Title
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Journal
Mathematical medicine and biology : a journal of the IMA, 34(2)

ISSN
1477-8599

Authors
Gao, Daozhou
Lietman, Thomas M
Dong, Chao-Ping
et al.

Publication Date
2017-06-01

DOI
10.1093/imammb/dqw005

Peer reviewed

HHS Public Access

Author manuscript

Math Med Biol. Author manuscript; available in PMC 2018 October 25.

Published in final edited form as:

Math Med Biol. 2017 June 01; 34(2): 241–260. doi:10.1093/imammb/dqw005.

Mass drug administration: the importance of synchrony

Daozhou Gao,
Mathematics and Science College, Shanghai Normal University, Shanghai 200234, China and Francis I. Proctor Foundation, University of California, San Francisco, CA 94143-0412, USA

Thomas M. Lietman,
Francis I. Proctor Foundation, University of California, San Francisco, CA 94143-0412, USA, Department of Ophthalmology, University of California, San Francisco, CA 94143-0412, USA and Department of Epidemiology & Biostatistics, University of California, San Francisco, CA 94143-0412, USA

Chao-Ping Dong, and
Institute of Mathematics, Hunan University, Changsha, Hunan 410082, China

Travis C. Porco*
Francis I. Proctor Foundation, University of California, San Francisco, CA 94143-0412, USA, Department of Ophthalmology, University of California, San Francisco, CA 94143-0412, USA and Department of Epidemiology & Biostatistics, University of California, San Francisco, CA 94143-0412, USA

Abstract

Mass drug administration, a strategy in which all individuals in a population are subject to treatment without individual diagnosis, has been recommended by the World Health Organization for controlling and eliminating several neglected tropical diseases, including trachoma and soil-transmitted helminths. In this article, we derive effective reproduction numbers and average post-treatment disease prevalences of a simple susceptible–infectious–susceptible epidemic model with constant, impulsive synchronized and non-synchronized drug administration strategies. In the non-synchronized model, the individuals in the population are treated at most once per period and their treatment times are uniformly distributed. Mathematically, the set of pulses for the non-synchronized model has the cardinality of the continuum. We show that synchronized and constant strategies are, respectively, the most and least effective treatments in disease control. Elimination through synchronized treatment is always possible when adequate drug efficacy and coverage are fulfilled and sustained. For a strategy with multiple rounds of synchronized treatment per period, the average post-treatment prevalence is irrelevant what the time differences between treatments are, as long as there are the same number of treatments per period.

Keywords

synchronized treatment; non-synchronized treatment; effective reproduction number; trachoma; cost-effectiveness

*Corresponding author: travis.porco@ucsf.edu.

1. Introduction

Mass drug administration (MDA) is the distribution of drugs to entire populations, regardless of ascertainment of disease or infection status. It was once widely implemented in the era of malaria eradication campaign with generally unsuccessful outcome, due to emerging drug and insecticide resistance. We ask the following questions: is it feasible to eliminate infection with repeat mass treatments, what is the minimum necessary frequency of mass treatment for a given population or geographic region, how can we maximize cost-effectiveness with limited resources and finally, when can MDA be terminated (Ray *et al.*, 2009)? Melese *et al.* (2004, 2008) conducted randomized clinical trials in the Gurage Zone in Ethiopia and their studies strongly suggests the feasibility of locally eliminating trachoma with repeat mass antibiotic distributions.

Repeat mass treatment may be studied using the theory of impulsive systems as a useful idealization. The transmission dynamics of infectious diseases undergoing impulse effects can be described by a system of impulsive differential equations (Lakshmikantham *et al.*, 1989; Bainov & Simeonov, 1993), i.e. continuous-time differential equations between impulses and impulsive equations at the time of impulse. The main difference between impulsive and periodic epidemic models is that the former describe instantaneous changes in the values of state variables at impulsive points, while the latter describe periodic changes in the values of model parameters (Bacaër & Ouifki, 2007; Gao *et al.*, 2014b). For example, there are numerous studies on disease control and elimination in the presence of pulse vaccination (Agur *et al.*, 1993; Shulgin *et al.*, 1998; Gao *et al.*, 2007; Yang *et al.*, 2013), pulse chemotherapy (Panetta, 1996; Lakmeche & Arino, 2000; Smith, 2006), pulse radiotherapy (Freedman & Belostotski, 2009), pulse immunotherapy (Bunimovich-Mendrazitsky *et al.*, 2008; Castiglione & Piccoli, 2007), pulse removal (Fuhrman *et al.*, 2004; Jin & Haque, 2007), and pulse birth (Roberts & Kao, 1998; Jiang & Yang, 2009).

MDA, however, differs from vaccination in that it helps infected people to recover from illness, infection or colonization, while vaccines are usually used to help uninfected people develop temporary or lifelong immunity. A theory of disease elimination by MDA is being developed (Anderson *et al.*, 2012). By fitting a stochastic model to observed data for trachoma, Lietman *et al.* (1999) concluded that moderate endemic areas need annual MDA in eliminating trachoma, while hyperendemic areas need biannual MDA. Ray *et al.* (2007) fitted a stochastic epidemic model to collected data from Ethiopia and found that local elimination is achievable, while large-scale elimination requires more frequent treatments and the reduction of imported transmission. On the basis of a periodic Ross–Macdonald model, Gao *et al.* (2014a) numerically found that the optimal timing of MDA for malaria is not at high mosquito season. Griffin and his collaborators (Griffin *et al.*, 2010; Griffin, 2015) studied the effect of pulsed interventions (such as MDA and indoor residual spraying) on the reproduction number for malaria with seasonally varying mosquito numbers.

In this article, we will use mass oral azithromycin administration for trachoma as a case study. Trachoma is an infectious ocular disease caused by the bacterium *Chlamydia trachomatis* and it has long been a leading cause of blindness and visual impairment. About 232 million people in 51 countries are at risk of trachoma worldwide, of whom

approximately 55 million people received antibiotic treatments for trachoma in 2013. Repeated administration of antibiotics has dramatically reduced the prevalence of active trachoma in many areas (Schachter *et al.*, 1999; Gaynor *et al.*, 2003; Burton *et al.*, 2010). A single dose of the macrolide antibiotic azithromycin takes less than a week to clear *C. trachomatis* with an average efficacy of 92–98% and the World Health Organization (WHO) recommended coverage for trachoma control programs is 80% or higher (Lietman *et al.*, 1999). There is no documented evidence of emerging azithromycin resistance after mass distribution of azithromycin for trachoma (Solomon *et al.*, 2005; Hong *et al.*, 2009).

Trachoma campaigns are typically conducted by having teams of field workers visit communities and apply antibiotics to everyone at the same time. While expensive, this reduces the possibility of creating a temporal refuge for the bacterium in individuals who are not treated at a particular time. But we may, however, consider an alternative strategy, in which mass administration is transferred to routine care, each child receiving his or her annual dose at (for instance) a birthday, avoiding the need for centrally coordinated field teams. Are asynchronous or decentralized MDA campaigns feasible? In what follows, we will explore idealized models to gain insight into the importance of synchrony in application of MDA, by examining models in which individuals are treated annually, but asynchronously.

In the next section, we consider three formulations of a deterministic susceptible–infectious–susceptible (SIS) epidemic model under: (1) constant treatment, (2) impulsive synchronized treatment (representing what might be seen in practice) and (3) a hypothetical non-synchronized treatment campaign, respectively. In the constant treatment model, antibiotics are constantly distributed to a population at random and an individual may receive multiple doses in one treatment period. In both the impulsive synchronized and non-synchronized treatment models, no one receives more than one dose in one treatment period; e.g. for annual mass treatment, no one receives more than one dose per year. The synchronized model represents the typical MDA where the whole population receives treatment nearly at the same time. In the non-synchronized model, each individual is still only treated once per period, but the individuals in the population are treated at different times, distributed uniformly throughout the time period. The effective reproduction numbers and average disease prevalences of the model under all three drug administration strategies are derived and compared in Section 3. Numerical examples are presented to confirm theoretical results and to determine right treatment frequency for regions with different levels of endemicity or disease intensity in Section 4.

2. Three treatment strategies

We consider a simple SIS infectious process with standard incidence, in which infection confers short-term immunity or none at all to an infectious individual upon recovery. For a constant population, let $S(t)$ and $I(t)$ be the fractions of uninfected and infected people at time t, respectively. The disease transmission is described by a system of two ordinary differential equations

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \gamma I, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \end{aligned} \tag{2.1}$$

where β is the transmission coefficient and γ is the recovery rate. It is well known that the basic reproduction number of the model (2.1) is $\mathcal{R}_0 = \beta/\gamma$ and the disease dies out for stochastic effects if $\mathcal{R}_0 \leq 1$ and persists at an endemic equilibrium $(1/\mathcal{R}_0, 1 - 1/\mathcal{R}_0)$ *if* $\mathcal{R}_0 > 1$ (Brauer & Castillo-Chavez, 2012).

The antibiotic efficacy depends not only on effective coverage but also on drug distribution strategies. A strategic distribution plan to maximize the effectiveness of antibiotics and minimize the risk of side effects is most desirable. This is particularly crucial in areas where health-care resources are very limited or antibiotic resistance is a big concern. In what follows, we will compare three typical drug distribution strategies (regardless of health status): constant treatment, impulsive synchronized MDA and impulsive non-synchronized treatment. Let T be the length of one treatment period (e.g. year), p be the curative efficacy, q be the coverage rate and $\theta = p \times q \in (0, 1)$ be the effective coverage of a single distribution (further details will be provided below). The medication is assumed to take effect instantaneously at dosing time and does not drive significant antibiotic resistance. In Table 1, we give a summary of parameter descriptions and ranges based on trachoma.

2.1 Constant treatment

The treatment is modeled as a continuous process in which individuals receive treatment at rate θ/T. The fraction of infected population follows the equation

$$\frac{dI}{dt} = \beta(1 - I)I - \gamma I - \frac{\theta}{T}I \text{ and } 0 < I(0) \leq 1. \tag{2.2}$$

The effective reproduction number of model (2.2) is $\mathcal{R}_c = \frac{\beta}{\gamma + \theta/T}$, the disease eventually disappears if $\mathcal{R}_c \leq 1$ and the disease prevalence stabilizes at $P_c = 1 - 1/\mathcal{R}_c$ *if* $\mathcal{R}_c > 1$.

In this model, e.g. we may consider each individual to receive treatments according to a Poisson process with intensity given by θ/T, so that some individuals receive more than one treatment per period, while others receive none.

2.2 Impulsive synchronized treatment

Assuming that drugs are distributed to the whole population at the same time with effective coverage θ (i.e. the fraction of people being successfully treated) and the effects of drugs are instantaneous. The proportion of the population who are infectious satisfies

$$\frac{dI}{dt} = \beta(1-I)I - \gamma I - \sum_{k=0}^{\infty} \delta(t-kT)\theta I \text{ and } 0 < I(0) \leq 1, \quad (2.3)$$

where $\delta(t)$ is the Dirac delta function (i.e. 1 when $t = 0$ and 0 otherwise). We define the effective reproduction number of model (2.3) as $\mathcal{R}_1 = \frac{\beta}{\gamma - \ln(1-\theta)/T}$ (see e.g. Melese *et al.* (2004)).

More generally, consider a treatment strategy with multiple rounds of impulsive synchronized MDA per period where the change in infectives is described by

$$\frac{dI}{dt} = \beta(1-I)I - \gamma I - \sum_{k=0}^{\infty} \delta(t-\tau_k)\theta_k I \text{ and } 0 < I(0) \leq 1. \quad (2.4)$$

We assume that $0 = \tau_0 < \tau_1 < \cdots < \tau_{m-1} < \tau_m = T$, $\tau_{k+m} = \tau_k + T$, $\theta_k \in (0, 1)$ and $\theta_{k+m}\ \theta_k$ for $k = 0, 1, \ldots$ and $m \in \{1, 2, \ldots\}$ Clearly, (2.4) is a logistic system with periodic impulsive perturbations and its effective reproduction number is defined as

$$\mathcal{R}_{m,1} = \frac{\beta}{\gamma - \sum_{k=0}^{m-1} \ln(1-\theta_k)/T}$$

(see Liu & Chen, 2004; Jin & Haque, 2007). If $\mathcal{R}_{m,1} > 1$ then (2.4) possesses a unique positive periodic solution, denoted by $I^*(t)$, which is globally attractive (Liu & Chen, 2004).

2.3 Impulsive non-synchronized treatment

In reality, individuals are not, in fact, simultaneously treated. We also, therefore, consider the opposite special case: each individual receives no more than one treatment per period and the distribution of treatment times in the entire population is uniform over the treatment period. Specifically, the nonsynchronized model divides one treatment period into infinitesimal intervals $(t, t + \Delta t)$, to each of which there corresponds a small fraction of the population, ΔH, who are treated at times t, $t + T$, $t + 2T, \ldots$, over time. In other words, we split a completely homogeneous population and one treatment period into the same number of portions satisfying $n \equiv 1/\Delta H = T/\Delta T$ and periodically treat the jth subpopulation of size $\Delta H = 1/n$ at time $t = (j-1)\Delta T + kT = ((j-1)/n + k)T$, $k = 0, 1, 2, \ldots$, for j = 1,…,n. All subpopulations are well mixed and each of them is subject to the same force of infection determined by the overall instantaneous prevalence, $I(t)$. The fraction of the infectives in the jth subpopulation, denoted by $I_j(t)$, satisfies

$$\frac{dI_j}{dt} = \beta\left(\frac{1}{n} - I_j\right)I - \gamma I_j - \sum_{k=0}^{\infty} \delta\left(t - \frac{j-1}{n}T - kT\right)\theta I_j,\ 1 \leq j \leq n, \quad (2.5)$$

where $I(t) = I_1(t) + I_2(t) + \cdots + I_n(t)$, $0 \le I_j(0) \le 1/n$ and $0 < I(0) \le 1$. System (2.5) is formed by a cooperative system with a recurrent pulse effect.

As the number of portions, n, increases to infinity, we obtain a limiting system of (2.5). Let $s(a, t)$ and $i(a, t)$ be the densities of the uninfected and infected at phase $a \in [0, T)$ and time t, respectively, $s(a, t)\Delta a$ and $i(a, t)\Delta a$ be the fraction of uninfected and infected people at phase interval $a, a + \Delta a)$ and time t, respectively. Obviously, we have

$$s(a, t) + i(a, t) = 1, \text{ for } \forall a \in [0, T) \text{ and } t \ge 0.$$

The overall fraction of infectives in the population at time $I(t) = \frac{1}{T}\int_0^T i(a, t)da$. By taking $I_j(t)/(1/n) \to i(a, t)$, the limiting form of (2.5) is

$$\frac{\partial i(a, t)}{\partial t} = \beta(1 - i(a, t))I(t) - \gamma i(a, t) - \sum_{k=0}^{\infty} \delta(t - a - kT)\theta i(a, t) \quad (2.6)$$

with initial condition satisfying $0 < I(0) \le 1$ and $0 \le i(a, 0) \le 1$ for $a \in [0, T)$. Note that system (2.6) has a continuum ($\aleph_1$) of pulses; this differs from the typical impulsive differential in which the number of pulses is countably infinite.

3. Mathematical results

In this section, we first solve the impulsive synchronized model (2.3) and obtain its average prevalence at the stable state if the disease remains persistent after repeat treatments. Then we study the impulsive nonsynchronized treatment model (2.6) and establish the global threshold dynamics in terms of the effective reproduction number. Finally, we compare the three treatment strategies through their corresponding effective reproduction numbers, stable average prevalences and other measures. By a change of variables: $\beta T \to \beta$, $\gamma T \to \gamma$ and $t/T \to t$, it suffices to consider the models (2.2)–(2.6) with $T = 1$.

3.1 The solution of the impulsive synchronized model

Solving the logistic differential equation

$$\frac{dI}{dt} = \beta(1 - I)I - \gamma I \text{ and } I(0) = I_0 \ne 1 - 1/\mathcal{R}_0$$

by separating variables, we obtain

$$I(t) = \frac{K}{1 + \left(K/I_0 - 1\right)e^{-rt}} \text{ with } k = \frac{\beta - \gamma}{\beta} \text{ and } r = \beta - \gamma\,.$$

It follows from $I^*(0+) = I^*(1+) = (1 - \theta)I^*(1)$ that

$$I_0 = \frac{e^r(1-\theta)-1}{e^r-1}K < K = 1 - 1/\mathscr{R}_0.$$

The average prevalence of the synchronized model (2.3) at the positive stable state is

$$P_1 \equiv \int_0^1 I^*(t)dt = \frac{K}{r}\ln\left(\frac{e^r + K/I_0 - 1}{K/I_0}\right) = \frac{K}{r}\ln(1 + e^r(1-\theta) - 1)$$
$$= \frac{K}{r}(r + \ln(1-\theta)) = 1 - \frac{\gamma - \ln(1-\theta)}{\beta} = 1 - \frac{1}{\mathscr{R}_1}.$$

We can derive the stable average prevalence of the m rounds of impulsive synchronized MDA model (2.4), denoted by $P_{m,1}$, without solving the model equation. If $\mathscr{R}_{m,1} > 1$ then the unique positive periodic solution $(S^*(t), I^*(t))$ of (2.4) exists and satisfies

$$\frac{dI^*}{dt} = \beta(1-I^*)I^* - \gamma I^* \Rightarrow \int_0^1 \frac{1}{I^*(t)}dI^*(t) = \int_0^1 (\beta - \gamma - \beta I^*(t))dt$$
$$\Rightarrow \int_{\tau 0}^{\tau m} \frac{1}{I^*(t)}dI^*(t) = \sum_{k=1}^{m}\int_{\tau_{k-1}}^{\tau_k} \frac{dI^*(t)}{I^*(t)} = \sum_{k=1}^{m}(\ln(I^*(\tau_k)) - \ln(I^*(\tau_{k-1}+)))$$
$$= \sum_{k=1}^{m}\ln(I^*(\tau_k)) - \sum_{k=1}^{m}\ln((1-\theta_{k-1})I^*(\tau_{k-1}))$$
$$= -\sum_{k=1}^{m}\ln(1-\theta_{k-1}) + \sum_{k=1}^{m}(\ln(I^*(\tau_k)) - \ln(I^*(\tau_{k-1})))$$
$$= -\sum_{k=0}^{m-1}\ln(1-\theta_k) + \ln(I^*(\tau_m)) - \ln(I^*(\tau_0)) = -\sum_{k=0}^{m-1}\ln(1-\theta_k)$$
$$= \int_0^1 (\beta - \gamma - \beta I^*(t))dt = (\beta - \gamma) - \beta\int_0^1 I^*(t)dt$$
$$\Rightarrow P_{m,1} \equiv \int_0^1 I^*(t)dt = \frac{\beta - \gamma + \sum_{k=0}^{m-1}\ln(1-\theta_k)}{\beta} = 1 - \frac{1}{\mathscr{R}_{m,1}}.$$

THEOREM 3.1 For system (2.4), if $\mathscr{R}_{m,1} \le 1$, then the disease always dies out; if $\mathscr{R}_{m,1} > 1$, then there exists a unique positive periodic solution with period 1, denoted by $I^*(t)$, i.e. globally asymptotically stable in the sense that $\lim_{t\to\infty}|I(t) - I^*(t)| = 0$, and the average disease prevalence converges to $1 - 1/\mathscr{R}_{m,1}$ where $I(t)$ is any solution of system (2.4) with $I(0) > 0$.

REMARK 3.2 It is worth noting that the effective reproduction number, $\mathscr{R}_{m,1}$, and the stable average disease prevalence, $P_{m,1}$, of model (2.4) are independent of the selection of treatment times $(\tau_1, \tau_2, \ldots, \tau_m)$. For an example of biannual treatment strategy, the post-treatment prevalence is independent of the time difference between two biannual treatments as long as they are twice per year.

3.2 The solution of the non-synchronized model

It follows from theoretical studies on impulsive cooperative systems (Jiang, 1994; Liu & Chen, 2006) and numerical simulations (see Fig. 1) of the discretized system (2.5) that the disease under non-synchronized treatment either dies out or persists at a positive periodic state, denoted by $\left(I_1^*(t), \ldots, I_n^*(t)\right)$. Moreover, the periodic solution satisfies $\left(I_j^*(t+1), \ldots, I_j^*(t)\right)$ and $I_j^*(t), \ldots, I_{j+1}^*(t+1/n)$. The overall instantaneous prevalence $I^*(t) = \sum_{j=1}^n I_j^*(t)$ is a $1/n$-periodic function. In fact,

$$\begin{aligned} I^*(t+1/n) &= \sum_{j=1}^{n} I_j^*(t+1/n) = I_1^*(t+1/n) + \sum_{j=2}^{n} I_j^*(t+1/n) \\ &= I_n^*(t+1) + \sum_{j=2}^{n} I_{j-1}^*(t) = I_n^*(t) + \sum_{j=1}^{n-1} I_j^*(t) = \sum_{j=1}^{n} I_j^*(t) = I^*(t). \end{aligned}$$

As the partition of population and time gets finer and finer, the period of the overall prevalence function $I^*(t)$ of (2.5) becomes smaller and smaller and $I^*(t)$ approaches a constant as $n \to \infty$. Hence the solution of the limiting system (2.6) either converges to zero or a time-periodic state, denoted by $i^*(a, t)$. Similarly, the time-periodic solution satisfies

$$i^*(a, t+1) = i^*(a, t) \text{ and } i^*(a, t) = i^*(a+s, t+s), t \geq 0, \quad (3.1)$$

for $a \in [0, 1)$ and $s \in [0, 1 - a)$. The overall prevalence $I^*(t) = \int_0^1 i^*(a, t)da$ of (2.6) is a positive constant. In fact, equalities (3.1) and the change of variables give

$$\begin{aligned} I^*(t+s) &= \int_0^1 i^*(a, t+s)da = \int_0^s i^*(a, t+s)da + \int_s^1 i^*(a, t+s)da \\ &= \int_0^s i^*(a+1-s, t+s+1-s)da + \int_s^1 i^*(a-s, t)da \\ &= \int_{1-s}^1 i^*(a, t)da + \int_0^{1-s} i^*(a, t)da = \int_0^1 i^*(a, t)da = I^*(t). \end{aligned}$$

We next establish the necessary and sufficient conditions for the disease persistence of the nonsynchronized model (2.6) and estimate the stable average prevalence $P_\infty \equiv I^*(t) = I^*(0)$ or I_0^*. It follows from (3.1) that it suffices to solve the linear impulsive differential equation

$$\begin{aligned} \frac{di(0,t)}{dt} &= \beta I_0^* - \left(\beta I_0^* + \gamma\right) i(0,t), t \neq 0, 1, \ldots, \\ i(0, t+) &= (1-\theta) i(0,t), t = 0, 1, \ldots \end{aligned} \quad (3.2)$$

at $t \in (0, 1]$. Direct calculations find that (3.2) has a unique globally stable periodic solution

$$I^*(0,t) = (A - Ce^{-Bt})/B, t \in (0, 1],$$

where

$$A = \beta I_0^*, B = \beta I_0^* + \gamma \text{ and } C = \frac{\theta A}{1 - (1-\theta)e^{-B}}. \quad (3.3)$$

Furthermore, following $i^*(0, 1 - a) = i^*(a, 1) = i^*(a, 0)$, we have

$$0 = \int_0^1 i^*(a,0)da - I_0^* = \int_0^1 i^*(0,1-a)da - I_0^* = \int_0^1 i^*(0,t)dt - I_0^*$$
$$= \int_0^1 \frac{A - Ce^{-Bt}}{B} dt - I_0^* = \frac{A}{B} - (1 - e^{-B})\frac{C}{B^2} - I_0^*.$$

Making the substitution (3.3) in above equation yields

$$F(I_0^*) \equiv \frac{\beta I_0^*}{\beta I_0^* + \gamma} - \frac{1 - e^{-(\beta I_0^* + \gamma)}}{(\beta I_0^* + \gamma)^2} \times \frac{\theta \beta I_0^*}{1 - (1-\theta)e^{-(\beta I_0^* + \gamma)}} - I_0^* = 0,$$

which is a complex transcendental equation of I_0^*. Before proceeding further, we present a lemma which is useful in later proofs and whose proof is postponed to Appendix A.

LEMMA 3.3 Let $h(x) = 1/x - 1/(e^x - 1)$ for $x \in [0, \infty)$ and $g(x) = 1/\ln(1 - x) + 1/x$ for $x \in [0, 1]$. Then we have

- **(i)** $h(x)$ is strictly decreasing and strictly convex on $[0, \infty)$ with $\lim_{x \to 0} h(x) = 1/2$, $\lim_{x \to \infty} h(x) = 0$, $\lim_{x \to 0} h'(x) = -1/12$ and $\lim_{x \to \infty} h'(x) = 0$;
- **(ii)** $g(x) = 1 - h(-\ln(1 - x))$, $x \in [0, 1]$;
- **(iii)** $g(x)$ is strictly increasing on $[0, 1]$ with $\lim_{x \to 0+} g(x) = 1/2$, $\lim_{x \to 1-} g(x) = 1$, $\lim_{x \to 0+} g'(x) = 1/12$ and $\lim_{x \to 1-} g'(x) = \infty$.

Since $F(0) = 0$ and $F(1) < -\gamma/(\beta + \gamma) < 0$, the transcendental equation $F(I) = 0$ has at least one positive root in (0, 1) provided that

$$F'(0) = \frac{\beta}{\gamma} - \frac{\beta(e^\gamma - 1)\theta}{\gamma^2(e^\gamma - 1 + \theta)} - 1 > 0.$$

Moreover, the condition $F'(0) > 0$ is also necessary for the existence and uniqueness of a positive zero of $F(I)$. The proof can be found in Appendix B.

LEMMA 3.4 The equation $F(I) = 0$ has exactly one positive root in (0, 1) when $F'(0) > 0$ and no positive root in (0, 1) when $F'(0) \leq 0$.

Now we define the effective reproduction number of the impulsive non-synchronized treatment model (2.6) as

$$\mathcal{R}_\infty = \frac{\beta}{\gamma + 1/(1/\theta + 1/(e^\gamma - 1) - 1/\gamma)}.$$

The model (2.6) also demonstrates global threshold dynamics which are determined by the reproduction number.

THEOREM 3.5 For model (2.6), assume that there always exists a globally stable solution. If $\mathcal{R}_\infty \le 1$ then the disease goes extinct; else if $\mathcal{R}_\infty > 1$ (implies $\mathcal{R}_0 > 1$) then there is a time-periodic positive solution $i^*(a, t)$ which is globally asymptotically stable, and the overall disease prevalence $I(t)$ converges $P_\infty \equiv I_0^*$ provided that the disease is initially present. Here $I_0^* = (Y^* - \gamma)/\beta$ and Y^* is the unique positive zero of the function

$$G(Y) = \frac{1}{\theta} - \frac{1}{\beta - Y} + \frac{1}{e^Y - 1} - \frac{1}{Y}$$

on $(\gamma, \beta - \theta)$ provided that $G(\gamma) > 0$ or equivalently $\mathcal{R}_\infty > 1$.

The proof of Lemma 3.4 indicates that $F'(0)$ and $G(\gamma)$ have the same sign, and $G(\gamma) > 0$ if and only if $\mathcal{R}_\infty > 1$. The above theorem is immediately followed by Lemma 3.4.

3.3 Comparison of the reproduction numbers and prevalences

We now determine the best treatment strategy through the comparison of their effective reproduction numbers, post-treatment prevalences, minimum required effective coverage rates and minimum allowable periods for elimination. Recall that $\mathcal{R}_c = \beta/(\gamma + \theta)$ and $\mathcal{R}_1 = \beta/(\gamma - \ln(1 - \theta))$. In the following, we ignore the trivial case where the disease will eventually go extinct with or without treatment.

PROPOSITION 3.6 For any given parameter set, we have $\mathcal{R}_c > \mathcal{R}_\infty > \mathcal{R}_1$ and $P_c > P_\infty > P_1$.

Proof. It follows from $h(\gamma) \in (0, 1/2)$ and $g(\theta) \in (1/2, 1)$ for $\gamma > 0$ and $\theta \in (0, 1)$ that

$$\mathcal{R}_c > \mathcal{R}_\infty \Leftrightarrow \frac{1}{\theta} > \frac{1}{\theta} + \frac{1}{e^\gamma - 1} - \frac{1}{\gamma} \Leftrightarrow h(\gamma) = \frac{1}{\gamma} - \frac{1}{e^\gamma - 1} > 0$$

and

$$\mathcal{R}_\infty > \mathcal{R}_1 \Leftrightarrow \frac{1}{\theta} + \frac{1}{e^\gamma - 1} - \frac{1}{\gamma} > \frac{1}{-\ln(1 - \theta)} \Leftrightarrow g(\theta) = \frac{1}{\theta} + \frac{1}{\ln(1 - \theta)} > h(\gamma).$$

On the other hand, if $\mathcal{R}_\infty > 1$ then

$$G(\beta P_c + \gamma) = G(\beta - \theta) = \frac{1}{e^{\beta - \theta} - 1} - \frac{1}{\beta - \theta} = -h(\beta - \theta) < 0$$

and

$$\begin{aligned} G(\beta P_1 + \gamma) &= G(\beta + \ln(1-\theta)) = \frac{1}{\theta} + \frac{1}{\ln(1-\theta)} + \frac{1}{e^{\beta + \ln(1-\theta)} - 1} - \frac{1}{\beta + \ln(1-\theta)} \\ &= g(\theta) - h(\beta + \ln(1-\theta)) > 0. \end{aligned}$$

We conclude that $G(\beta P_c + \gamma) < 0 = G(\beta P_\infty + \gamma) < G(\beta P_1 + \gamma)$ and hence $P_c > P_\infty > P_1$.

REMARK 3.7 Note that $P_c = 1 - 1/\mathcal{R}_c$ and $P_1 = 1 - 1/\mathcal{R}_1$. However, $P_\infty > 1 - 1/\mathcal{R}_\infty > P_1$. Actually, by the strict monotonicity of $h(x)$ on $[0,\infty)$, we know that

$$G(\beta(1 - 1/\mathcal{R}_\infty) + \gamma) = h(\gamma) - h(\beta(1 - 1/\mathcal{R}_\infty) + \gamma) > 0 = G(\beta P_\infty) + \gamma) \text{ if } \mathcal{R}_\infty > 1.$$

For a general value of the treatment cycle T, the minimum required effective coverage $\theta_{\min}$ for elimination of infection using constant treatment, impulsive synchronized MDA and impulsive nonsynchronized treatment, if it exists, are

$$\theta_c = (\beta - \gamma)T, \theta_1 = 1 - e^{-(\beta - \gamma)T} < 1 \text{ and } \theta_\infty = \frac{1}{\frac{1}{(\beta - \gamma)T} + \frac{1}{\gamma T} - \frac{1}{e^{\gamma T} - 1}},$$

respectively, provided that $\mathcal{R}_0 = \beta/\gamma > 1$. For any given effective coverage $\theta \in (0, 1)$, the maximum allowable period $T_{\max}$ of constant treatment, impulsive synchronized MDA and impulsive non-synchronized treatment for elimination of infection are

$$T_c = \frac{\theta}{\beta - \gamma}, T_1 = -\frac{\ln(1-\theta)}{\beta - \gamma} \text{ and } T_\infty = \frac{\theta}{\beta - \gamma} + \theta\left(\frac{1}{\gamma} - \frac{T_\infty}{e^{\gamma T_\infty} - 1}\right), \quad (3.4)$$

respectively, provided that $\mathcal{R}_0 = \beta/\gamma > 1$. Here $T_\infty > 0$ is the unique zero of the strictly increasing function

$$\hat{G}(T) = \frac{1}{\theta} - \frac{1}{(\beta - \gamma)T} + \frac{1}{e^{\gamma T} - 1} - \frac{1}{\gamma T}.$$

It follows from Lemma 3.3 that

$$\begin{aligned} \theta_\infty > \theta_1 &\Leftrightarrow \frac{1}{1 - e^{-(\beta - \gamma)T}} > \frac{1}{(\beta - \gamma)T} + \frac{1}{\gamma T} - \frac{1}{e^{\gamma T} - 1} \\ &\Leftrightarrow g(1 - e^{-(\beta - \gamma)T}) = \frac{1}{1 - e^{-(\beta - \gamma)T}} + \frac{1}{-(\beta - \gamma)T} > h(\gamma T) = \frac{1}{\gamma T} - \frac{1}{e^{\gamma T} - 1} \end{aligned}$$

and

$$\hat{G}(T_c) = -h(\gamma T_c) < 0 = \hat{G}(T_\infty) < \hat{G}(T_1) = g(\theta) - h(\gamma T_1).$$

Hence $\theta_c > \theta_\infty > \theta_1$ and $T_c < T_\infty < T_1$, so that *impulsive synchronized MDA uses the least antibiotic to achieve elimination*. For any given transmission setting and treatment cycle, the impulsive synchronized MDA is always able to eradicate the disease with sufficiently high effective coverage, while the other two treatment strategies may fail.

In addition, if we equally split one pulse into m pulses at time kT, $kT + T/m, \ldots, kT + T(m-1)/m$, then the corresponding effective reproduction number and stable average prevalence for impulsive synchronized MDA and impulsive non-synchronized treatment are

$$\mathcal{R}_{1,m} = \frac{\beta}{\gamma - \ln(1-\theta/m)/(T/m)}, P_{1,m} = 1 - 1/\mathcal{R}_{1,m}$$

and

$$\mathcal{R}_{\infty,m} = \frac{\beta T/m}{\gamma T/m + 1/(m/\theta + 1/(e^{\gamma T/m} - 1) - 1/(\gamma T/m))}, P_{\infty,m} \neq 1 - 1/\mathcal{R}_{\infty,m},$$

respectively, where $P_{\infty,m}$ is the unique positive root of the equation

$$G_m(\beta I + \gamma) = \frac{m}{\theta} - \frac{m}{\beta T - (\beta I + \gamma)T} + \frac{1}{e^{(\beta I+\gamma)T/m} - 1} - \frac{1}{(\beta I + \gamma)T/m} = 0.$$

As expected, both $\mathcal{R}_{1,m}$ and $\mathcal{R}_{\infty,m}$ are strictly increasing to $\mathcal{R}_c$ as $m \to \infty$. By the squeeze theorem, $P_{1,m}$ and $P_{\infty,m}$ converge to P_c as $m \to \infty$.

REMARK 3.8 It follows from Remark 3.2 that the results throughout this section still hold for the comparison among constant treatment ($T \to T/m$), impulsive non-synchronized treatment ($T \to T/m$) and the m rounds of impulsive synchronized MDA model (2.4) with identical effective coverage$\to(\theta_0 = \cdots = \theta_{m-1} = \theta)$ and randomly selected initial treatment times ($0 = \cdot\tau_0 \cdot < \tau_1 \cdot < \cdots < \tau_{m-1} < \tau_m = T$).

The main results we obtained in this article are summarized in Table 2.

4. Numerical simulations

In this section, using trachoma as a case study, we give examples to compare the maximum allowable period for elimination, minimum required effective coverage and the speed of convergence of three treatment strategies. We discuss the situations when trachoma can be administrated by a single dose of azithromycin on an annual or biannual basis. Unless stated otherwise, time is measured in years in what follows.

EXAMPLE 4.1 Choose $\beta = 1.8$ and $\gamma = 0.9$. Using formula (3.4), the relationship between $T_{\max}$ and θ under three treatment strategies is plotted in Fig. 2a. With 90% effective coverage, the maximum allowable period of impulsive synchronized MDA is 2.6-fold longer than that of constant treatment. When individuals are treated annually, Fig. 2b describes the average prevalence at the stable state of each treatment strategy versus effective coverage. The minimum effective coverage requirements are $\theta_c = 90\%$, $\theta_1 = 59.3\%$ and $\theta_\infty = 65.1\%$, and the impulsive synchronized MDA is most effective.

Moreover, the impulsive synchronized MDA takes less time to achieve elimination than either constant or impulsive non-synchronized treatment does (see Fig. 3a). However, if the impulsive synchronized MDA cannot eliminate infections, then it may take longer time to stabilize at a stable periodic state than others do (see Figure 3b).

EXAMPLE 4.2 With parameter ranges in Table 1, we use the Latin hypercube sampling method to generate 100,000 parameter sets of the form $\{\beta, \gamma, \theta\}$. Since the goal of the WHO trachoma control program is to reduce active trachoma to less than 5% in children aged 1–9 years (Melese *et al.*, 2004; Taylor *et al.*, 2014), and impulsive synchronized MDA may be discontinued if the trachoma prevalence falls below the set threshold, we choose 45,418 scenarios whose equilibrium prevalences before treatment are greater than 5%. Among these qualified scenarios, 15,919 have pretreatment prevalence less than 35%, 7,929 have pretreatment prevalence from 35 to 50% and the remaining 21,570 have pretreatment prevalence greater than 50%. The maximum allowable treatment periods of all qualified scenarios (solid line) and scenarios with pretreatment prevalence less than 35% (dash-doted line), from 35 to 50% (dashed line) and greater than 50% (dotted line) are presented in Fig. 4. In particular, 85.6% of simulations that start with less than 35% pretreatment prevalence, representing low to moderately endemic areas, end in elimination with annual mass treatment, while 43.9% simulations that start with over 50% pretreatment prevalence, representing hyperendemic areas, cannot eliminate infections with biannual treatment. It somewhat differs from previous work (Lietman *et al.*, 1999), because we used broader parameter ranges. These numerical results provide a quantitative exploration of the impulsive synchronized model, but direct applicability to any particular setting would require detailed parameter fitting based on prevalence surveys.

In addition, based on qualified scenarios, the partial rank correlation coefficients for maximum allowable treat period with respect to β, γ and θ are −0.83, 0.82 and 0.73, respectively. This suggests that all three parameters are almost equally important in determining T_1.

5. Discussion

MDA i.e. the treatment of all at-risk populations without assessment of infection, is being implemented as a core strategy for the control and elimination of several neglected tropical diseases (NTDs) around the globe. The success of MDA programs depends on the treatment coverage and efficacy of the drugs, as well as the costs, side effects, and drug resistance. In this article, we use a simple SIS model to determine the feasibility of disease elimination via synchronized MDA and compare it with constant treatment and impulsive non-synchronized

treatment. In terms of post-treatment prevalence, synchronized MDA is far more effective than impulsive non-synchronized treatment, while impulsive non-synchronized treatment is slightly better than constant treatment ($P_c > P_\infty > P_1$). MDA as currently implemented is substantially better than non-synchronized alternatives. For a given treatment frequency (i.e. times per year), elimination by synchronized MDA is always possible with appropriate effective coverage, while the other two treatment strategies may fail $(\mathscr{R}_c > \mathscr{R}_\infty > \mathscr{R}_1)$. Our analysis of the maximum allowable period and minimum required effective coverage may provide guidance in specific settings on the appropriate treatment frequency and coverage. The idea behind the nonsynchronous model is applicable to other impulsive non-synchronized processes such as periodic mass immunization program. This model could, for instance, be extended to assess the consequences of year round field teams visiting each region once per year (for instance) but visiting each region at a different time. For the treatment strategy with multiple rounds of synchronized MDA per period, we note that the average prevalence only depends on the number of rounds but not on their timing within the period. However, the timing of MDA does matter if seasonal effects are considered (Lee *et al.*, 2005). Numerical calculations suggest that the selection of treatment times does make a difference for the discretized model (2.5). We conjecture that the impulsive non-synchronized treatment is the least effective periodic unrepeated treatment strategy.

We note that MDA has considerably broader application than trachoma. It has been successfully used for malaria and lymphatic filariasis in China and onchocerciasis in Latin America. MDA can be used to contain and eliminate an infectious disease if inexpensive, safe and highly effective medicines are available (Hotez, 2009; Smits, 2009). The WHO recommends repeat use of albendazole with ivermectin or diethylcarbamazine for lymphatic filariasis, ivermectin for onchocerciasis, praziquantel for schistosomiasis, albendazole or mebendazole for soil-transmitted helminths and azithromycin for trachoma (Hotez, 2009; Smits, 2009). About 711 million people received MDA treatments in 2010 and more than 1.9 billion people in 124 countries require annual MDA for at least one NTD (World Health Organization, 2013). Note that Anderson *et al.* (2014), Truscott *et al.* (2014a,b) studied the possibility for control and elimination of soil-transmitted helminths through repeated mass treatment programs. The 2012 London Declaration on NTDs aims to eliminate or control 10 of the 17 NTDs by 2020. Extensions of the model we presented for trachoma could be used to examine alternative implementations of MDA-based control in such macroparasitic settings.

This study provides insight into the important role of synchrony in the implementation of MDA. More comprehensive studies should consider the influence of partial acquired immunity (Liu *et al.*, 2013), chemoprophylaxis in susceptible persons, seasonality in transmission (Lee *et al.*, 2005), age-structure in the host population (Bailey *et al.*, 1999; Lietman *et al.*, 1999; Gambhir *et al.*, 2009), bacterial load (Shattock *et al.*, 2015), case importation, and other ecological or epidemiological factors (Lietman *et al.*, 1999). Changes in population size, structure and distribution need to be reflected in a long-term MDA program. In clinical trials, antibiotic treatment may only target those at the highest risk of infection (e.g. people with symptoms or those under a certain age (Lietman *et al.*, 1999)), known as targeted MDA which is similar to targeted mass vaccination (Keeling & Rohani,

2008). A large-scale MDA campaign involving millions of people takes neither a day nor a full period, so a more general model based on the non-synchronized model and the non-treatment model may be more realistic. In the presence of antibiotic resistance, a strategy to reach the goal of elimination and to reduce the risk of emerging resistance associated repeat treatments is expected. In cases where the efficacy of oral azithromycin for trachoma is lower than previously estimated (Liu *et al.*, 2014), more repeated distributions per period are required for elimination. A combination of MDA and other interventions (e.g. the SAFE strategy for trachoma—Surgery, Antibiotics, Facial cleanliness and Environmental improvement) could interrupt disease transmission more rapidly and reduce the use of antibiotics.

Acknowledgements

Helpful comments by the anonymous referees, and by Dr Long Zhang and Dr Jifa Jiang are deeply appreciated.

Funding

This work was partially supported by the Models of Infectious Disease Agent Study (MIDAS) (NIGMS U01GM087728), the TANA II (TIRET) Study (NEI U10EY016214), NSFC (Nos. 11201261 and 11571097), the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (No. TP2015050) and Shanghai Gaofeng Project for University Academic Program Development.

Appendix A.: Proof of Lemma 3.3

Proof. (i) The first and second derivatives of $h(x)$ are

$$h'(x) = \frac{2e^x(1 + x^2/2 - \cosh x)}{(e^x - 1)^2 x^2} \text{ and } h''(x) = \frac{2e^{3x} - (x^3 + 6)e^{2x} - (x^3 - 6)e^x - 2}{(e^x - 1)^3 x^3},$$

respectively. It follows from L'Hospital's rule that

$$\lim_{x \to 0} h(x) = \frac{1}{2} \text{ and } \lim_{x \to 0} h'(x) = -\frac{1}{12}.$$

Let $h_1(x)$ and $h_2(x)$ be the numerator of $h'(x)$ and $h''(x)$, respectively. Thus

$$h_1(x) = 2e^x\left(1 + \frac{x^2}{2} - \sum_{k=0}^{\infty} \frac{x^{2k}}{(2k)!}\right) = -2e^x \sum_{k=2}^{\infty} \frac{x^{2k}}{(2k)!} \langle 0, \forall x \rangle 0,$$

and

$$h'_2(x) = e^x(6e^{2x} - (12 + 3x^2 + 2x^3)e^x + 6 - 3x^2 - x^3) \equiv e^x h_3(x),$$
$$h_2(0) = h_3(0) = 0,$$
$$h_3^{(4)}(x) = e^x(96e^x - 96 - 96x - 27x^2 - 2x^3) \equiv e^x h_4(x),$$
$$h'_3(0) = h''_3(0) = h_3^{(3)}(0) = h_3^{(4)}(0) = h_4(0) = 0,$$
$$h_4^{(3)}(x) = 96e^x - 12 > 0, \forall x \geq 0,$$
$$h'_4(0) = 0, h''_4(0) = 42.$$

So $h'(x) < 0$ and $h''(x) > 0$ for $x > 0$.

(ii) The second part can be easily verified.

(iii) Let $y = -\ln(1 - x)$. Then $\lim_{x \to 0+} g(x) = 1 - \lim_{y \to 0+} h(y) = 1/2$ and $\lim_{x \to 1-} g(x) = 1 - \lim_{y \to \infty} h(y) = 1$.

Differentiating $g(x) = 1 - h(-\ln(1 - x))$ gives

$$g'(x) = -h'(y) \times \frac{1}{1 - x} > 0 \text{ for } x \in [0, 1].$$

Therefore, $\lim_{x \to 0+} g'(x) = -\lim_{y \to 0+} h'(y) \times 1 = 1/12$ and

$$\lim_{x \to 1-} g'(x) = \lim_{x \to 1-} \left(-\frac{1}{x^2} + \frac{1}{(1 - x)(\ln(1 - x))^2} \right) = -1 + \lim_{y \to \infty} \frac{e^y}{y^2} = \infty.$$

Appendix B.: Proof of Lemma 3.4

Proof. Denote $Y = \beta I + \gamma \in [\gamma, \beta + \gamma]$ and transform the transcendental function $F(I)$ as

$$\begin{aligned} F(I)\frac{(\beta I + \gamma)^2}{I} &= -(\beta I + \gamma)^2 + \beta(\beta I + \gamma) - \frac{\beta\theta(e^{\beta I + \gamma} - 1)}{e^{\beta I + \gamma} - 1 + \theta} \\ &= -Y^2 + \beta Y - \frac{\beta\theta(e^Y - 1)}{e^Y - 1 + \theta} < (\beta - Y)Y \leq 0 \text{ if } Y \geq \beta \\ &= \frac{\beta}{\frac{1}{Y} + \frac{1}{\beta - Y}} - \frac{\beta}{\frac{1}{\theta} + \frac{1}{e^Y - 1}} = \frac{\beta G(Y)}{(\frac{1}{Y} + \frac{1}{\beta - Y})(\frac{1}{\theta} + \frac{1}{e^Y - 1})} \text{ if } Y < \beta, \end{aligned}$$

where $G(Y) = G_1(Y) + G_2(Y)$ with $G_1(Y) = \frac{1}{\theta} - \frac{1}{\beta - Y}$ and $G_1(Y) = \frac{1}{e^Y - 1} - \frac{1}{Y}$ It is easy to show that $G_1(Y)$ is positive and strictly decreasing on $(\gamma, -\beta - \theta)$ and $G_2(Y) = -h(Y)$ is negative and strictly increasing on $(0, \infty)$.

Note that $F(I_0^*) = 0$ for some $I_0^* \in (0,1)$ is equivalent to $G(Y^*) = 0$ for $Y^* = \beta I_0^* + \gamma \in (\gamma, \beta + \gamma)$ Since $G(Y) < 0$ for $Y \geq \beta - \theta$, it suffices to solve $G(Y)$ 0 on $(\gamma, \beta - \theta)$. follows from $G''_1 = \frac{-2}{(\beta - Y)^3} < 0$ on (γ, β) and $G''_2(Y) = -h''(Y) < 0$ on $(0,\infty)$ that $G''_2(Y) < 0$ on (γ, β). This means that $G(Y)$ is *strictly concave* on (γ, β). Since $G(Y) < 0$ on $[\beta - \theta, \beta)$, $G(Y) = 0$ has exactly one positive root on $(\gamma, \beta - \theta)$ if $G(\gamma) > 0$. The proof of the first part is complete by noting that $F'(0)$ and $G(\gamma)$ have the same sign because of

$$F'(0) = \lim_{I \to 0} \frac{F(I) - F(0)}{I - 0} = \lim_{I \to 0} \frac{F(I)}{I}$$
$$= \lim_{I \to 0} \frac{\beta G(Y)}{(\frac{1}{Y} + \frac{1}{\beta - Y})(\frac{1}{\theta} + \frac{1}{e^Y - 1})} \frac{1}{Y^2} = \frac{\beta G(\gamma)}{(\frac{1}{\gamma} + \frac{1}{\beta - \gamma})(\frac{1}{\theta} + \frac{1}{e^\gamma - 1})} \frac{1}{\gamma^2}.$$

For the second part, using the strict concavity of $G(Y)$, it suffices to show that $G(\gamma) \leq 0$ implies $G'(\gamma) \leq 0$. In fact

$$G(\gamma) \leq 0 \Leftrightarrow \frac{1}{\beta - \gamma} \geq \frac{1}{\theta} + \left(\frac{1}{e^\gamma - 1} - \frac{1}{\gamma}\right) > \frac{1}{2} \Leftrightarrow \frac{1}{(\beta - \gamma)^2} \geq \left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1} - \frac{1}{\gamma}\right)^2,$$
$$G'(\gamma) = \frac{-1}{(\beta - \gamma)^2} - \frac{e^\gamma}{(e^\gamma - 1)^2} + \frac{1}{\gamma^2} \leq 0 \Leftrightarrow \frac{1}{(\beta - \gamma)^2} \geq \frac{1}{\gamma^2} - \frac{e^\gamma}{(e^\gamma - 1)^2}$$

and

$$\left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1} - \frac{1}{\gamma}\right)^2 - \left(\frac{1}{\gamma^2} - \frac{e^\gamma}{(e^\gamma - 1)^2}\right)$$
$$= \left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1} - \frac{2}{\gamma}\right)\left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1}\right) + \frac{e^\gamma}{(e^\gamma - 1)^2}$$
$$= \left(\frac{1}{\theta} - \frac{1}{e^\gamma - 1} + 2\left(\frac{1}{e^\gamma - 1} - \frac{1}{\gamma}\right)\right)\left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1}\right) + \frac{e^\gamma}{(e^\gamma - 1)^2}$$
$$> \left(\frac{1}{\theta} - \frac{1}{e^\gamma - 1} - 1\right)\left(\frac{1}{\theta} + \frac{1}{e^\gamma - 1}\right) + \frac{e^\gamma}{(e^\gamma - 1)^2}$$
$$= \frac{1}{\theta^2} - \frac{1}{(e^\gamma - 1)^2} - \frac{1}{\theta} - \frac{1}{e^\gamma - 1} + \frac{e^\gamma}{(e^\gamma - 1)^2} = \frac{1}{\theta}\left(\frac{1}{\theta} - 1\right) \geq 0.$$

This completes the proof of the theorem.

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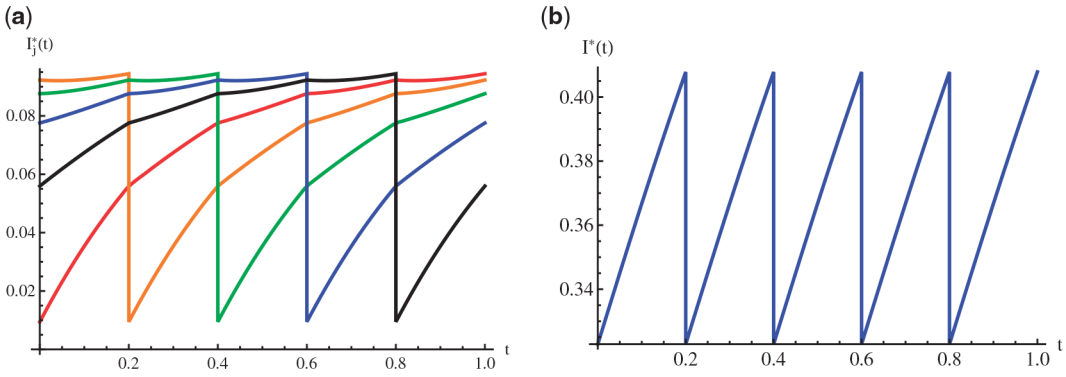

Fig. 1.

The disease prevalence of each subpopulation and whole population through one time period. (a) The plot of $I_j^*(t)$ for the jth subpopulation under one impulsive synchronized treatment per period, $1 \le j \le n$. (b) The plot of $I^*(t)$ under n impulsive treatments per period. The parameter values are $\beta = 5$, $\gamma = 2$, $\theta = 90\%$, $T = 1$ and $n = 5$.

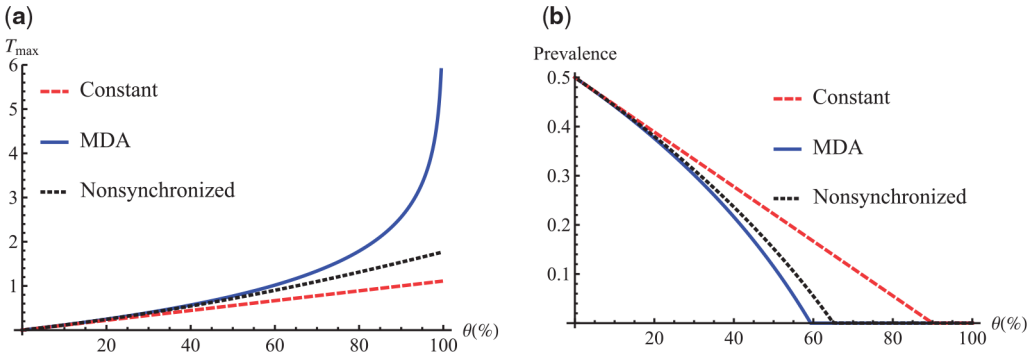

Fig. 2.

(a) The curves of maximum allowable period for elimination of infection and (b) the curves of stable average prevalence under constant treatment (dashed line), impulsive synchronized MDA (solid line) and impulsive non-synchronized treatment (dotted line). Parameter values are $\beta = 1.8$, $\gamma = 0.9$ in both figures and $T = 1$ in the right figure.

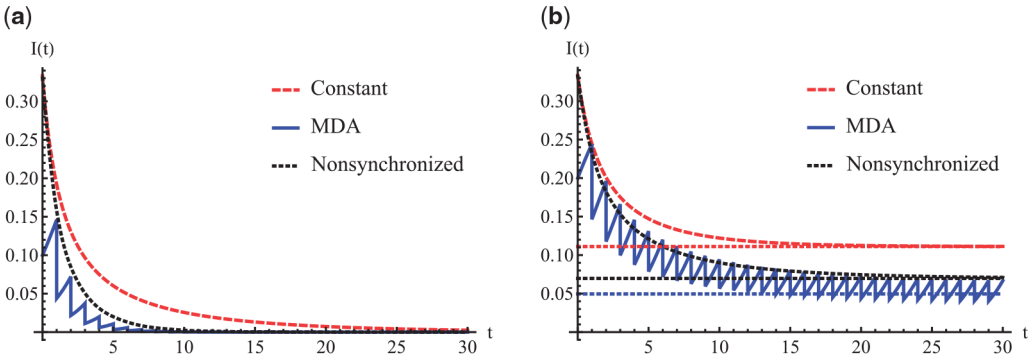

Fig. 3.

Numerical solutions of the system under constant treatment (dashed line), impulsive synchronized MDA (solid line) and impulsive non-synchronized treatment (dotted line). (a) Even if all three treatment strategies can eliminate an infectious disease in one population, synchronized MDA is still the best one in the speed of achieving elimination. (b) If all three treatment strategies fail to eliminate an infectious disease, then synchronized MDA may spend the longest time in attaining a stable state. Dotted horizontal lines in the right figure are at the stable average prevalence of the system under constant treatment, impulsive synchronized MDA and impulsive non-synchronized treatment, respectively. Parameter values are $\beta = 1.8$, $\gamma = 1.2$, $T = 1$, $\theta = 70\%$ in (a) and $\theta = 40\%$ in (b).

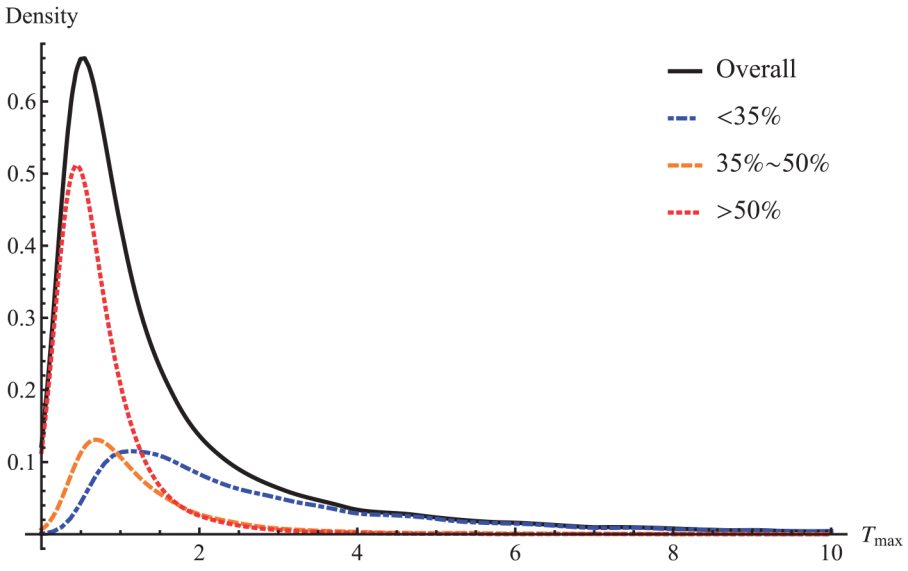

Fig. 4.

Smoothed probability density plot of maximum allowable period of impulsive synchronized MDA. Solid line—all qualified scenarios, dash-doted line—scenarios with pretreatment prevalence less than 35%, dashed line—scenarios with pretreatment prevalence from 35 to 50% and dotted line—scenarios with pretreatment prevalence greater than 50%. The parameter ranges are listed in Table 1.

Table 1

Ranges and baseline values for model parameters.

	Description	Range	Baseline	Unit	Reference
β:	transmission rate	0.516–5.28	2.4	$year^{-1}$	Lietman *et al.* (1999); Ray *et al.* (2007) and Liu *et al.* (2014)
γ:	recovery rate	0.264–5.76	1.2	$year^{-1}$	Bailey *et al.* (1999); Lietman *et al.* (1999) and Liu *et al.* (2014)
p(%):	antibiotic efficacy	92–98	95	–	Lietman *et al.* (1999) and Lee *et al.* (2005)
q(%):	antibiotic coverage	60–100	80	–	Lee *et al.* (2005) and Melese *et al.* (2008)
θ(%):	effective coverage	50–98	90	–	Ray *et al.* (2007) and Liu *et al.* (2014)
T:	treatment cycle	0.5–3	1	year	Lietman *et al.* (1999); Ray *et al.* (2007) and Liu *et al.* (2014)

Table 2

Summary of measures for three treatment models. The full names of abbreviations in the first column are basic reproduction number (BRN), stable average prevalence (SAP), minimum required effective coverage (MREC) and maximum allowable period (MAP), respectively. Here Y^* and T_∞ are the unique positive zero to $\frac{1}{\theta} - \frac{1}{(\beta - Y)T} + \frac{1}{e^{YT} - 1} - \frac{1}{YT}$ with respect to Y and T, respectively. We show that $\mathcal{R}_c > \mathcal{R}_\infty > \mathcal{R}_1$, $P_c > P_\infty > P_1$, $\theta_c > \theta_\infty > \theta_1$ and $T_c < T_\infty < T_1$.

	Constant treatment	Non-Synchronized treatment	Impulsive Synchronized treatment (MDA)
BRN	$\mathcal{R}_c = \frac{\beta}{\gamma + \theta/T}$	$\mathcal{R}_\infty = \frac{\beta}{\gamma + 1/\left(\frac{T}{\theta} + \frac{T}{e^{\gamma T} - 1} - \frac{1}{\gamma}\right)}$	$\mathcal{R}_1 = \frac{\beta}{\gamma - \ln(1-\theta)/T}$
SAP	$P_c = 1 - \frac{1}{\mathcal{R}_c}$	$P_\infty = \frac{Y^* - \gamma}{\beta}$	$P_1 = 1 - \frac{1}{\mathcal{R}_1}$
MREC	$\theta_c = (\beta - \gamma)T$	$\theta_\infty = \frac{1}{\frac{1}{(\beta-\gamma)T} + \frac{1}{\gamma T} - \frac{T}{e^{\gamma T} - 1}}$	$\theta_1 = 1 - e^{-(\beta - \gamma)T}$
MAP	$T_c = \frac{\theta}{\beta - \gamma}$	T_∞	$T_1 = -\frac{\ln(1-\theta)}{\beta - \gamma}$