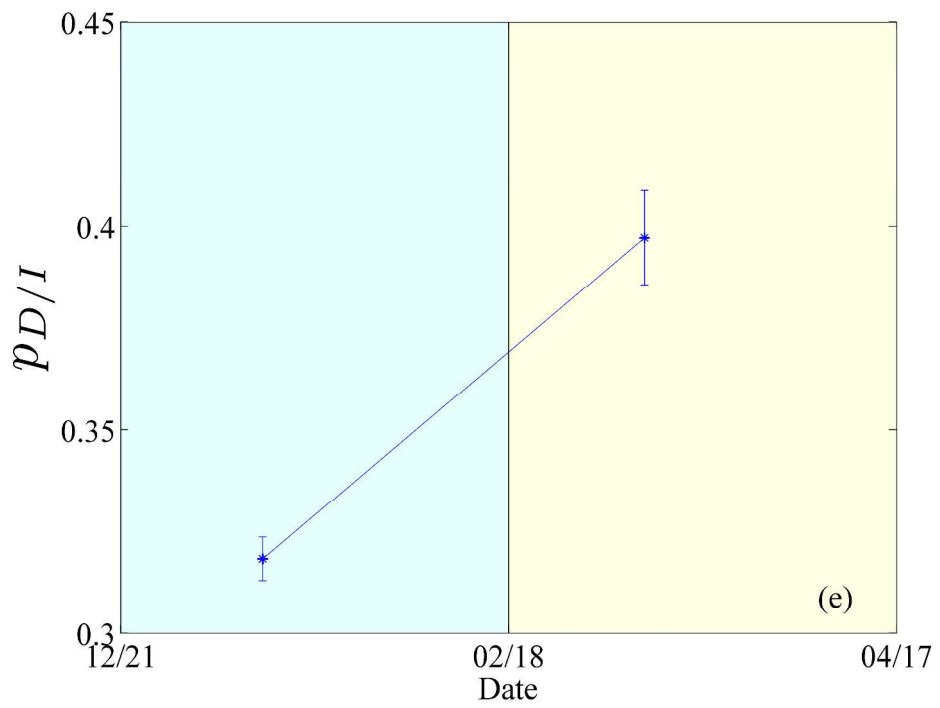
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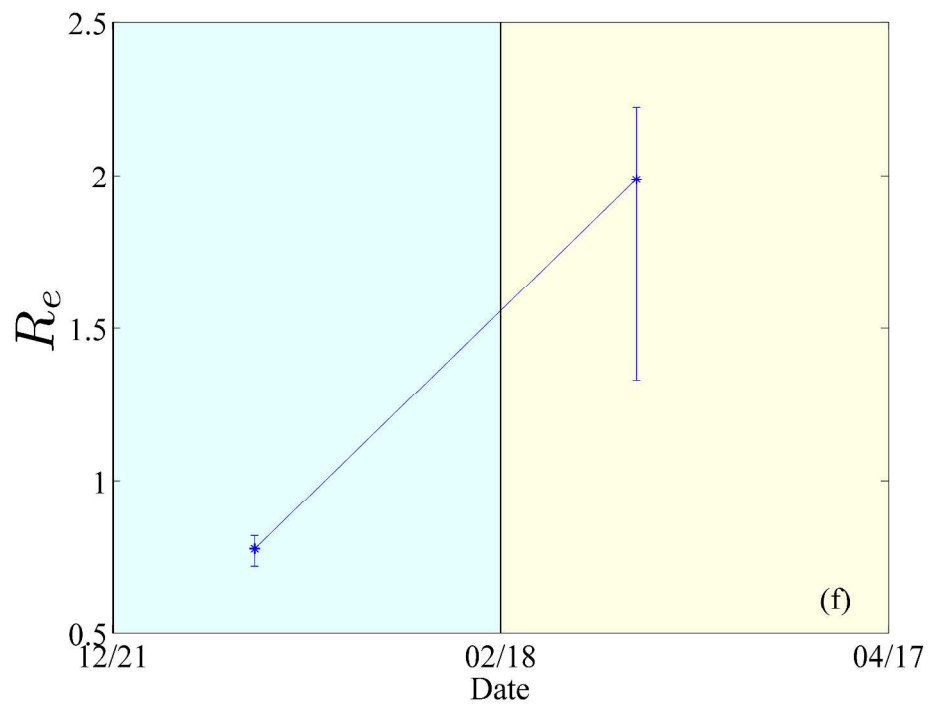
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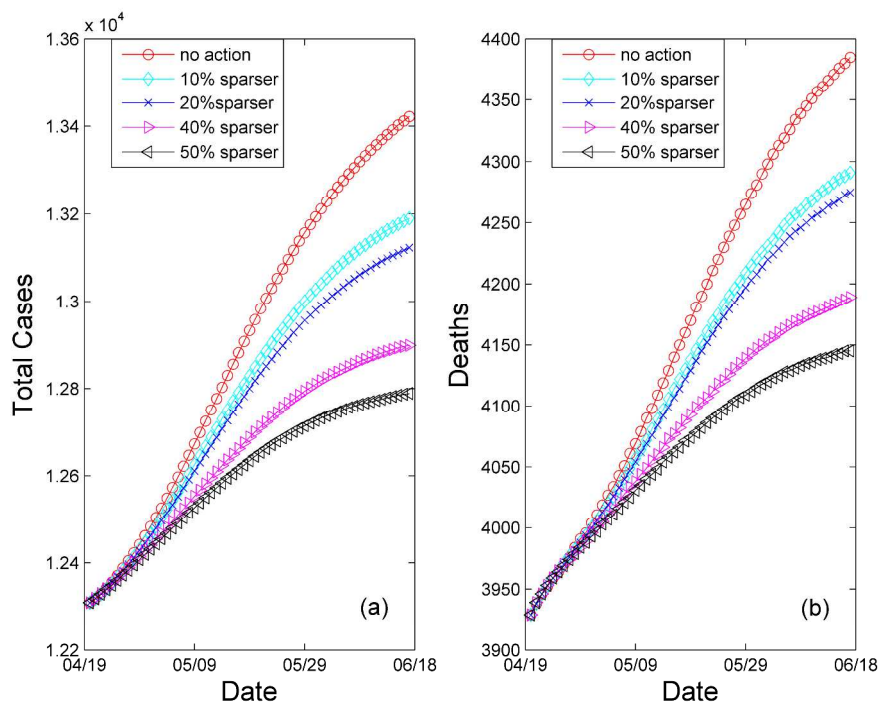


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Review only



Forecasting of the evolution of the epidemic from April 18 to June 17, 2015 under different control scenarios. Network density values were compared to the density of the social network estimated for the period February 18-April 17, 2015. (a) Total Cases, (b) Deaths. The “no further action” scenario is also depicted.

View only

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