We assume that vaccination is applied periodically in time. In this case, the optimal protocol is to apply the vaccine as a sequence of δ-like pulses. The disease extinction rate can strongly depend on the period of this sequence. Furthermore, the extinction rate can display exponentially sharp peaks when the pulse sequence period is close to the characteristic period of oscillations of the system in the absence of fluctuations, or to its multiples. We illustrate this resonant phenomenon for the Susceptible-Vaccinated-Infected-Recovered (SVIR) model.

Epidemics often display seasonal modulation [18]. It is natural to apply a vaccine with period equal to the modulation period. As we show, there is a qualitative difference between the effect of a periodic vaccination in this case and in the case where seasonal modulation is absent. For a system with seasonal modulation, an improperly applied pulsed vaccination can actually *reduce* the disease extinction rate and therefore prolong the duration of the epidemic. The overall effect of the pulsed vaccination critically depends here on the *phase* at which the periodic pulses are applied.

The analysis of periodic vaccination, with and without seasonal variations, necessitates a general formulation of the extinction problem in periodically modulated stochastic populations. We extend the previous results for single-population systems [19, 20] to provide a complete extinction theory for multi-population systems in the eikonal approximation, and emphasize the distinction from the well-understood problem of switching between metastable states in periodically modulated systems with noise [21].

Section II describes the class of epidemic models we consider in this work and develops an eikonal theory of disease extinction rate in periodically modulated systems. Section III formulates the optimization problem for vaccination and presents its solution for a time-periodic vaccination in the limit of a small average vaccination rate. In Section IV we discuss the vaccination-induced reduction of the disease extinction barrier for two types of constraints on the vaccination period, a limited lifetime of the vaccine and a limited vaccine accumulation. Section V illustrates, on the example of the stochastic SVIR model, the phenomenon of resonant response to vaccination. Section V contains concluding remarks.

II. THE DISEASE EXTINCTION RATE

A. The model of population dynamics

We consider stochastic disease dynamics in a well-mixed population which includes infected (I) and susceptible (S) individuals and possibly other population groups such as recovered or vaccinated. The system state is described by a vector $\mathbf{X} = (S, I, \ldots)$ with integer components equal to the sizes of different population groups. Along with $\mathbf{X}$ it is convenient to consider a quasi-continuous vector $\mathbf{x} = \mathbf{X}/N$, where N is the characteristic total population size, $N \gg 1$. We assume that the population dynamics is Markovian. It is quite generally described by the master equation for the probability distribution $P(\mathbf{X}, t)$,

$$\begin{aligned} \dot{P}(\mathbf{X}, t) &= \sum_{\mathbf{r}} [W(\mathbf{X} - \mathbf{r}, \mathbf{r}, t) P(\mathbf{X} - \mathbf{r}, t) \\ &- W(\mathbf{X}, \mathbf{r}, t) P(\mathbf{X}, t)] . \end{aligned} \tag{1}$$

Here $W(\mathbf{X}, \mathbf{r}, t)$ is the rate of an elementary transition $\mathbf{X} \to \mathbf{X} + \mathbf{r}$ in which the population size changes by $\mathbf{r} = (r_1, r_2, \ldots)$. Examples of such transitions are infection of a susceptible individual as a result of contacting an infected individual, recovery of an infected individual or arrival of a susceptible individual.

We assume that there is no influx of infected individuals into the population. Therefore, there are no transitions from states where there are no infected to states where infected are present,

$$W(\mathbf{X}, \mathbf{r}, t) = 0 \qquad \text{for} \quad X_E = 0,\, r_E \neq 0, \tag{2}$$

where subscript E is used for the component of $\mathbf{X}$ which enumerates infected, $X_E \equiv I$.

In the neglect of demographic noise the population dynamics can be described by the deterministic (mean-field) equation for the population size $\bar{\mathbf{x}}$,

$$\dot{\bar{\mathbf{x}}} = \sum_{\mathbf{r}} \mathbf{r} w(\bar{\mathbf{x}}, \mathbf{r}, t), \qquad w(\mathbf{x}, \mathbf{r}, t) = W(\mathbf{X}, \mathbf{r}, t)/N. \tag{3}$$

It immediately follows from Eq. (1) if the width of the probability distribution $P(\mathbf{X}, t)$ is set equal to zero.

1. *Stationary systems*

We start with the case where the transition rates $W(\mathbf{X}, \mathbf{r})$ are independent of time. An endemic state, where a finite fraction of population is infected for a long time, corresponds to an attracting fixed point $\mathbf{x}_A$ of the dynamical system, Eq. (3). We will assume throughout this work that there is only one such point. We will also assume that Eq. (3) has one fixed point $\mathbf{x}_{\mathcal{S}}$ in the hyperplane $x_E = 0$. The state $\mathbf{x}_{\mathcal{S}}$ is stable with respect to all variables except x_E. We call it the disease extinction state. If $x_E > 0$ (there is a nonzero number of infected), the deterministic trajectory leaves the vicinity of $\mathbf{x}_{\mathcal{S}}$ and approaches the endemic state $\mathbf{x}_A$.

Due to demographic noise the endemic state is actually *metastable*. A rare large fluctuation ultimately drives the population into a disease-free state. The most probable fluctuation brings the system to the fixed point $\mathbf{x}_{\mathcal{S}}$ [13, 14]. The probability of such a fluctuation per unit time, *i.e.*, the disease extinction rate W_e, is given by the probability current to $\mathbf{x}_{\mathcal{S}}$, similarly to the problem of escape from a metastable state [22]. For time-independent $W(\mathbf{X}, \mathbf{r})$ this current is quasistationary for