1 **Title: After the honeymoon, the divorce: unexpected outcomes of disease control measures**

2 **against endemic infections**

3 Short Title: Unexpected outcomes of disease control measures against endemic infections

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15

Abstract

17 The lack of effective vaccines for many endemic diseases often forces policymakers to enact

18 control programs that rely on non-immunizing controls, such as vector control, in order to

19 reduce the massive burden of these diseases. It is well known that controls can have

20 counterintuitive effects, such as the honeymoon effect, in which partially effective controls

21 cause not only a greater initial reduction in infection than expected for an infection near its

22 endemic equilibrium, but also large outbreaks during control as a result of accumulation of

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23   susceptibles. Unfortunately, many control measures cannot be maintained indefinitely, and the

24   results of cessation are not well understood. Here, we examine the results of stopped or failed

25   non-immunizing control measures in endemic settings. By using a mathematical model to

26   compare the cumulative number of cases expected with and without the control measures, we

27   show that deployment of control can lead to a larger total number of infections, *counting from*

28   *the time that control started*, than without any control – the *divorce effect*. This result is

29   directly related to the population-level loss of immunity resulting from non-immunizing

30   controls and is seen in model results from a number of settings when non-immunizing controls

31   are used against an infection that confers immunity. Finally, we also examine three control

32   plans for minimizing the magnitude of the divorce effect in seasonal infections and show that

33   they are incapable of eliminating the divorce effect. While we do not suggest stopping control

34   programs that rely on non-immunizing controls, our results strongly argue that the

35   accumulation of susceptibility should be considered before deploying such controls against

36   endemic infections when indefinite use of the control is unlikely. We highlight that our results

37   are particularly germane to endemic mosquito-borne infections, such as dengue virus, both for

38   routine management involving vector control and for field trials of novel control approaches.

39

40   **Author Summary**

41   Many common endemic infections lack effective, inexpensive vaccinations, and control relies

42   instead on transmission reduction, e.g. mosquito population reduction for dengue. Often,

43   these controls are used with the immediate goal of decreasing the current incidence with little

44   importance placed on what will happen at later points in time, and much less what will happen

45   once the control is stopped. Here, by looking at the cumulative incidence since the beginning

46   of the control period, instead of the instantaneous incidence, we show that when controls are

47   stopped, or fail, the resulting outbreaks can be large enough to completely eliminate any

48   benefit of the control. We call this result the *divorce effect*. Further, we show that this result is

49   not limited to specific transmission pathways or epidemiological parameters, but is instead tied

50   directly to the reduction of herd immunity inherent in non-immunizing controls. Lastly, by

51   evaluating programs to minimize the magnitude of the divorce effect, we show that without

52   maintaining herd immunity, or successfully continuing control for decades, it is impossible to

53   keep the costs of post-control outbreaks from outweighing the benefits of the control program.

54

Introduction

56   An estimated 200 million cases of malaria, 390 million cases of dengue fever, and 9 million

57   cases of measles occurred in 2016 [1,2], representing only a portion of the total impact of

58   endemic disease that year. The burden that this places on local populations, both in terms of

59   morbidity and mortality and both direct and indirect economic costs, often pressures policy

60   makers to act to suppress these infections. However, the scientific rationale on which the

61   implemented policies are based is not always clear, making it difficult to assess whether the

62   risks associated with control have been adequately addressed.

63

64   Eradication— the permanent reduction of worldwide incidence to zero [3]— is the ideal aim of

65   all control programs. This goal is unrealistic, with only two infections having been successfully

66   eradicated to date: smallpox and rinderpest [4]. Often, a more realistic goal for a control

3

67   program is either long-term suppression or local elimination of the infection. These goals hold

68   their own challenges though, as they require long-term or even indefinite control programs,

69   which can face budgetary and public support issues, not to mention the potential for some

70   controls to fail due to evolution of resistance. Further, if there is a loss of herd immunity in the

71   population due to the control lowering population exposure to the pathogen, there is the

72   additional risk that when a control program ends the infection will re-emerge in a post-control

73   epidemic and reestablish in the population [4].

74

75   Naively, one might imagine that lowering the incidence of infection will have no detrimental

76   effects for the population. However, mathematical modeling has previously revealed

77   numerous perverse outcomes of application of ineffective control measures (by which we mean

78   ones that do not bring the basic reproductive number, R_0, below one) in endemic settings.

79   Perhaps the most famous example is the increased age at infection that results when a

80   population is partially vaccinated for rubella, leading to more infections occurring in women of

81   child-bearing age, where severe complications, such as congenital rubella syndrome, can result

82   when pregnant women become infected [5–7]. While this certainly represents a potential

83   downside of the control, the population sees a reduction in rubella prevalence. McLean and

84   Anderson (1988) showed that when an ineffective control is used against an endemic infection

85   it often results in an initial drop in prevalence to well below the endemic level, the "honeymoon

86   effect", but this is followed by outbreaks that periodically increase prevalence above the

87   endemic level as a consequence of a build-up of susceptible individuals. Similarly, in a

88   seasonally-forced setting, Pandey and Medlock [9] found that vaccination against dengue virus

89   could result in a transient period with periodic outbreaks of larger peak prevalence than

90   occurred before vaccination. These last two examples illustrate possible negative side effects

91   of ineffective controls: they can cause transient increases in prevalence while still resulting in a

92   decrease in total incidence.

93

94   In the results above, there is higher incidence than expected, but Okamoto et al.[10] described

95   an even more troubling theoretical result while exploring a model of failed or stopped

96   combined strategies aimed at controlling dengue virus, e.g. vaccination along with transgenic

97   vector control. They observed that when control was only transient the **total** number of

98   infections that occurred, counting from the time that control started, a quantity they called the

99   cumulative incidence (CI), could exceed the number of cases that would have been observed

100   had no control been deployed. Even in situations where control measures had a significant

101   positive impact over a period of years, the outbreaks that ensued following the cessation, or

102   failure, of control could lead to an outbreak that was large enough to outweigh the number of

103   cases prevented during the control period.

104

105   While Okamoto et al. [10] showed that it was possible for transient transgenic controls to

106   increase the total number of infections, here we demonstrate that this effect—which we call

107   the *divorce effect*—is not an artifact of very specific complex models, but quite a general

108   phenomenon that can occur across a range of models and parameter space when deploying a

109   control measure that does not confer immunity. By exploring the dynamics of the divorce effect

110   in the setting of several simple models we gain insights that were not obtainable using the

111   previous complex models. Conversely, we find that for immunizing controls (e.g. vaccination)

112   the divorce effect does not occur, even when the duration of protection is relatively short-lived.

113

114   We demonstrate the generality of this result for endemic infections by simulating cessation of

115   control measures in three commonly-used models for pathogen transmission. Unlike the

116   honeymoon effect, the divorce effect occurs for both ineffective and effective controls,

117   provided that they are transient. As anticipated, control results in the accumulation of

118   susceptible individuals resulting in the potential for a large outbreak following the cessation of

119   control. This outbreak is either triggered by infective individuals that remain in the population

120   or by reintroduction of infection from outside the control area, and its size increases

121   asymptotically towards the size of a virgin-soil epidemic as the length of the control period is

122   increased and herd immunity is lost. Counterintuitively, and comparable to results in Okamoto

123   et al. [10], we see that the post-control outbreak often results in there being timeframes over

124   which the cumulative incidence of infection since the start of control is higher than would have

125   occurred in the absence of control. Further, these outbreaks are significantly larger than the

126   endemic levels of the infection and would likely overwhelm healthcare providers in the area.

127

128   This paper is organized as follows. We first describe the three models we choose to illustrate

129   the divorce effect: a non-seasonal SIR model, a seasonal SIR model, and a host-vector model.

130   We then demonstrate, in each setting, the occurrence of the divorce effect and its sensitivity to

131   relevant parameters, namely R_0 and the duration and strength of control. Further, for the

132   seasonal SIR model, we explore the sensitivity of the strength of the divorce effect on the

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133   timing of the start and end of the control. Then for the seasonal SIR and seasonal host-vector

134   model we look at three possible strategies for mitigating the divorce effect and show they are

135   incapable of eliminating the divorce effect. A crude analytical approximation for the divorce

136   effect and additional models are explored in the Supplemental Information, as is the impact of

137   using immunizing controls.

138

Models

140   To evaluate the magnitude of the Divorce Effect, we simulate the cessation of a short-term

141   control affecting transmission in three infection systems: a SIR model, a seasonal SIR model,

142   and a host-vector SIR model. While these are the only models we discuss in detail here, this

143   result can be seen in most models that have a replenishment of the susceptible population,

144   including the more general SIRS model, for which host immunity is not life-long, and an age-

145   structured model with realistic mixing parameters (see Supplemental Information for

146   exploration of additional forms of transmission models). These results are parameterized for a

147   human population and mosquito vector, but the results are generalizable to other species.

148

SIR Model:

150   We assume a well-mixed population of one million hosts and a non-fatal infection that is

151   directly transmitted and confers complete life-long immunity. The numbers of susceptible,

152   infective, and removed individuals are written as S, I and R, respectively. We allow for

153   replenishment of the susceptible population by births, but assume the population size is

154   constant by taking per-capita birth and death rates, μ, to be equal (this assumption is relaxed in

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155   the supplemental information). This results in the standard two-dimensional representation of

156   the SIR model, where the number of removed individuals is $R = N - S - I$ (Equation 1).

$$\dot{S} = \mu(N - S) - \beta\frac{S(I + I_b)}{N} \tag{1}$$

$$\dot{I} = \beta\frac{S(I + I_b)}{N} - (\gamma + \mu)I$$

159   For our simulations, we assume parameters resembling a short-lived infection in a human

160   population, lasting on average 5 days (average recovery rate, $\gamma = 73/\text{year}$) and that individuals

161   live on average 60 years ($\mu = .0167/\text{year}$), allowing the transmission parameter, β, to be

162   adjusted to achieve the desired value of R_0. In order to reseed infection following cessation of

163   control and to counter the well-known weakness of infective numbers falling to arbitrarily low

164   levels in deterministic transmission models, we follow numerous authors in including a constant

165   background force of infection [11,12] in the model. This represents infectious contacts made

166   with other populations, and occurs at a rate that is equivalent to there being I_b additional

167   infective individuals within our focal population. For our simulations, we take $I_b = 1$(sensitivity

168   of our results to I_b can be found in the supplemental information).

169

170   **Seasonal SIR Model:**

171   For the seasonal SIR model, we allow the transmission parameter to fluctuate seasonally

172   (annually) around its mean, β_0, taking the form given in Equation 2. Seasonal oscillations in the

173   parameter have relative amplitude $\beta_1 = .02$ with maxima occurring at integer multiples of 365

174   days. Noting that seasonally forced models are particularly susceptible to having the number of

175   infectives fall to unreasonably low numbers between outbreaks [13], we again take $I_b = 2$ in

176   the background force of infection term.

177

$$\beta(t) = \beta_0\big(1 + \beta_1 \cos(2\pi t)\big) \tag{2}$$

178

179   **Host-Vector Model:**

180   We model an infection with obligate vector transmission. As in other models, we assume that

181   the host population size is held constant ($R = N - S - I$), but we allow the vector population

182   size to fluctuate—so that, for instance, we can model vector control. For simplicity, we only

183   model the female adult vector population and assume density-dependent recruitment into the

184   susceptible class (U), with a logistic-type dependence on the total female adult population size.

185   Infectious vectors (V) arise from interactions with infected hosts (Equation 3).

186

$$\dot{S} = \mu(N - S) - \beta_{VH}\frac{SV}{N}$$

187

$$\dot{I} = \beta_{VH}\frac{SV}{N} - (\gamma + \mu)I \tag{3}$$

188

$$\dot{U} = (U + V)\big(r - k(U + V)\big) - \beta_{HV}\frac{U(I + I_b)}{N} - \delta(t)U$$

189

$$\dot{V} = \beta_{HV}\frac{U(I + I_b)}{N} - \delta I$$

190   We assume that host demography and recovery rates are the same as in the SIR model, with a

191   host population of one million individuals. We assume that the vector lives on average 10 days

192   ($\delta = 36.5$/year), the growth constant (r) and density dependence parameter (k) are

193   parameterized as in Okamoto et al. (2016): $r = 304.775$/year and $k =$

194   1.341×10^{-7}/(vector*year), resulting in an equilibrium vector population of 2 million

195   individuals. The transmission parameter from host to vector (β_{HV}) is assumed to be 109.5/year

196   and the parameter for vector to host (β_{VH}) is changed to produce the desired R_0. We again

197   assume a background force of infection (with $I_b = 2$), representing reintroduction of infection

198   from outside our focal population.

199

200   Seasonality plays a large role in vector-borne infections and affects many aspects of the

201   infection and its vector. Temperature affects breeding rates, larval development, and death

202   rates of the vector, the extrinsic incubation period and transmissibility of the infection itself,

203   and host encounter rates, while precipitation can affect the availability of appropriate habitat

204   and encounter rates [14–16]. However, most of these add a level of model complexity which is

205   unnecessary for this study, so we choose to use a simple forcing term for mosquito recruitment

206   that fluctuates seasonally with relative magnitude r_s ($r_s = 0.02$) about its baseline ($r_0 = $

207   304.775 /year) (Equation 4).

208
$$r(t) = r_0(1 + r_s \cos(2\pi t)) \tag{4}$$

209

210   **Control:**

211   We model a control that is applied instantaneously and consistently from time t_0 (which, for

212   simplicity, we usually take to be equal to zero) to time t_{end} and is instantaneously removed at

213   the end of the control period. In the SIR and seasonal SIR models, control reduces the

214   transmission rate by some proportion, ε, and, in the host vector model, causes a proportional

215   increase, σ, in the vector mortality rate. This results in the transmission parameter given in

10

216   Equation 5 for directly transmitted infections and the vector death rate given in Equation 6 for

217   the vector-borne infections.

218
$$\beta(t) = \begin{cases} (1 - \varepsilon)\beta_0 & t_0 < t < t_{end} \\ \beta_0 & \text{otherwise} \end{cases} \tag{5}$$

219

220
$$\delta(t) = \begin{cases} (1 + \sigma)\delta_0 & t_0 < t < t_{end} \\ \delta_0 & \text{otherwise} \end{cases} \tag{6}$$

221

222   While we only look at these control measures in the main text, other controls (such as an

223   increase in the recovery rate, γ) are explored in the Supplemental Information (Figure S2), and

224   give similar results.

225

226   **Measuring Effectiveness:**

227   There are a number of measures that can be used to quantify the effectiveness of a control. We

228   want to characterize the total number of cases that occur from the start of control until a

229   particular point in time, a quantity we call the cumulative incidence (CI). For a directly

230   transmitted infection, this is calculated as follows

231

232
$$CI(t) = \int_{t_0}^{t} \frac{\beta(\tau)S(\tau)I(\tau)}{N} d\tau, \tag{7}$$

233

234   i.e. by integrating the transmission term over the time interval from the start of control until

235   the time, t, of interest. This quantity could be calculated both in the presence of control and in

11

236   the baseline, no-control, setting; we distinguish between these two by labeling quantities (e.g.

237   state variables) in the latter case with a subscript B to denote baseline.

238

239   One commonly-used measure of effectiveness is the number of cases averted by control (CA),

240    $CI_B(t)$ - $CI(t)$. This has the disadvantage (particularly in terms of graphical depiction) that it can

241   become arbitrarily large as t increases. Consequently, some authors choose to utilize a relative

242   measure of cases averted, dividing by the baseline cumulative incidence (see, for instance, the

243   work of Hladish et al. [17]). We instead follow our earlier work and use the relative cumulative

244   incidence (RCI) measure employed by Okamoto et $al.$ [10], calculating the cumulative incidence

245   of the model with the control program relative to the cumulative incidence of the model

246   without the control program (Equation 8).

247

248
$$RCI(t) = \frac{\int_{t_0}^{t} \beta(\tau)S(\tau)I(\tau)d\tau}{\int_{t_0}^{t} \beta S_B(\tau)I_B(\tau)d\tau}. \tag{8}$$

249

250   RCI(t) values above one imply that the control measure has resulted in an increase in the total

251   number of cases compared to the baseline. Importantly, as time becomes larger, RCI becomes

252   less sensitive to outbreaks in the system. For a transient control, RCI will approach 1 as t

253   becomes larger.

254

255   We see that the relative cases averted measure employed by Hladish et al. [15] is simply 1-

256   RCI(t). Both relative measures have properties that make them attractive for graphical

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257   depiction although it should be borne in mind that both involve a loss of information on the

258   actual number of cases averted. For example, an RCI of 1.1 after one year is a much smaller

259   increase in total cases than an RCI of 1.1 after 10 years, and an RCI of just below one after many

260   years can represent a large reduction in total incidence. In cases where this information is

261   pertinent, it may be more appropriate to use non-relative measures such as cases averted. The

262   choice of measure does not impact the occurrence of the divorce effect; figures that show

263   cases averted are included in the Supplemental Information (Figure S1).

264

265   Analogous expressions for CI and RCI can be written for the host-vector model using the

266   appropriate transmission terms.

267

268   **Results**

269   **SIR Model**

270   Simulations show the successful suppression of infection following the implementation of a

271   control which reduces the transmission parameter, β, in the population. With infection at

272   endemic equilibrium, the honeymoon effect [8] states that even a modest reduction in the

273   transmission parameter will have a large effect on the incidence of the infection due to the

274   effective reproductive number, R_t, the expected number of new infections each infectious

275   individual causes, being one. After the control is stopped, the incidence of the infection

276   remains low for some time as the number of infective individuals builds from very low numbers

277   (Figure 1(a), curve). However, once control ends R_t immediately rises above one and continues

278   to increase while prevalence is low, due to the buildup of the susceptible population (plots of R_t

13

279   and $S(t)$ are provided in the supplemental information: see Figure S3). This increased R_t

280   eventually drives a large outbreak, quickly depleting the susceptible population, at which point

281   incidence (Figure 1(a), black curve), and R_t, again fall to low numbers.

282

283   To evaluate the success of the control, we examine the RCI in the period following introduction

284   of control and see that during and immediately following the control period, when incidence is

285   low, the RCI decreases towards 0, suggesting a successful control program. However, once the

286   post-control outbreak begins, RCI increases rapidly resulting in the divorce effect (RCI>1) before

287   dropping back below one once the epidemic begins to wane and incidence falls below endemic

288   levels (Figure 1(a)). During the period where RCI>1, lasting approximately 2 years in our

289   example, the control has not only failed to decrease the total incidence of infection but has

290   resulted in an increase in total incidence, the divorce effect. Following this initial outbreak and

291   trough, RCI continues to oscillate around one, and approaches one in the long run (see Figure

292   S4).

293

294   Exploring values of R_0 and the duration and strength of control shows that the divorce effect is

295   present over a wide region of parameter space. Figure 1(b) shows the magnitude of the divorce

296   effect, quantified by the maximum RCI seen, as a function of R_0 and duration of control for a

297   perfect control measure ($\beta = 0$ during the control period). Perfect control was employed here to

298   eliminate any confounding effects from the honeymoon effect that could occur during an

299   imperfect control. We find that for the most biologically relevant area of parameter space

300   (R_0<20, control lasting less than 20 yrs) the divorce effect always occurs and will result in a 20-

14

301   60% increase in cumulative incidence (RCI=1.2-1.6) at its peak. However, we also find that it is

302   possible to avoid the divorce effect if controls are maintained long enough. For infections with

303   a high R_0, this requires maintaining the control for decades, and the length of time needed

304   grows as R_0 is decreased. The non-monotonic relationship between the magnitude of the

305   divorce effect and the length of the control seen here suggests that a control program should

306   either be discontinued immediately, if R_0 is small, or continued as long as possible to avoid the

307   divorce effect (Figure 1(b); see also Figure S5 in Supplemental Information).

308

309   Relaxing our assumption of a completely effective control and focusing on a fixed R_0 (R_0=5,

310   Figure 1(c)), we see that the relationship between the magnitude of the divorce effect and the

311   length of the control period varies with the strength of the control. A steep edge-like pattern is

312   seen in Figure 1c when control is ineffective but carried out for a long period of time, a

313   consequence of the honeymoon effect. For populations at endemic equilibrium, the

314   honeymoon effect means that any reduction in transmission will be sufficient to significantly

315   reduce transmission for a period of time. For controls that are relatively short lived, here

316   approximately 5 years, the control does not outlast the honeymoon period, resulting in the

317   magnitude of the divorce effect being relatively insensitive to the effectiveness of the control in

318   this region of parameter space. How the interaction between the effectiveness of control and

319   R_0 affects the magnitude of the divorce effect is explored in the supplemental information

320   (Figure S6).

321

322   **Seasonal SIR Model**

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323   Temporary control measures in the seasonal SIR model show many of the same dynamics as in

324   the non-seasonal model, namely that a successful control is followed by a period of low

325   incidence and eventually a post-control outbreak leading to a divorce effect (Figure 2(a)) before

326   settling back into regular seasonal outbreaks (Figure S7). However, the timing and size of the

327   post-control epidemic, and thus the magnitude of the divorce effect, depend not only on R_0 and

328   the length of the control but also the timing of both the onset and end of the control (Figures

329   2(b) and 2(c)). This leads to a highly nonlinear dependence of the magnitude of the divorce

330   effect on R_0 and the duration of control (Figure 2(b)). However, the presence of ranges of

331   parameter space with smaller magnitudes of the Divorce Effect at regular intervals could allow

332   policy makers to determine optimal times to stop control. These effects become more

333   apparent with an increase in seasonality (Figure S8). As seasonality increases, the differences

334   due to timing become more pronounced, resulting in more potential for mitigating the divorce

335   effect with a properly timed treatment. Conversely, this also means a larger divorce effect will

336   be seen with a poorly timed treatment (Figure S8).

337

338   The oscillatory nature of the relationship between the maximum RCI and R_0 (Figure 2(b))

339   implies a relationship between the timing of the control period and the severity of the divorce

340   effect. While the magnitude is only highly sensitive to the start time for very short control

341   periods, lasting around a year, it is highly sensitive to the end time (Figure 2(c)). This means

342   that controls of similar lengths can have significantly different outcomes depending on their

343   timing, e.g. a 1 year control ending day 700 results in a maximum RCI around 1.4 while a control

344   of the same length ending day 515 results in a maximum RCI near 1.7. This is a direct result of

16

345   the seasonal forcing function and delaying the outbreak until a period in which R_0 is larger,

346   similar to results seen when controls are used against epidemics in seasonal settings [18,19].

347   Regardless of start time, the optimal end time occurs shortly after the peak in the transmission

348   parameter, $\beta(t)$, (days 750 and 1155 in Figure 2(c)), suggesting this would be the best time to

349   end control programs.

350

351   **Host-Vector Model**

352   The non-seasonal host-vector model has broadly similar dynamics to the non-seasonal SIR

353   model in terms of the divorce effect (Figures S10 and S11), so here we focus instead on the

354   seasonal host-vector model. Following one year of insecticide treatment that reduces the

355   average mosquito lifespan by a half (i.e. increases the mosquito death rate by 100%, $\sigma = 1$) the

356   infection is suppressed and there is no seasonal outbreak for the next two years (Figure 3). A

357   major outbreak, with approximately eight times the peak prevalence of the pre-control

358   seasonal outbreaks, occurs in the third year and results in a maximum RCI of around 1.50,

359   before the epidemic fades and incidence again returns to low levels. The size of this outbreak

360   would almost certainly risk overwhelming even the most well-funded medical services. RCI then

361   remains above 1 until year 7. The population continues to see large periodic outbreaks, each

362   bringing RCI back above 1, for decades until the endemic equilibrium is reached again (Figure

363   S12).

364

365   **Mitigating the Divorce Effect**

17

366   It is apparent from earlier results (e.g. Figure 1(b)) that avoiding the divorce effect in a non-

367   seasonal setting is only possible with a non-immunizing control by maintaining suppression for

368   decades, due to the inevitable build-up of susceptible individuals. Therefore, the goal in these

369   situations should be to maintain the control as long as possible or until a vaccine becomes

370   available, and we focus instead on the seasonal SIR and host-vector models. In this section, we

371   look at three different treatment plans for deploying a set amount of treatment, twelve one-

372   month treatments, and their ability to mitigate the divorce effect. The first relies on annual

373   controls lasting one month when R_0 is at its maximum, the second has a month-long control

374   applied in response to the prevalence reaching some set level—which we might imagine

375   corresponding to an outbreak becoming detectable or reaching a sufficient level to cause

376   concern to local authorities—that we take here to be when two hundred individuals out of a

377   million are infective, and the third chooses when to implement a month-long control based on

378   minimizing the peak RCI. For comparison, all three use 12 total months of control.

379

380   With annual monthly control for a directly transmitted seasonal infection, the population sees a

381   significant initial reduction in prevalence. However, as predicted by the honeymoon effect, the

382   repeated use of controls results in a diminished effect on the prevalence and seasonal

383   outbreaks begin to occur between control periods. The peak prevalence of these outbreaks

384   quickly grows to be significantly larger than the seasonal outbreaks before the control program

385   was begun, however they are blunted by the next control period before RCI rises above one.

386   Once the program is ended, however, a post-control outbreak quickly brings RCI above one

387   (Figure 4(a)).

388

389   The reactive control has a similar effect following the initial control period, however it results in

390   ever more rapid need for control, exhausting all 12 months of treatment in the first four years

391   for both the directly transmitted infection (Figure 4(b)). We see that while this results in a

392   lower RCI during the control program, it results in an even larger post-control outbreak and a

393   larger maximum RCI for both transmission pathways.

394

395   Intuitively, Figure 2(c) suggests choosing a time period to implement the control that will

396   minimize the divorce effect. To do this, we implement a third method which optimally chooses

397   the time at which to begin the next control period. For this, we simulate the first one month

398   control period, beginning at time 0. Then we run simulations with the next one month control

399   beginning on all possible days over the next 365 days after the control ends, choosing the day

400   that results in the lowest maximum RCI over the next decade, simulating through that control

401   period, and repeating. This plan results in implementing the first three control periods in rapid

402   succession and the remainder after the peak of an outbreak, when the control will have the

403   least effect on transmission (Figure 4(c)), minimizing the magnitude of the divorce effect albeit

404   at the cost of not providing significant protection against the infection. This result, along with

405   other earlier results, suggests that the divorce effect is unavoidable and the potential for a

406   divorce effect will continue to grow in magnitude unless the control is maintained for decades,

407   regardless of the timing of the treatments. While it may not be possible to eliminate the

408   divorce effect for relatively short controls, it may be possible to extend programs without

409   worsening the divorce effect and to minimize the divorce effect by carefully choosing the timing

410   of the end of the control program once cessation becomes necessary.

411

412   In the case of host-vector transmission, the yearly control successfully suppresses the infection

413   for the first 1.5 years, however the population begins to experience outbreaks during what was

414   traditionally the off-season. After the control program is ended, the population enters a period

415   of larger outbreaks occurring every three years (Figure S15(a)). The reactive control sees a

416   similar result as the directly transmitted disease, with all twelve treatments used in the first 4

417   years (Figure S15(b)). For the third method, the optimal plan was to wait the maximum amount

418   of time to deploy the control (Figure S15(c)). This is likely due to the peak of on outbreak not

419   occurring within a year of the end of treatment in the seasonal host-vector model.

420

421   **Additional Results**

422   Results for additional models, along with an analytical approximation to the magnitude of the

423   divorce effect are included in the supplemental information.

424

425   **Discussion**

426   It has long been appreciated that non-immunizing control measures deployed against endemic

427   infections will result in a large short-term reduction in prevalence but will lead to a reduction in

428   herd immunity, leaving the population at risk of large outbreaks after the cessation of control.

429   Here we have shown, in quite general settings, that these outbreaks can be so large as to

430   increase, counting from the time that control started, the total incidence of infection above

431   what would have occurred if no control had been used—a result we call the divorce effect. This

432   represents a failure for control of the worst kind, namely a control that increases the total

433   incidence of the infection. Unfortunately, many commonly used disease control plans rely on

434   temporary non-immunizing controls, meaning that populations may be left at risk of the divorce

435   effect once the control measure is ended.

436

437   Controls that do not confer immunity—including isolation, use of drugs as a prophylaxis or to

438   shorten duration of infectiousness or behavioral changes such as social distancing—are often

439   deployed in epidemic settings, particularly for new pathogens for which a vaccine is

440   unavailable, but may also be used to blunt seasonal outbreaks of endemic diseases.   In these

441   endemic settings, we have shown that it is important to weigh any potential benefit from these

442   controls against the risk of post-control outbreaks and the divorce effect. While there are

443   timeframes over which a temporary non-immunizing control has benefits, the severity of the

444   post-control outbreak that results in the divorce effect will risk overwhelming even well-

445   maintained healthcare systems.

446

447   Vector-borne infections represent the most common situation in which non-immunizing

448   controls are regularly used against endemic diseases, e.g. insecticide spraying to combat

449   seasonal dengue outbreaks. The honeymoon effect predicts that insecticides can provide

450   short-term benefits in endemic settings but that the additional benefit of continued spraying

451   will decrease over time due to the accumulation of susceptibles (i.e. depletion of herd

452   immunity) that results. Indeed, Hladish *et al.* [17] saw precisely these effects using a detailed

453   agent-based model for dengue control that employs indoor residual spraying. Cessation of

454   spraying will be expected to lead to large post-control outbreaks: again, Hladish *et al.*'s model

455   exhibited annualized incidence of 400% compared to the uncontrolled baseline setting in

456   certain years. Here, we examine the divorce effect directly and show that they are not specific

457   to a host-vector model and that if the control is not maintained indefinitely, or at least for a few

458   decades, the damage of the divorce effect can quickly outweigh the short-term benefits.

459   Further, programs implementing insecticides may be intended to be indefinite, but the

460   evolutionary pressure imposed can result in the rapid and unpredictable evolution of

461   resistance. Without proper monitoring, this could result in an increase in total incidence due to

462   the divorce effect before officials realize that resistance has developed. While insecticides, and

463   other non-immunizing controls, will, and should, continue to play an important role in epidemic

464   settings, where herd immunity is negligible, the results of this study raise important questions

465   about their use in combating endemic infections.

466

467   In some instances, control measures are deliberately transient in nature, such as field trials for

468   assessing the impact of proposed novel control methods, e.g. a review of field trials of dengue

469   vector control showed they lasted between 5 months and 10 years [20]. Multiple year field

470   trials such as these can result in considerable build-up of the susceptible population, meaning

471   consideration needs to be given to the consequences of this accumulation and the potential for

472   large outbreaks to occur in the wake of cessation of the trial. If our results are validated, they

473   must be factored not only into the design of such trials but also into the informed consent

474   process for trial participation, with participants made aware of the risk of the divorce effect and

475   plans put in place to provide a reasonable level of protection during and following the study. As

476   we have shown, these outbreaks can occur months or even many years later, and while disease

477   incidence would be observed closely during the trial, our results argue that monitoring should

478   continue for an appropriate length of time following the cessation of control. Furthermore, we

479   emphasize that the epidemiological consequences of the honeymoon effect—specifically the

480   relative ease of reducing incidence for an infection near endemic equilibrium—must be kept in

481   mind when interpreting the results of such trials. Together, these dynamical effects argue that

482   susceptibility of the population to infection should be monitored together with incidence to

483   fully assess the impact and effectiveness of the control.

484

485   Additional concerns are raised when an endemic and an epidemic infection share the same

486   transmission pathway (e.g. *Aedes aegypti* vectoring both dengue and Zika). Emergency control

487   against the epidemic infection also impacts the endemic infection, leading to the potential for

488   the divorce effect to occur in the latter if the control is ceased once the epidemic has subsided.

489   It may be that policy makers have to choose to allow an epidemic of a highly publicized, but low

490   risk, epidemic in order to maintain immunity levels of another lower profile, but more

491   dangerous, disease. On the other hand, if the risk due to the epidemic is sufficiently high, it

492   may still be advantageous to use the control, however the risks need to be carefully compared

493   and an informed decision, that accounts for the divorce effect, needs to be made.

494

495   While transient non-immunizing controls are common and provide opportunities to observe the

496   divorce effect, researchers tend to focus on prevalence or incidence over short periods of time

23

497   and not cumulative measures such as CI or relative measures such as RCI or CA, which would

498   expose the divorce effect. Even when relative measures are used, such as Hladish et al. [17],

499   the time frame over which incidence is compared can have a drastic effect on the

500   interpretation of the result. The divorce effect is an easily missed phenomenon, even when

501   examining models that lack much of the real-world complexity, but real-world data comes with

502   a myriad of other problems. Often the divorce effect may occur when the system is poorly

503   monitored, as with field trials and unintentional control, in systems that, like dengue, have

504   large year-to-year variation, or in systems where the failure is associated with other

505   confounding socio-economic events such as war or natural disaster, resulting in data that is

506   either scarce or difficult to interpret. The divorce effect may become more apparent in coming

507   years, though, as mosquito control is lessened following the end of the Zika epidemic, allowing

508   for a rebound in dengue in areas such as South America, and as insecticide resistance problems

509   continue to grow.

510

511   Careful thought should be given to whether or not it is appropriate to begin new programs that

512   rely on non-immunizing controls in endemic settings. This is an inherently complicated decision

513   that must take into account numerous factors, both scientific and sociopolitical, but, in light of

514   our results, policymakers should carefully weigh the risks of the divorce effect against other

515   factors, e.g. imminent approval of a new vaccine or political pressure, before implementing

516   disease management plans that rely on non-immunizing controls. Further, it is important that

517   when non-immunizing controls are included in these management plans that they are not

24

518   considered possible solutions but instead stop-gaps, and emphasis is placed on the

519   development of vaccination as opposed to the indefinite continuation of the program.

520

521   Currently, control of endemic diseases worldwide, especially vector-borne diseases, relies

522   heavily on non-immunizing controls such as insecticide. Policy makers should begin developing

523   exit plans for these disease management programs —guidelines for safely ending the program

524   when it becomes clear that indefinite maintenance is unlikely, which should be designed to

525   minimize the impact of the divorce effect. In this paper, we have shown three possible designs

526   for exit plans that could minimize the divorce effect. However, none of these designs were

527   capable of eliminating the divorce effect. Our results suggest there is an inherent cost

528   associated with the loss of immunity resulting from these programs.

529

530

531   **Acknowledgements**

534

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596   **Figure 1: The divorce effect in the SIR model. (a) Typical time-series showing the divorce**

597   **effect.** Beginning at time zero, a year-long 50% reduction in the transmission parameter of an

598   endemic infection ($R_0 = 5, \beta = 365$ /year, $\gamma = 73$ /year) reduces prevalence of the infection

599   to near zero for the length of the control, where it remains until time 1.5 yrs, at which point a

600   large post-control outbreak occurs. RCI falls towards zero as prevalence remains low, but the

601   post-control outbreak is large enough to bring RCI well above 1 (peak RCI is approx. 1.4). **(b)**

602   **Magnitude of divorce effect in terms of relative cumulative incidence (RCI).** Maximum RCI is

603   found as the highest value of RCI observed within 25 yrs following a 100% effective control of

604   an infection with 1<R_0<20 and lasting between 1 month and 35 years. RCI>1 indicates the

605   divorce effect and we see that the divorce effect occurs across a large portion of the parameter

606   space, and ubiquitously for controls lasting less than 20 years. β is varied to attain the desired

607   R_0, all other parameters as in (a). **(c) Maximum RCI for a given effectiveness and duration of**

608   **control.** The maximum RCI is found as the maximum observed RCI within 25 yrs after the end

609   of a control that is between 0% and 100% effective and lasts between 1 month and 20 years

610   (R_0=5). The ridge between areas of high and low maximum RCI results from ineffective controls

611   being maintained long enough for outbreaks due to the honeymoon effect deplenishing the

612   population of susceptible individuals before the control periods end. All other parameters as in

613   (a).

614

615

616   **Figure 2: The divorce effect in the seasonal SIR model. (a) Typical time-series showing the**

617   **divorce effect.** Beginning at time zero, when the transmission parameter is at its maximum, a

618   year-long 90% reduction in the transmission parameter of an endemic infection ($R_0 = 5, \beta_0 =$

619   365 /year, $\beta_1 = .02, \gamma = 73$/year) is implemented at the beginning of a seasonal outbreak and

620   reduces prevalence of the infection to near zero for the length of the control. Following the

621   end of the control, a large outbreak, many times the size of the regular seasonal outbreaks,

622   occurs during the next season. RCI falls towards zero as prevalence remains low while the

623   control is in effect and rises above 1 during the large outbreak the following year (Maximum RCI

624   = 1.2). **(b) Magnitude of divorce effect in terms of relative cumulative incidence (RCI).**

625   Maximum RCI is found as the highest value of RCI observed within 25 yrs following a 100%

626   effective control of an infection with 1<R_0<20 and lasting between 1 month and 35 years. RCI>1

627   indicates the divorce effect and we see that the divorce effect occurs in most of the parameter

628   space. β_0 is varied to attain the desired R_0, with all other parameters as in (a). **(c) Effect of**

629   **timing on the magnitude of the divorce effect.** Maximum RCI is the highest RCI observed

630   within 25 yrs following a 100% effective control of an infection with $R_0 = 10$ $(\beta =$

631   730 /year, all other parameters as in (a)) beginning and ending on specified days. Dashed

632   lines represent controls lasting either 1, 2, or 3 years. Unlike the non-seasonal SIR model

633   (Figure 1), the magnitude of the divorce effect is not solely dependent on R_0 and the length of

634   the control. Maximum RCI is most sensitive to the day the control is ended, moderately

635   sensitive to the day it is started, and only slightly sensitive to the length of the control. This is

636   due to the timing of the end of the control determining the timing of the outbreak. We also see

637   that continuing the control for another year often has little impact on the magnitude of the

638   divorce effect.

639

640   **Figure 3: Divorce Effect in a Seasonal Host-Vector model.** Control is shown in a seasonal $(r_s =$

641   .02) host-vector model with $R_0 = 5$. Beginning at time zero, a control is implemented that

642   increases the vector mortality rate by 100% (corresponding to a 50% drop in vector life

643   expectancy). This results in a reduction in prevalence (black curve) of the infection to near zero

644   during the control period, where it remains until roughly time 3 yrs, at which point a large post-

645   control outbreak occurs. RCI (red curve) falls towards zero during the control period and while

646   prevalence remains low, but the post-control outbreak is large enough to bring RCI above 1

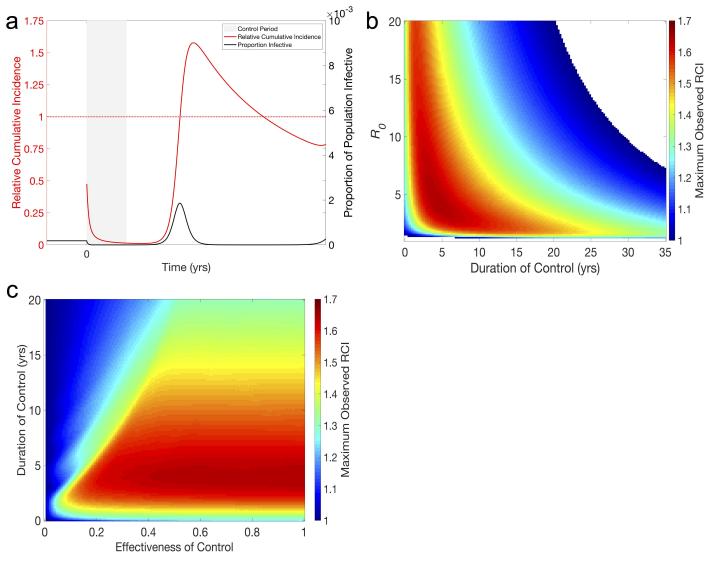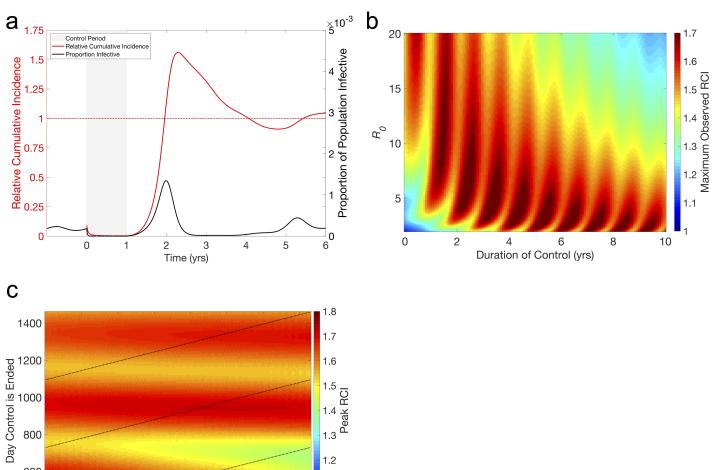647   (peak of approx. 1.49).

648

649 **Figure 4: Suggested techniques for mitigating the divorce effect with seasonal transmission.**

650 We consider an endemic disease, parameterized as in Figure 2(a). In all cases, twelve 1/12 yr.

651 controls are used, to be consistent with the 1 yr. controls used in other figures, reducing the

652 transmission parameter by 90% ($\epsilon = .9$). **(a) Pulsed control for Seasonal SIR model.** Control

653 occurs yearly at a fixed time (when R_0 is highest) for a fixed time (1/12 yr.) to control an

654 endemic disease (parameterized as in Figure 2(a)). The control is effective at stopping the

655 outbreak the first year, but seasonal outbreaks in subsequent years are larger, driven by an

656 increasing population of susceptible individuals. Stopping the control program still results in a

657 large post-control outbreak and a divorce effect. **(b) Reactive Control for Seasonal SIR.** A fixed

658 length (1/12 yr.) control is implemented to control an endemic disease (parameterized as in

659 Figure 2(a)) once prevalence rises above a threshold (200 individuals in a population of 1

660 million). This stops the large early season outbreaks seen in the pulsed control, however the

661 frequency of treatment increases as the susceptible population grows. Stopping the control

662 program results in a large outbreak and divorce effect. **(c) Informed Control in seasonal SIR**

663 **model.** The first control period occurs at time 0. The beginning of the next control period is

664 decided at the end of the previous control period, and is the day (allowed to be up to a

665 maximum of 365 days later) that will result in the smallest divorce effect if control was stopped

666 after that period. This plan finds that it is optimal to perform the first few treatments relatively

667 quickly, then to perform subsequent treatments during the peak in prevalence. We see that

668 this is capable of nearly eliminating the Divorce Effect, but there is only a minimal benefit to the

669 control, with large yearly outbreaks.

670

31