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ORIGINAL ARTICLE

Measures to assess a warning vaccination level in a stochastic SIV model with imperfect vaccine

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Abstract

A stochastic Markovian Susceptible-Infectious-Susceptible (SIS) model, with infection reintroduction is considered to represent the evolution of an epidemic process within a finite population. Disease is assumed to be a contact disease whose effect can be prevented by a vaccine. Before the epidemic process emerges, v_0 individuals got vaccinated to assure that the population is protected by herd immunity. In consequence, we formulate the model by adding a new compartment for vaccine protected individuals. The administered vaccine is not a perfect one and consequently it fails in a proportion of vaccinated individuals that are not protected against the vaccine preventable communicable disease. Hence, while the infectious process is in progress, the initial vaccine coverage declines and herd immunity could be lost. A threshold on the size of the vaccinated group is included as a warning measure on the protection of the community. Our objective is to define and study random characteristics, depending on the vaccination eligible group, that could advise health authorities when to launch a new vaccination program to recover the initial immunity level.

KEYWORDS
eligible group, imperfect vaccine, Markov chain, stochastic epidemic model, warning level

1 | INTRODUCTION

Mathematical representation of the spread of infectious diseases has been helpful in the understanding of contagious processes. Even simple models permit to derive key insights into the transmission dynamics and to compare the effect of different intervention strategies[1–3]; serving as a starting point that can be adapted to real-world complexities by adding or refining assumptions in the light of the achieved results. Even in the absence of updated information of the epidemic parameters, mathematical models aim to describe adequately the patterns of interest.[4]

Compartmental models are versatile enough to capture social dynamics and disease characteristics with the purpose of representing the evolution of infectious diseases within a population. Individuals are classified into several mutually exclusive groups according to their status regarding the infectious disease. In the course of epidemics, each individual belongs to a single group or compartment at a given time, and can move from one to another depending on disease characteristics and/or community interventions. Since the pioneering Susceptible-Infectious-Removed (SIR) model, by Kermack and McKendrick,[5] numerous and more complex compartmental models have been developed and applied to describe epidemic infections.[6,7] Roughly speaking, mathematical models can be classified into two types: deterministic and stochastic, whose main difference lies in the mathematical description of the evolution of the epidemic process. Deterministic models are formulated in terms of a system of difference or differential equations, reflecting the variation in the number of individuals in each compartmental group by assuming that all the individuals present the same behavior regarding the disease of interest. Stochastic models introduce a source of stochasticity that could arise from the transmission process, experimental procedures and from individual characteristics. These models are formulated in terms of a stochastic process, whose solution predicts distributions of random variables involving incidence, transmission, or duration of the random process. Stochastic models are preferable and useful when dealing with small communities, due to the influence on the impact of the epidemics of random differences in infectiousness and susceptibility of an individual, while these random effects tend to cancel out each other as population size increases.

Health protection measures, designed to ensure health safety, become effective in reducing the consequences of infectious diseases. In the absence of effective antiviral drugs and vaccines, nonpharmaceutical interventions based on control strategies, such as social distance, lockdown, isolation, quarantine, hygiene measures, spraying, and so forth, would reduce the incidence by interrupting transmission.[8–10] Vaccines help the immune system to create and keep antibodies specific to a bacteria or a virus in the way that, in case of encountering the disease, the immune system prevents the infection from developing. Hence, when available, vaccination drastically reduces chances of contracting many diseases.[11–13]

Literature on compartmental epidemic models includes many papers where vaccination was used as an intervention mechanism. Some of them introduce vaccination as a control or strategy on a selected model[14–16] but most of the studies rely on models including additional compartments for vaccinated individuals.[17–20] Models are flexible enough to match vaccine characteristics, such as efficacy,[21,22] life-long or waning protection,[23,24] eligibility,[25] number of doses,[26] vaccine uptake,[27] and so forth.

For contact diseases, when a large proportion of individuals of a community is protected by vaccination, it makes it difficult for the infection to spread within the community due to the small number of people susceptible to this disease. Seen that people immune to the disease protect vulnerable people, this type of protection is known as herd immunity. Herd immunity level varies with each disease, it depends on the infectiousness of the pathogen and also on the duration of the infectivity of affected individuals. In consequence, herd immunity is linked to appropriate estimates of the basic reproduction number R_0, that measures the reproductive potential of a disease regarding population characteristics and also vaccine attributes, when available.[28–32]

Public health objective of vaccination is to increase the level of herd immunity to keep the infection controlled or even eliminated from the population, and in the longer term to eradicate the infection world or region-wide. To achieve this goal, vaccination coverage must be optimal. Usually, following a national immunization schedule, routine vaccination campaigns are conducted to prevent epidemics. In addition, mass vaccinations may be organized to help control an epidemic in a short period. Compartmental models can be employed to assess and compare incidence and cost benefit of different vaccination policies.[33,34] As vaccines are not fully effective and induced-immunity can be lost over time, to maintain community protection it is necessary to revise vaccine coverage periodically and to plan supplementary vaccination programs if necessary. Recommendations to evaluate strategies can focus on vaccine allocation (see Ref. 35, Chapter 3) and also on optimizing time periods.[36] Alternatively, in the present paper we propose to schedule activities based on thresholds controlling vaccinated and susceptible compartments.

In this paper, we deal with a stochastic compartmental Susceptible-Infectious-Vaccinated (SIV) model, that represents the propagation of a contact disease by means of a continuous time Markov chain (CTMC). We deal with a constant size population and assume that it is initially protected against the disease because a vaccine has been administered to a proportion of individuals, which is large enough to provide herd protection. However, a vaccine is not fully effective and some vaccinated individuals can get the infection and, after recovery, they are unprotected from the disease. In consequence, the proportion of vaccinated individuals decreases within the course of the epidemic process. To control the loss of protection, in Ref. 37, we introduced an alarm threshold w on the number of protected individuals and we focused on the period of time going from the start of an epidemic outbreak until the number of vaccinated individuals drops to the alarm level. To fix the warning level w, in this paper we introduce two random variables, S_w and R_w, investigating the population in the susceptible group at the time the threshold is reached and the required time to have the sufficient number of susceptible individuals, eligible to be vaccinated, to raise the vaccine coverage to the initial level.

The paper is organized as follows. In Section 2, we describe the stochastic SIV model and introduce the Markov chain representing disease evolution within a population of constant size. In Section 3, we introduce the random measures S_w and R_w, related to the warning vaccination level w. We present theoretical and algorithmic results involving the stochastic distribution of these random measures. Section 4 illustrates our analysis in the setting of diphtheria infections, and concluding remarks and future work appear in Section 5.

2 MODEL DESCRIPTION

The model represents the evolution of a contagious disease within a closed homogeneous and uniformly mixed population. This disease is transmitted by direct contact with an infected individual. We assume that the population is not isolated. Hence, there is an additional source of infection

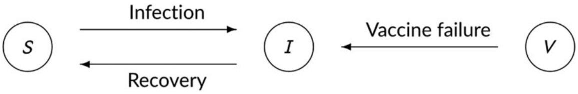

FIGURE 1 Movement of individuals among compartments of the SIVS model

due to external contacts that contributes to the spread of the disease. In any case, we assume that during the epidemic time span there are not noticeable demographic changes in the population so, the standard constant population hypothesis is accepted.

To prevent large disease outbreaks, part of the population has been vaccinated against the disease with an available vaccine that confers immunity, but it is not a perfect vaccine and not all vaccinated individuals develop immunity. Consequently, some contacts between vaccinated and infectious individuals produce an effective contagion. When this occurs, the vaccinated individual loses vaccine protection and becomes an infectious individual. Once an infected individual recovers he becomes susceptible to the disease, no matter if he was previously vaccinated or not.

According to the above description, the involved model is a standard SIS/logistic one, with external infection and the additional feature that some of the population is initially vaccinated, with imperfect immunity. More specifically, mathematical model was introduced in the paper[31] as a compartmental model that, at any particular instant t, classifies individuals as susceptible (S), vaccinated (V), or infected (I). Figure 1 represents the movement of individuals among the three epidemiological classes.

The rates of transition between classes depend on disease and vaccine characteristics, and also on model assumptions. Infectious periods of different individuals, no matter if they were previously vaccinated or not, are assumed to be independent and identically distributed according to an exponential law, with rate γ. While infected, local infectious individuals make contact with susceptible and vaccinated ones within the population, at the time points of a time homogeneous Poisson process with intensity $\frac{\beta}{N}$, where N represents the population size. In addition, we assume that there is an external source of infection that occurs at a constant rate ξ, independently of the internal contacts. Any contact between susceptible and infected individuals produces a new case of infection. However, pathogenic transmission in the vaccinated group depends on vaccine effectiveness. Hence, when the contacted individual was previously vaccinated and had not yet got the infection, she/he could become infected with a constant probability h, independently of the time the vaccinated individual is contacted by an infectious one.

In a nutshell, from now on, model parameters will be related to the following concepts: γ will represent the *recovery rate*, β the *disease internal transmission rate*, ξ the *disease external transmission rate*, and h the *vaccine failure probability*.

The evolution of the epidemic process, at each time point t, is described by the random variables $S(t), V(t)$, and $I(t)$, where $S(t)$ records the number of susceptible, $V(t)$ the number of vaccine protected, and $I(t)$ the number of infected individuals. In accordance with the fixed population size assumption, we have that $S(t) + V(t) + I(t) = N$. Consequently, there is no need to record all the compartment occupancy levels. Thus, the number of susceptible individuals is not reported and the evolution of the disease within the population is represented in terms of a bidimensional CTMC as follows:

$$X = \{(V(t), I(t)); t \geq 0\}, \tag{1}$$

whose state space contains a number of states that depends on the initial vaccine coverage. In that sense, for an initial number of vaccinated individuals v_0, with $0 < v_0 \leq N$, the finite

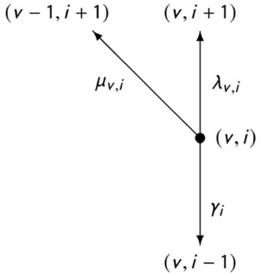

FIGURE 2 Outgoing transitions and rates from a generic state

countable state space of X is $\mathbf{S} = \{(v, i) : 0 \leq v \leq v_0, 0 \leq v + i \leq N\}$, that contains $(v_0 + 1)(N + 1 - v_0/2)$ states.

We assume that the epidemic process begins with a single infectious individual and v_0 vaccinated individuals. Subsequent infections jointly with vaccine failures, diminish the number of vaccine protected individuals. Once $v = 0$, the vaccination compartment is empty and the underlying model behaves as the standard SIS epidemic model with an external source of infection described in Ref. 38. Moreover, the set of states $\{(0, i) : 0 \leq i \leq N\}$ is an absorbing set. Hence, once the process X enters into this set it never leaves it because launching a new vaccination schedule in the population is not considered in our model.

Markovian models rely on the memoryless hypothesis, that guarantees that the rate of leaving any of the states in $\mathbf{S}$ depends only on the current state of the process and not on the trajectory leading to the state itself. Hence, transition rates of the Markov chain are subject to the events that cause a change in the current model state, $(v, i) \in \mathbf{S}$. Namely, the effective events correspond to new infections, either of susceptible or of vaccinated individuals, and recoveries. The exponential transition rates are given by

$$q_{(v,i),(v^*,i^*)} = \begin{cases} h\left(\frac{\beta i}{N} + \xi\right)v, & \text{if } (v^*, i^*) = (v-1, i+1), \\ \gamma i, & \text{if } (v^*, i^*) = (v, i-1), \\ -q_{v,i}, & \text{if } (v^*, i^*) = (v, i), \\ \left(\frac{\beta i}{N} + \xi\right)(N - v - i), & \text{if } (v^*, i^*) = (v, i+1), \\ 0, & \text{otherwise}, \end{cases} \tag{2}$$

where $q_{v,i} = (\frac{\beta i}{N} + \xi)(N - v - i) + h(\frac{\beta i}{N} + \xi)v + \gamma i$ and represents the total sojourn rate in the state $(v, i) \in \mathbf{S}$.

The matrix structure of the infinitesimal generator $\mathbf{Q} = [q_{(v,i),(v^*,i^*)}]$ of X was fully described in Appendix A of our previous paper[31] and it shows a block bidiagonal representation, which is really appropriate for computational purposes.

In more detail, the transitions out of a specific general state $(v, i) \in \mathbf{S}$ are depicted in Figure 2, where the appearing rates are introduced to ease the notation in the sequel.

More explicitly, we define the rates in Figure 2 as follows:

$$\begin{aligned} \gamma_i &= \gamma i, \\ \lambda_{v,i} &= \left(\frac{\beta i}{N} + \xi\right)(N - v - i), \end{aligned} \tag{3}$$

$$\mu_{v,i} = h\left(\frac{\beta i}{N} + \xi\right)v.$$

When no vaccination takes place after $t = 0$ and $\xi > 0$, the long-term behavior of X is given by the stationary distribution, which is concentrated in the set of states with no vaccinated individuals.[31] That is, the protection provided by the vaccine fades away almost surely in finite expected time, leaving the population unprotected and vulnerable to the disease. A new vaccination program should be scheduled to raise vaccine coverage to the initial level.

The aim of this paper is to use the warning threshold for the number of vaccinated individuals, $w < v_0$, introduced in Ref. 37, to get information about the distribution of susceptible and infectious individuals, when the number of vaccinated individuals first reaches the level w. This information could help health authorities to take a decision about when a new vaccination campaign should be scheduled to prevent massive outbreaks of the disease.

3 | RANDOM MEASURES RELATED TO THE WARNING VACCINATION LEVEL

We recall that there is an allowable vaccine that has been administered to a group of v_0 individuals in the population. Vaccine directly protects these individuals from infection but the vaccinated group also indirectly protects the community because it serves as a shield to interrupt the chain of transmission of a contact disease.

According to disease characteristics, there is a minimum percentage of people in the population that should be vaccinated to ensure that the disease will not persist in the population. This threshold is known as the herd immunity and, in the case of large population, its value depends on the reproductive number, R_0, associated to the model representing the evolution of the disease itself. Specifically for the model on hand, in Ref. 31 we derive stochastic measures, alternative to the reproductive number, that assess the choice of vaccine coverage depending on disease transmission parameters and on the effectiveness of a vaccine.

In some communities, due to vaccine rare effects, individuals tend to refrain from being vaccinated and consequently vaccination rates decline below the ideal herd immunity threshold, causing a resurgence of outbreaks of preventable diseases.[39–41] Community protection decreases not only when vaccination rates do. Notice that, even though vaccination objective is to establish lifelong immunity, vaccine-induced protection wanes over time for a number of infectious diseases (pertussis, meningococcal, influenza, mumps, malaria, etc.). In addition, vaccination does not guarantee that vaccinated individuals are protected. We recall that vaccines do not produce immunity it is the body's immune system that produces antibodies triggering immune response. Hence, the effectiveness of a vaccine may also cause a decrease in the number of protected individuals.

For a given warning level w, in Ref. 37 we quantified the time from the start of an outbreak until the number of vaccinated individuals descends to the warning level. During this period, the infection is relatively controlled and we identified this interval of time as the *sleeping period* for health measures. Obviously, the end of any sleeping period is linked to the so-called *wake-up time*, T_w, which indicates the moment at which the number of vaccine protected individuals drops to w. Knowledge on T_w provides information that can be used by health authorities to reallocate resources, in case that they were below the demand for health care services.

More precisely, T_w was formally defined as the random variable

$$T_w = \inf\{t \geq 0 \,:\, V(t) = w\} \tag{4}$$

and the sleeping period corresponds to the random interval $[0, T_w]$.

Next, we introduce two random variables focusing on the eligibility of susceptible individuals to receive new doses of vaccine to restore the initial immunity level. In more detail, we define S_w, the size of the susceptible group when the wake-up time arrives, and the revaccination time R_w or the elapsed time until the susceptible group contains a number of eligible individuals to be vaccinated large enough to recover the initial mass of vaccinated individuals. More properly, the above random variables are defined in terms of the wake-up time as $S_w = S(T_w)$ and $R_w = \inf\{t \geq 0 \,:\, S((T_w + t) + V(T_w + t) \geq v_0\}$. Our aim is to use the analytic properties of both variables to set an appropriate warning level w that triggers an alert to organize a new vaccination campaign.

3.1 | Susceptible population at the wake-up time, S_w

In this section, we are interested in the probabilistic description of the susceptible group that can be found when the number of vaccinated individuals drops down to the warning level w. This means that, this warning or wake-up time has been reached and the alert for a new vaccination program has been triggered. As vaccine is administrated to susceptible individuals, it is really of interest to have information about the size of this group.

Given a warning level for vaccination, w, random variable S_w is defined as the number of susceptible individuals that can be found in the population by the time the number of vaccinated individuals drops down to the alert level w.

We are going to assume that the epidemic process is detected as soon as the first infectious case appears, but the study can be conducted under any other initial condition. To ease the notation and without loss of generality, the random variable S_w will represent the number of susceptible individuals at time horizon T_w, conditioned to the initial situation $(V(0) = v_0, I(0) = 1)$ of the outbreak.

The mathematical analysis will be developed using the information provided by the CTMC X, that keeps track of the number of vaccinated and infectious individuals at any time. As we assume that the population size remains unchanged while the epidemic is in progress, we can use the information provided by X to understand the behavior of S_w. More precisely, we introduce auxiliary random variables $I^w_{v,i}$, defined as the number of infected individuals in the population at the wake-up time, given that the current situation is $(v, i) \in \widehat{W} = \{(v, i) \in \mathbf{S} \,:\, w \leq v \leq v_0, 0 \leq i \leq N - v\}$, that represents the set of states X takes up to the time T_w, when we first have $V(t) = w$.

We notice that S_w is a discrete random variable, with finite support in the set of integer values $\{0, 1, 2, \ldots, N - w - 1\}$, that links to the auxiliary variable $I^w_{v_0,1}$ according to the following equation:

$$S_w = N - w - I^w_{v_0,1}. \tag{5}$$

Relationship (5) will be the key to determine the distribution and moments of S_w.

Let us first deal with the probability distribution of S_w. According to (5), for $0 \le k \le N-w-1$ we have that

$$P\{S_w = k\} = P\left\{ I^w_{v_0,1} = N - w - k \right\}. \tag{6}$$

Hence, the distribution of S_w depends on a set of probabilities involving the auxiliary variable $I^w_{v_0,1}$.

For a fixed warning level w, to simplify the notation we will write $I_{v,i}$ instead of $I^w_{v,i}$ unless the value of a warning level must be explicitly shown. Therefore, for $(v,i) \in \widehat{W}$, let us denote by $x^k_{v,i} = P\{I_{v,i} = k\}$, for any integer k such that $1 \le k \le N-w$.

Theorem 1 provides a computationally stable recursive scheme, from which the computation of the auxiliary probabilities can be done at a low computational cost.

Theorem 1. *Given k, $1 \le k \le N-w$, the set of auxiliary probabilities $\{x^k_{v,i} : (v,i) \in \widehat{W}\}$ are computed by the equations*

$$x^k_{w,i} = \delta_{i,k}, \quad \textit{when } 0 \le i \le k, \tag{7}$$

where $\delta_{i,j}$ represents the Kronecker's delta function, defined as 1, when $i = j$, and 0, otherwise.

For $w+1 \le v \le v_0$, we have

$$x^k_{v,N-v} = \frac{D^k_{v,N-v}}{C_{v,N-v}}, \tag{8}$$

$$x^k_{v,i} = \sum_{j=i}^{N-v-1} \frac{D^k_{v,j}}{C_{v,j}} \left(\prod_{m=i}^{j-1} \frac{\lambda_{v,m} C_{v,m-1}}{C_{v,m}} \right) + \left(\prod_{m=i}^{N-v-1} \frac{\lambda_{v,m} C_{v,m-1}}{C_{v,m}} \right) x^k_{v,N-v}, \quad \textit{for } 0 \le i \le N-v-1, \tag{9}$$

where coefficients $C_{v,j}$ and $D^k_{v,j}$ are determined recursively as follows:

$$C_{v,j} = \begin{cases} 1, & \textit{if } j < 0, \\ q_{v,0}, & \textit{if } j = 0, \\ q_{v,j} C_{v,j-1} - \gamma_j \lambda_{v,j-1} C_{v,j-2}, & \textit{if } 1 \le j \le N-v, \end{cases} \tag{10}$$

$$D^k_{v,j} = \begin{cases} \mu_{v,0} x^k_{v-1,1}, & \textit{for } j = 0, \\ \gamma_j D^k_{v,j-1} + \mu_{v,j} C_{v,j-1} x^k_{v-1,j+1}, & \textit{for } 1 \le j \le N-v. \end{cases} \tag{11}$$

Here and throughout the paper, empty products are interpreted as 1.

Proof. Recall that wake-up time, T_w, is defined as the time point at which the warning level for vaccination w is reached. Thus, at this time point the CTMC enters in the set $\{(w, i) \in \widehat{W} : 0 \leq i \leq N - w\}$. Consequently, at wake-up time, the number of infected individuals is i, almost surely, whenever the current situation is (w, i). That is, probabilities associated to the warning level w satisfy

$$x_{w,i}^{k} = \delta_{i,k}, \quad \text{for } 0 \leq i \leq N - w \quad \text{and} \quad 1 \leq k \leq N - w, \tag{12}$$

that is the result shown in Equation (7).

Remaining set of auxiliary probabilities will be determined by using a first-step argument, conditioning on the exponentially distributed time to the first transition. Given k and v, such that $1 \leq k \leq N - v$ and $w + 1 \leq v \leq v_0$, we have that

$$x_{v,i}^{k} = \frac{\gamma_i}{q_{v,i}} x_{v,i-1}^{k} + \frac{\lambda_{v,i}}{q_{v,i}} x_{v,i+1}^{k} + \frac{\mu_{v,i}}{q_{v,i}} x_{v-1,i+1}^{k}, \quad \text{for } 0 \leq i \leq N - v, \tag{13}$$

or equivalently

$$-\gamma_i x_{v,i-1}^{k} + q_{v,i} x_{v,i}^{k} - \lambda_{v,i} x_{v,i+1}^{k} = \mu_{v,i} x_{v-1,i+1}^{k}, \quad \text{for } 0 \leq i \leq N - v. \tag{14}$$

Observe that the expression in the right-hand side of Equation (14) depends on model parameters and auxiliary probabilities of one level of vaccination less. For every mass point k, it is possible to solve the equations in (14) in a recursive way, in the natural order for v, starting from the boundary result (7).

By using a *Forward Elimination Backward Substitution* (FEBS) procedure,[42] Equation (14) can be written in triangular form as follows:

$$C_{v,i} x_{v,i}^{k} - \lambda_{v,i} C_{v,i-1} x_{v,i+1}^{k} = D_{v,i}^{k}, \quad \text{for } 0 \leq i \leq N - v - 1, \tag{15}$$

where the constants $C_{v,i}$ and $D_{v,i}^{k}$ match the definition in the statement of the Theorem 1.

Now, working on Equation (15), for $i = N - v - 1$, and on Equation (14), for $i = N - v$, we get that

$$C_{v,N-v} x_{v,N-v}^{k} = D_{v,N-v}^{k}, \tag{16}$$

which gives the explicit value of the probability $x_{v,N-v}^{k}$ as appears in Equation (8).

Furthermore, for $1 \leq k \leq N - v$ and $w + 1 \leq v \leq v_0$, Equation (15) gives auxiliary probabilities $x_{v,i}^{k}$ in terms of probabilities $x_{v,i+1}^{k}$

$$x_{v,i}^{k} = \frac{D_{v,i}^{k} + \lambda_{v,i} C_{v,i-1} x_{v,i+1}^{k}}{C_{v,i}}, \quad \text{for } 0 \leq i \leq N - v - 1. \tag{17}$$

Finally, iterating (17) we obtain the relationship appearing in expression (9). ■

Next algorithm implements Theorem 1, providing the scheme to compute probabilities associated to the random variable S_w.

Algorithm 1 (S_w-distribution). *For any k, $1 \leq k \leq N-w$, the set $\{x^k_{v,i} : (v,i) \in \widehat{W}\}$ of point probabilities and the distribution of the random variable S_w are determined from the following scheme:*

```
Step 1: Set $v = w$.
Step 2: Set $k = 1$. If $k > N - w$, go to Step 3.
    Step 2a: Set $i = 0$ and compute $x^k_{v,i}$ from Equation (7).
    Step 2b: Set $i = i + 1$. While $i \leq k$, compute $x^k_{v,i}$ from Equation (7).
    Step 2c: Set $k = k + 1$. While $k \leq N - w$, go to Step 2a.
Step 3: Set $v = v + 1$. If $v > v_0$, stop.
    Step 3a: Set $k = 0$ and $i = -1$. Define $C_{v,i} = 1$.
    Step 3b: Set $i = i + 1$. While $i \leq N - v$, compute $C_{v,i}$ from Equation (10).
Step 4: Set $k = k + 1$. If $k > N - w$, go to Step 3.
    Step 4a: Compute $D^k_{v,i}$, for $0 \leq i \leq N - v$, from Equation (11).
    Step 4b: Set $i = N - v$ and compute $x^k_{v,i}$ from Equation (8).
    Step 4c: Set $i = i - 1$. If $i < 0$, go to Step 4.
    Step 4d: Compute $x^k_{v,i}$ from Equation (9).
    Step 4e: If $v = v_0$ and $i = 1$, set $P\{S_w = N - w - k\} = x^k_{v,i}$.
    Step 4f: Go to Step 4c.
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Any order moment of S_w could be determined directly from the mass distribution function of the random variable due to the finiteness of its support. Instead of that, we deduce a result involving moments of the auxiliary variable $I_{v_0,1}$ that provides a computational scheme which is stable even for large populations.

First, we introduce the following notation for probability generating functions and factorial moments. Given z, $|z| \leq 1$, and $(v,i) \in \widehat{W}$, let us define

$$\phi_{S_w}(z) = E\left[z^{S_w}\right] = \sum_{n=0}^{N-w-1} z^n P\{S_w = n\}, \tag{18}$$

$$\varphi_{v,i}(z) = E\left[z^{I_{v,i}}\right] = \sum_{n=1}^{N-w} z^n x^n_{v,i}, \tag{19}$$

$$M^k_{S_w} = \begin{cases} 1, & \text{for } k = 0, \\ E\left[\prod_{n=0}^{k-1}(S_w - n)\right], & \text{for } k \geq 1, \end{cases} \tag{20}$$

$$m^k_{v,i} = \begin{cases} 1, & \text{for } k = 0, \\ E\left[\prod_{n=0}^{k-1}(I_{v,i} - n)\right], & \text{for } k \geq 1. \end{cases} \tag{21}$$

Since S_w and $\{I_{v,i} : (v,i) \in \widehat{W}\}$ are random variables with finite support included in the set $\{0, 1, \dots, N-w\}$, probability calculus provide an elementary result for factorial moments, namely, $M^k_{S_w} = m^k_{v,i} = 0$, for $k \geq N - w$. Next proposition shows a nontrivial relationship between factorial moments of S_w and of $I_{v_0,1}$.

Proposition 1. *Given k, $1 \leq k \leq N-w-1$, the factorial moment of order k for S_w, $M^k_{S_w}$, can be recovered from factorial moments of $I_{v_0,1}$ according to the following expression:*

$$M^k_{S_w} = \sum_{n=0}^{k}(-1)^n\binom{k}{n}\prod_{j=n}^{k-1}(N-w-j)m^n_{v_0,1}. \tag{22}$$

Proof. Well-known properties of the expected value operator $E[\cdot]$ and relationship (5) give

$$\phi_{S_w}(z) = z^{N-w}\varphi_{v_0,1}\left(\frac{1}{z}\right), \quad \text{for } z \neq 0, |z| \leq 1. \tag{23}$$

On the other hand, factorial moments arise by differentiating generating functions with respect to z. More precisely, $M^k_{S_w} = \frac{\partial^k[\phi_{S_w}(z)]}{\partial z^k}|_{z=1}$ and $m^k_{v_0,1} = \frac{\partial^k[\varphi_{v_0,i}(z)]}{\partial z^k}|_{z=1}$, for $k \geq 1$. Hence, we begin by taking derivatives on Equation (23), k times with respect to z. After that, an iterative application of the Leibniz rule and the mathematical induction principle give

$$\frac{\partial^k\phi_{S_w}}{\partial z^k}(z) = \sum_{n=0}^{k}(-1)^n\binom{k}{n}\prod_{j=n}^{k-1}(N-w-j)z^{N-w-k-n}\frac{\partial^n\varphi_{v_0,1}}{\partial z^n}(\frac{1}{z}). \tag{24}$$

Finally, result in Equation (22) follows by evaluating the expression (24) at $z = 1$. ■

Following result presents a recursive scheme for computing factorial moments of auxiliary variables $\{I_{v,i} : (v,i) \in \widehat{W}\}$, which is the basis for obtaining moments of the random variable S_w by means of Proposition 1.

Theorem 2. *For a given warning level w, with $0 \leq w < v_0$, and a nonnegative integer k, factorial moments of order k $m^k_{v,i}$, for $(v,i) \in \widehat{W}$, are determined as follows:*

$$m^0_{v,i} = 1. \tag{25}$$

For order k, with $1 \leq k \leq N-w$, we have that

$$m^k_{w,i} = \begin{cases} 0, & \text{if } 0 \leq i < k, \\ \frac{i!}{(i-k)!}, & \text{if } k \leq i \leq N-w. \end{cases} \tag{26}$$

Moreover, for $w+1 \leq v \leq v_0$, we have

$$m^k_{v,N-v} = \frac{H^k_{v,N-v}}{C_{v,N-v}}, \tag{27}$$

$$m^k_{v,i} = \sum_{j=i}^{N-v-1}\frac{H^k_{v,j}}{C_{v,j}}\left(\prod_{n=i}^{j-1}\frac{\lambda_{v,n}C_{v,n-1}}{C_{v,n}}\right) \tag{28}$$

$$+\left(\prod_{n=i}^{N-v-1}\frac{\lambda_{v,n}C_{v,n-1}}{C_{v,n}}\right)m^k_{v,N-v}, \quad \textit{for } 0\le i\le N-v-1,$$

where coefficients $C_{v,j}$ match the definition (10), in Theorem 1, and

$$H^k_{v,j}=\begin{cases}\mu_{v,0}m^k_{v-1,1}, & \textit{for } j=0,\\ \gamma_j H^k_{v,j-1}+\mu_{v,j}C_{v,j-1}m^k_{v-1,j+1}, & \textit{for } 1\le j\le N-v.\end{cases} \tag{29}$$

Finally, for order $k>N-w$ we have that

$$m^k_{v,i}=0. \tag{30}$$

Proof. First, we notice that results in (25) and (30) follow from factorial moments definition and the elementary result mentioned prior the statement of Proposition 1.

Now, for $1\le k\le N-w$ and $v=W$ using Equation (7) we have that

$$\varphi_{w,i}(z)=z^i, \quad \text{for } 0\le i\le N-w. \tag{31}$$

By differentiating Equation (31) repeatedly $k\ge 1$ times with respect to z and evaluating at $z=1$, we get the expression (26) for kth order moment of $I_{w,i}$, when $0\le i\le N-w$.

Again, a first-step argument conditioning on the possible transitions out of the state (v,i), shows that generating functions $\varphi_{v,i}(z)$ satisfy the following set of linear equations, for $w+1\le v\le v_0$ and $0\le i\le N-v$:

$$\varphi_{v,i}(z)=\frac{\gamma_i}{q_{v,i}}\varphi_{v,i-1}(z)+\frac{\lambda_{v,i}}{q_{v,i}}\varphi_{v,i+1}(z)+\frac{\mu_{v,i}}{q_{v,i}}\varphi_{v-1,i+1}(z). \tag{32}$$

Once more, by differentiating repeatedly Equation (32) with respect to z and evaluating at $z=1$, we obtain the following system of equations

$$-\gamma_i m^k_{v,i-1}+q_{v,i}m^k_{v,i}-\lambda_{v,i}m^k_{v,i+1}=\mu_{v,i}m^k_{v-1,i+1}, \tag{33}$$

whose solution gives factorial moments of order k, for states (v,i) such that $w+1\le v\le v_0$ and $0\le i\le N-v$.

Observe that Equation (33) looks like Equation (14) just by substituting probabilities $x^k_{v,i}$ for kth order moments $m^k_{v,i}$. Consequently, the proof of Theorem 2 follows along the lines stated on the proof of Theorem 1. Thus, we do not proceed any further. ■

A computational recursive scheme, implementing Theorem 2, allows computation of factorial moments of the auxiliary variables $\{I_{v,i} : w\le v\le v_0, 0\le i\le N-v\}$ and of S_w.

Algorithm 2 (S_w-moments). *Let k be a nonnegative integer. Given a warning level w, with $0\le w<v_0$, the moment of order k of the random variable S_w can be determined numerically according to the following scheme:*

Step 1: If $k>N-w$, set $M^k_{S_w}=0$ and stop.

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Step 2: Set $n = 0$, $v = w$, and $M^n_{S_w} = 1$. If $k = 0$, stop.
Step 3: Set $v = v + 1$. If $v > v_0$, go to Step 4.
    Step 3a: Set $i = -1$ and define $C_{v,i} = 1$.
    Step 3b: Set $i = i + 1$. While $i \leq N - v$, compute $C_{v,i}$ from expression (10).
    Step 3c: Go to Step 3.
Step 4: Set $n = n + 1$. If $n > k$, stop.
    Step 4a: Set $v = w$. Compute $m^n_{v,i}$, for $0 \leq i \leq N - v$, from expression (26).
    Step 4b: Set $v = v + 1$. If $v > v_0$, go to Step 5.
    Step 4c: Compute $H^n_{v,i}$, for $0 \leq i \leq N - v$, using expression (29).
    Step 4d: Set $i = N - v$. Compute $m^n_{v,N-v}$, from Equation (27).
    Step 4e: Set $i = i - 1$. If $i < 0$, go to Step 4b.
    Step 4f: Compute $m^n_{v,i}$, from Equation (28) and go to Step 4e.
Step 5: Compute $M^n_{S_w}$ from Equation (22) and go to Step 4.
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3.2 | Revaccination time, R_w

Management of vaccine routines depends, of course, on the vaccine availability and vaccination services but also it depends on the size of the susceptible group, because infectious and still-vaccinated individuals, usually, are not eligible for vaccination. The objective of the current section is to study the possibility of launching a supplementary vaccination program at the wake-up time, in order that population recovers the level of protection provided by the initial vaccine coverage as soon as possible. To ease the problem, we assume that revaccination is instantaneous or involves a negligible time in comparison with the time to observe a small number of new infections.

Hence, we focus on the time that is required to launch a new vaccination program with the purpose of increasing vaccination level to the initial coverage v_0. This elapsed time is represented by the random variable R_w, that was defined in terms of the wake-up time as $R_w = \inf\{t \geq 0 : S((T_w + t) + V(T_w + t) = v_0\}$ and it studies the interval of time going from T_w, when the alarm is triggered, until the instant at which the susceptible group has a large enough size to start a new vaccination campaign. For a given warning level w, the analysis of R_w relies on the initial outbreak condition but, again to ease the notation as we did in Section 3.1, we do not include the initial condition $(V(0) = v_0, I(0) = 1)$ in the representation of the time for revaccination.

Notice that a new vaccination program can be launched at time T_w whenever the size of the susceptible group will be of at least $(v_0 - w)$ individuals. There is a basic fact that can be stated with the help of the random variables S_w and $I_{v_0,1}$, introduced in the preceding section. Thus, with the help of the relationship (5), we get the probability of an immediate arrangement for vaccination.

$$P\{R_w = 0\} = P\{S_w \geq v_0 - w\} = \sum_{i=1}^{N-v_0} x^i_{v_0,1}. \tag{34}$$

To investigate R_w, when it is strictly positive, let us introduce the set of states $\widetilde{W} = \{(v, i) : 0 \leq v \leq w, 0 \leq i \leq N - v\}$ and the conditioned random variables $R_{v,i}$, which describe the revaccination time given that the current state of the underlying Markov chain is $(v, i) \in \widetilde{W}$.

We notice again that, whenever the current state (v, i) guarantees enough susceptible individuals to schedule an immediate supplementary vaccination, random variables $R_{v,i}$ are degenerate with a single mass point corresponding to 0 time units. That is,

$$P\{R_{v,i} = 0\} = 1, \quad \text{for } 0 \le v \le w, 0 \le i \le N - v_0. \tag{35}$$

If the current state does not have enough number of susceptible individuals to schedule an immediate supplementary vaccination, the conditional variables are continuous ones with support in $(0, \infty)$.

Now we introduce some notation for density functions, Laplace–Stieltjes transforms and moments of the random variable R_w and the auxiliary variables $R_{v,i}$, for $(v, i) \in \widetilde{W}$.

Let us denote by $f_w(t)$, for $t > 0$, the density function of the continuous part of R_w and we represent by $f_{v,i}(t)$ the density functions of the continuous random variables $\{R_{v,i} : 0 \le v \le w, N - v_0 + 1 \le i \le N - v\}$.

Laplace–Stieltjes transforms and moments will be represented as follows:

$$\Psi_w(z) = E\left[e^{-zR_w}\right], \quad \text{for } z \in \mathbb{C}, Re(z) \ge 0, \tag{36}$$

$$\psi_{v,i}(z) = E\left[e^{-zR_{v,i}}\right], \quad \text{for } z \in \mathbb{C}, Re(z) \ge 0, \tag{37}$$

$$\widetilde{M}^k_{R_w} = E\left[R^k_w\right], \quad \text{for } k \ge 0, \tag{38}$$

$$\widetilde{m}^k_{v,i} = E\left[R^k_{v,i}\right], \quad \text{for } k \ge 0. \tag{39}$$

Next, Proposition 2 summarizes results dealing with Laplace–Stieltjes transforms and moments of the auxiliary variables.

Proposition 2. *Given* $(v, i) \in \widetilde{W}$ *and* $z \in \mathbb{C}$*, with* $Re(z) \ge 0$*, the Laplace–Stieltjes transform of* $R_{v,i}$ *and the central moment of order zero satisfy:*

$$\psi_{v,i}(z) = \begin{cases} 1, & \textit{for } 0 \le i \le N - v_0, \\ \int_0^\infty e^{-zy} f_{v,i}(y)dy, & \textit{for } N - v_0 + 1 \le i \le N - v \end{cases} \tag{40}$$

$$\widetilde{m}^0_{v,i} = 1. \tag{41}$$

Proof. Result in (40) comes trivially from the definition of Laplace–Stieltjes transforms and from result shown in Equation (35). Result in Equation (41) is consequence of the relationship $\widetilde{m}^0_{v,i} = \psi_{v,i}(0)$ and (40). ■

Coming back to the revaccination time, R_w, next proposition contains relationships for density functions, Laplace–Stieltjes transforms and moments of R_w with their counterparts of the auxiliary variables $R_{v,i}$.

Proposition 3. *For a fixed warning level w, the distribution of the revaccination time R_w can be obtained from the distribution of the auxiliary random variables $\{R_{w,i} : 1 \leq i \leq N - w\}$ as follows:*

$$f_w(t) = \sum_{i=N-v_0+1}^{N-w} x^i_{v_0,1} f_{w,i}(t), \quad \textit{for } t > 0, \tag{42}$$

$$\Psi_w(z) = \sum_{i=1}^{N-w} x^i_{v_0,1} \psi_{w,i}(z), \quad \textit{for } z \in \mathbb{C}, Re(z) \geq 0, \tag{43}$$

$$\widetilde{M}^k_{R_w} = \begin{cases} 1, & \textit{for } k = 0, \\ \sum_{i=N-v_0+1}^{N-w} x^i_{v_0,1} \widetilde{m}^k_{w,i}, & \textit{for } k \geq 1. \end{cases} \tag{44}$$

Proof. First we notice that R_w-distribution is the mixture distribution derived from auxiliary variables $R_{w,i}$ with weights $x^i_{v_0,1}$, for $1 \leq i \leq N - w$. Therefore, results in Equations (42) and (43) follow from this remark.

Regarding moments, for order zero we have that $\widetilde{M}^0_{R_w} = \Psi_w(0)$. Particularizing Equation (43) at $z = 0$ and plugging Equation (41) we get the stated result in (44) for $k = 0$.

To deal with higher central order moments, we take into account that all of them arise as derivatives of its corresponding generating function. More explicitly, for $k > 0$ we have that

$$\widetilde{M}^k_{R_w} = (-1)^k \left. \frac{\partial^k \Psi_w(z)}{\partial z^k} \right|_{z=0}, \tag{45}$$

and similarly for central moments and generating functions of the auxiliary variables.

Finally, we differentiate Equation (43) k-times regarding z and evaluating at $z = 0$ we get

$$\widetilde{M}^k_{R_w} = \sum_{i=1}^{N-w} x^i_{v_0,1} \widetilde{m}^k_{w,i}. \tag{46}$$

Result in (44) comes after taking into account that, as it was stated in Equation (35), random variables $R_{w,i}$ for $1 \leq i \leq N - v_0$ are degenerate at value 0. ■

To find the distribution of the revaccination time, R_w, we need to characterize the distribution of the auxiliary variables $R_{v,i}$, for $(v, i) \in \widetilde{W}$. Next theorem provides a recursive scheme to determine their Laplace–Stieltjes transforms, which will be the basis to derive central moments of any order.

Theorem 3. *Given $z \in \mathbb{C}$, $Re(z) \geq 0$. The Laplace–Stieltjes transforms of the random variables $\{R_{v,i} : (v, i) \in \widetilde{W}\}$ are determined as follows:*

$$\psi_{v,i}(z) = 1, \quad \textit{for } 0 \leq v \leq w, 0 \leq i \leq N - v_0. \tag{47}$$

For $v = 0$ *and* $N - v_0 + 1 \leq i \leq N$*,*

$$\psi_{0,i}(z) = \prod_{j=N-v_0+1}^{i} \frac{A_{0,j}(z)}{B_{0,j}(z)}. \tag{48}$$

For $1 \leq v \leq w$*, we have*

$$\psi_{v,N-v_0+1}(z) = \frac{A_{v,N-v_0+1}(z) + G_{v,N-v_0+1}(z)}{B_{v,N-v_0+1}(z)}, \tag{49}$$

$$\begin{aligned}\psi_{v,i}(z) = & \sum_{j=N-v_0+2}^{i} \left(\frac{G_{v,j}(z)}{B_{v,j}(z)}\right) \prod_{k=j+1}^{i} \left(\frac{A_{v,k}(z)}{B_{v,k}(z)}\right) \\ & + \prod_{j=N-v_0+2}^{i} \left(\frac{A_{v,j}(z)}{B_{v,j}(z)}\right) \psi_{v,N-v_0+1}(z), \quad \text{for } N - v_0 + 2 \leq i \leq N - v.\end{aligned} \tag{50}$$

Functions $A_{v,j}(z)$*,* $B_{v,j}(z)$*, and* $G_{v,j}(z)$ *are determined recursively in reverse order, according to the following scheme:*

$$A_{v,j}(z) = \begin{cases} \gamma_{N-v}, & \text{for } j = N - v, \\ \gamma_j B_{v,j+1}(z), & \text{for } N - v_0 + 1 \leq j \leq N - v - 1, \end{cases} \tag{51}$$

$$B_{v,j}(z) = \begin{cases} z + q_{v,N-v}, & \text{for } j = N - v, \\ (z + q_{v,j}) B_{v,j+1}(z) - \lambda_{v,j} A_{v,j+1}(z), & \text{for } N - v_0 + 1 \leq j \leq N - v - 1, \end{cases} \tag{52}$$

$$G_{v,j}(z) = \begin{cases} \mu_{v,N-v} \psi_{v-1,N-v+1}(z), & \text{for } j = N - v, \\ \mu_{v,j} \psi_{v-1,j+1}(z) B_{v,j+1}(z) + \lambda_{v,j} G_{v,j+1}(z), & \text{for } N - v_0 + 1 \leq j \leq N - v - 1. \end{cases} \tag{53}$$

Proof. First, we notice that Equation (47) comes directly from result (40) in Proposition 2.

For a given state $(v, i) \in \widetilde{W}$, we condition on the next state the process visits, getting the relationship

$$\psi_{v,i}(z) = \frac{\gamma_i}{z + q_{v,i}} \psi_{v,i-1}(z) + \frac{\lambda_{v,i}}{z + q_{v,i}} \psi_{v,i+1}(z) + \frac{\mu_{v,i}}{z + q_{v,i}} \psi_{v-1,i+1}(z). \tag{54}$$

That is equivalent to

$$-\gamma_i \psi_{v,i-1}(z) + (z + q_{v,i}) \psi_{v,i}(z) - \lambda_{v,i} \psi_{v,i+1}(z) = \mu_{v,i} \psi_{v-1,i+1}(z). \tag{55}$$

At any point $z \in \mathbb{C}$, with $Re(z) \geq 0$, to get the value of the Laplace–Stieltjes transforms we have to solve the set of equations arising from (55) when we consider states $(v, i) \in \widetilde{W}$.

Let us begin by considering states with no vaccinated individuals, that is $v = 0$. By using the Gaussian elimination technique we express the initial system of equations (55) into a new system of triangular form:

$$-A_{0,i}(z)\psi_{0,i-1}(z) + B_{0,i}(z)\psi_{0,i}(z) = 0, \quad \text{for } N - v_0 + 2 \leq i \leq N, \tag{56}$$

where functions $A_{0,N}(z) = \gamma_N$, $B_{0,N}(z) = z + q_{0,N}$ and the remaining functions are determined in reverse order using the recursive expressions for $N - v_0 + 2 \leq i \leq N - 1$

$$A_{0,i}(z) = \gamma_i B_{0,i+1}(z), \tag{57}$$

$$B_{0,i}(z) = (z + q_{0,i})B_{0,i+1}(z) - \lambda_{0,i}A_{0,i+1}(z). \tag{58}$$

Therefore, we can write any transform involving i infected individuals in terms of the transform involving $(i - 1)$ infected individuals

$$\psi_{0,i}(z) = \frac{A_{0,i}(z)}{B_{0,i}(z)}\psi_{0,i-1}(z), \quad \text{for } N - v_0 + 2 \leq i \leq N. \tag{59}$$

Iterating this procedure, we can write transforms related to zero vaccinated individuals in terms of $\psi_{0,N-v_0+1}$.

$$\psi_{0,i}(z) = \prod_{j=N-v_0+2}^{i} \frac{A_{0,j}(z)}{B_{0,j}(z)}\psi_{0,N-v_0+1}. \tag{60}$$

On the other hand, plugging result (47) in Equation (55) for $i = N - v_0 + 1$, we obtain

$$(z + q_{0,N-v_0+1})\psi_{0,N-v_0+1}(z) - \lambda_{0,N-v_0+1}\psi_{0,N-v_0+2}(z) = \gamma_{N-v_0+1}. \tag{61}$$

Which jointly with Equation (56), particularized at $i = N - v_0 + 2$, gives

$$\psi_{0,N-v_0+1}(z) = \frac{A_{0,N-v_0+1}(z)}{B_{0,N-v_0+1}(z)}, \tag{62}$$

where functions $A_{0,N-v_0+1}(z)$ and $B_{0,N-v_0+1}(z)$ fit the structure given in the statement of the theorem.

Finally, substituting expression (62) in Equation (60) we get the expression stated in Equation (48).

For any v, with $0 < v \leq w$, Equation (55) can be solved recursively in an iterative manner by using the Laplace–Stieltjes transforms involving one vaccinated individual less. By applying again the Gaussian elimination procedure, we write the system of equations appearing in (55), for $N - v_0 + 1 \leq i \leq N - v$, as follows:

$$-A_{v,i}(z)\psi_{v,i-1}(z) + B_{v,i}(z)\psi_{v,i}(z) = G_{v,i}(z), \tag{63}$$

where $A_{v,N-v}(z) = \gamma_{N-v}$, $B_{v,N-v}(z) = (z + q_{v,N-v})$, $G_{v,N-v}(z) = \mu_{v,N-v}\psi_{v-1,N-v+1}(z)$ and the remaining functions for $N - v_0 + 1 \leq i \leq N - v + 1$ are determined in reverse order according to the following expressions:

$$A_{v,i}(z) = \gamma_i B_{v,i+1}(z), \tag{64}$$

$$B_{v,i}(z) = (z + q_{v,i})B_{v,i+1}(z) - \lambda_{v,i}A_{v,i+1}(z), \tag{65}$$

$$G_{v,i}(z) = \mu_{v,i}\psi_{v-1,i+1}(z)B_{v,i+1}(z) + \lambda_{v,i}G_{v,i+1}(z), \tag{66}$$

that correspond to the expressions (51)–(53) in the statement of the theorem.

Using the explicit result given in Equation (47), for $0 < v \leq N - v_0$, we get the closed-form expression for the Laplace–Stieltjes transform corresponding to $i = N - v_0 + 1$. That is,

$$\psi_{v,N-v_0+1}(z) = \frac{A_{v,N-v_0+1}(z) + G_{v,N-v_0+1}(z)}{B_{v,N-v_0+1}(z)}. \tag{67}$$

After some algebra on Equation (63), we can express transforms $\psi_{v,i}(z)$, for $0 < v \leq w$ and $N - v_0 + 2 \leq i \leq N - v$, in terms of $\psi_{v,N-v_0+1}(z)$ as it is written in Equation (50) in the statement of the theorem. ■

Now we focus on the central moments of order k of the revaccination time, $\widetilde{M}^k_{R_w} = E[R^k_w]$, for $k \geq 0$. First we recall the result stated in Equation (44) of the Proposition 3. Hence, moments of order $k \geq 1$ can be determined from moments of the random variables $\{R_{v,i} : (v, i) \in \widetilde{W}\}$ through the relationship appearing in the expression (44).

Consequently, we will develop an iterative scheme that will provide central moments $m^k_{v,i}$, for $(v, i) \in \widetilde{W}$. Moments of order zero come from the explicit results shown in Equations (41) and (44). For $k \geq 1$, we start from Equations (47) and (55). Taking derivatives of order k regarding z on both equations, and setting $z = 1$, we get for any $0 \leq v \leq w$:

$$\widetilde{m}^k_{v,i} = 0, \quad \text{for } 0 \leq i \leq N - v_0, \tag{68}$$

$$-\gamma_i\widetilde{m}^k_{v,i-1} + q_{v,i}\widetilde{m}^k_{v,i} - \lambda_{v,i}\widetilde{m}^k_{v,i+1} = t^k_{v,i}, \quad \text{for } N - v_0 + 1 \leq i \leq N - v, \tag{69}$$

where $t^k_{v,i} = \mu_{v,i}\widetilde{m}^k_{v-1,i+1} + k\widetilde{m}^{k-1}_{v,i}$.

Notice that the right-hand side of Equation (69) depends on moments of one order less and on moments of one vaccinated individual less. Therefore, it is possible to obtain the moments of any order $k \geq 1$ in a recursive manner, starting from the explicit results of order zero moments stated in Equation (41). The following theorem provides this recursive scheme.

Theorem 4. *Given any integer $k \geq 0$, the central order moments $\widetilde{m}^k_{v,i} = E[R^k_{v,i}]$, for $(v, i) \in \widetilde{W}$, can be recursively determined in the following way:*

For $0 \le v \le w$ *and* $0 \le i \le N - v$*,*

$$\widetilde{m}^{0}_{v,i} = 1. \tag{70}$$

Given $k \ge 1$*, for* $0 \le v \le w$ *we have that*

$$\widetilde{m}^{k}_{v,i} = 0, \quad \textit{for } 0 \le i \le N - v_0, \tag{71}$$

$$\widetilde{m}^{k}_{v,N-v_0+1} = \frac{G^{k}_{v,N-v_0+1}}{B^{k}_{v,N-v_0+1}}, \tag{72}$$

$$\begin{aligned}\widetilde{m}^{k}_{v,i} = &\sum_{l=N-v_0+2}^{i} \left(\frac{G^{k}_{v,l}}{B^{k}_{v,l}}\right) \prod_{j=l+1}^{i} \left(\frac{A^{k}_{v,j}}{B^{k}_{v,j}}\right) \\ &+ \prod_{l=N-v_0+2}^{i} \left(\frac{A^{k}_{v,l}}{B^{k}_{v,l}}\right) \widetilde{m}^{k}_{v,N-v_0+1}, \quad \textit{for } N - v_0 + 2 \le i \le N - v,\end{aligned} \tag{73}$$

where the coefficients $A^{k}_{v,j}$*,* $B^{k}_{v,j}$*, and* $G^{k}_{v,j}$ *are determined, in reverse order from* $N - v$ *to* $N - v_0 + 1$*, according to the following scheme:*

$$A^{k}_{v,j} = \begin{cases} \gamma_{N-v}, & \textit{for } j = N - v, \\ \gamma_j B^{k}_{v,j+1}, & \textit{for } N - v_0 + 1 \le j \le N - v - 1, \end{cases} \tag{74}$$

$$B^{k}_{v,j} = \begin{cases} q_{v,N-v}, & \textit{for } j = N - v, \\ q_{v,j} B^{k}_{v,j+1} - \lambda_{v,j} A^{k}_{v,j+1}, & \textit{for } N - v_0 + 1 \le j \le N - v - 1, \end{cases} \tag{75}$$

$$G^{k}_{v,j} = \begin{cases} t^{k}_{v,N-v}, & \textit{for } j = N - v, \\ t^{k}_{v,j} B^{k}_{v,j+1} + \lambda_{v,j} G^{k}_{v,j+1}, & \textit{for } N - v_0 + 1 \le j \le N - v - 1. \end{cases} \tag{76}$$

Proof. For $k = 0$, $0 \le v \le w$, and $0 \le i \le N - v$ result in Equation (70) is given by Equation (41).

Given any integer $k \ge 1$, the moments $\widetilde{m}^{k}_{v,i}$, for $0 \le v \le w$ and $0 \le i \le N - v$, can be determined by solving Equations (68)–(69).

We start with the first-order moments, that is $k = 1$. We notice that plugging in Equation (69) the result given in Equation (41), the right-hand side term of (69) becomes $t^{1}_{v,i} = \nu_{v,i} \widetilde{m}^{1}_{v-1,i+1} + 1$, that depends on first-order moments of one vaccinated individual less.

In more detail, for $0 \le v \le w$ and $N - v_0 + 1 \le i \le N - v$, we get

$$-\gamma_i \widetilde{m}^{1}_{v,i-1} + q_{v,i} \widetilde{m}^{1}_{v,i} - \lambda_{v,i} \widetilde{m}^{1}_{v,i+1} = t^{1}_{v,i}. \tag{77}$$

Hence, Equation (77) presents the same structure as Equation (55). Therefore, first-order moments can be recursively determined using the Gaussian elimination technique presented in the proof of Theorem 3, by substituting in Equation (55) transforms $\psi_{v,i}(z)$ with $\widetilde{m}^1_{v,i}$, functions $q_{v,i}(z)$ with $q_{v,i}$ and the right-hand side term with $t^1_{v,i}$.

Hence, the resulting triangular form is

$$-A^1_{v,i}\widetilde{m}^1_{v,i-1} + B^1_{v,i}\widetilde{m}^1_{v,i} = G^1_{v,i}, \quad \text{for } 0 \le v \le w, N - v_0 + 1 \le i \le N - v. \tag{78}$$

Now, by considering Equation (77), for $i = N - v_0 + 1$, and Equation (78), for $i = N - v_0 + 2$, with the help of the explicit result (41), we finally get that

$$B^1_{v,N-v_0+1}\widetilde{m}^1_{v,N-v_0+1} = G^1_{v,N-v_0+1}, \tag{79}$$

which gives the first-order moment $\widetilde{m}^1_{v,N-v_0+1}$ as appears in Equation (72), when $k = 1$.

Finally, iterating this procedure we can get moments of any order $k \ge 2$ from moments of one order less. ■

To compute the moments of the revaccination time R_w, the recursive scheme appearing in Theorem 4 is implemented in the following algorithm.

Algorithm 3 (R_w-moments)**.** *For a given integer k, the central moments of the revaccination time* $\{\widetilde{M}^k_{R_w} \ : \ \text{for } k \ge 0\}$ *are determined according to the following scheme:*

```
Step 1: Set $j = 0$.
Step 2: Set $v = 0$
    Step 2a: Set $i = 0$. Set $\widetilde{m}^j_{v,i} = 1$.
    Step 2b: Set $i = i + 1$. While $i \le N - v$, compute $\widetilde{m}^j_{v,i}$ using Equation (41).
    Step 2c. Set $v = v + 1$. While $v \le w$, go to Step 2a.
Step 3. Set $\widetilde{M}^j_{R_w} = 1$.
Step 4: Set $j = j + 1$. If $j > k$, stop.
Step 5: Set $v = 0$.
    Step 5a: Set $i = N - v$ and compute coefficients $A^j_{v,i}$, $B^j_{v,i}$, and $G^j_{v,i}$ through Equations (74)–(76).
    Step 5b: Set $i = i - 1$. While $i \ge N - v_0 + 1$, compute coefficients $A^j_{v,i}$, $B^j_{v,i}$, and $G^j_{v,i}$ through
             Equations (74)–(76).
    Step 5c: Set $i = 0$. While $i \le N - v_0$, set $\widetilde{m}^j_{v,i} = 0$ and $i = i + 1$.
    Step 5d: For $i = N - v_0 + 1$, compute $\widetilde{m}^j_{v,i}$ through Equation (72) and set $i = i + 1$.
    Step 5e: While $N - v_0 + 2 \le i \le N - v$, compute $\widetilde{m}^j_{v,i}$ through Equation (73) and set $i = i + 1$.
Step 6: Set $v = v + 1$. If $v \le w$, go to Step 5a.
Step 7: Compute $\widetilde{M}^j_{R_w}$ using Equation (44) and go to Step 4.
```

Note that Step 7 in Algorithm 3 requires the set of probabilities $\{x^i_{v_0,1} \ : \ N - v_0 + 1 \le i \le N - w\}$ that can be computed by means of Algorithm 1.

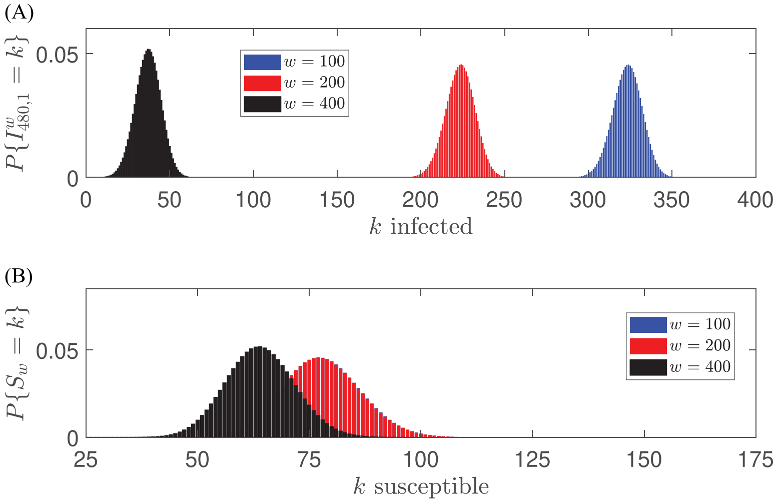


FIGURE 3 Probability mass functions of $I^{w}_{480,1}$ and of S_w for $w \in \{100, 200, 400\}$, when $h = 0.1$

4 | NUMERICAL RESULTS

Next we proceed to show numerical insights and applicability of theoretical and algorithmic results shown in previous sections. We will apply theoretical derivations to a mathematical model representing the evolution of diphtheria outbreaks taking place in a population of moderate size.

Diphtheria is a serious respiratory illness, caused by strains of *Corynebacterium diphtheriae* that spread from person to person mainly through respiratory droplets but also through close contact with an infected individual. Diphtheria toxoid-based vaccines have been part of the WHO Expanded Programme of Immunization since 1974. Vaccination campaigns have resulted in a more than 90% decrease in number of cases worldwide during the period 1980–2000.[43] However, diphtheria is still a potentially fatal disease that is found in many areas such as Asia, the South Pacific, the Middle East, eastern Europe, and the Caribbean.

From now on, we consider that a diphtheria outbreak has been detected in a boarding school or orphanage institution with an overall population of $N = 500$ residents. We assume that initially v_0 dwellers have received a vaccine against this disease. We fix the time unit to be the recovery time, therefore the recovery rate is taken as $\gamma = 1.0$. The internal rate of transmission is $\beta = 6.5$, that is selected by assuming a basic reproduction number $R_0 = \beta/\gamma = 6.5$, in agreement with the estimate of diphtheria transmission given in Ref. 44. Values for the vaccine failure probability, h, will be chosen from 0.05 to 0.2, in accordance to clinical evidences[43] that show that diphtheria vaccines are effective at least among 80% of the vaccinated individuals. The external transmission rate is taken as $\xi = 0.01$, to represent that most of the contacts occur within the institution premises and to guarantee infection reintroduction when occasionally the disease is faded away.

In Figure 3, we display mass distribution functions of the number of infected individuals ($I^{w}_{v_0,1}$, in Figure 3A) and the number of susceptible individuals (S_w, in Figure 3B), that can be found in the institution when the number of vaccinated persons decreases to the level w. We assume an initial vaccination coverage of $v_0 = 480$ individuals, for a vaccine that is 90% effective, and the warning level w is taken as 100, 200, or 400 individuals. We can observe that the distribution of $I^{w}_{480,1}$ is displaced to the left when the warning level w increases. This is what is expected because high control values for triggering the alarm give fewer possibilities of a higher number of

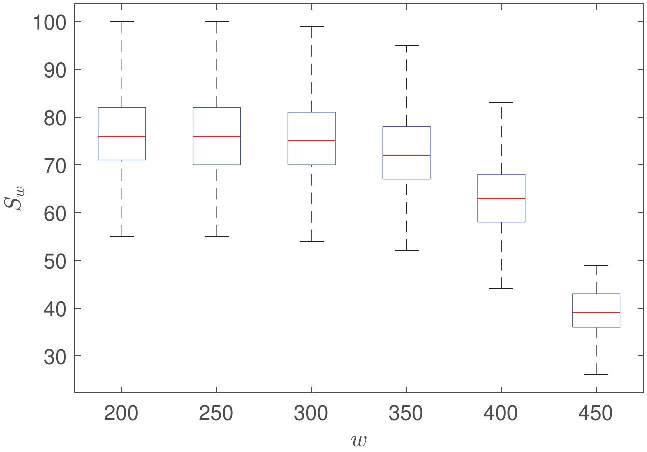


FIGURE 4 Box-plot for S_w under several warning levels when $v_0 = 480$ and $h = 0.1$

infectious cases. On the other hand, notice that the basic reproduction number R_0 is large enough as to increase much more the number of infectious in comparison with the number of susceptible individuals, when the warning level decreases. Hence, distributions of S_w depicted in Figure 3B are graphically indistinguishable for $w = 100$ and 200. This fact is in accordance with the pattern show in Figure 3A for the distribution of $I^w_{480,1}$ and the relationship: $S_w + I^w_{v_0,1} = N - w$, appearing in Equation (5) that links both random variables. Hence, lowering the warning level leads to an increase in the number of infected individuals in the institution, while the number of susceptible individuals is mostly concentrated in low values of the interval (50, 100).

The box-plot appearing in Figure 4 corresponds to the distribution of S_w, the number of susceptible individuals at the wake-up time; that is, the epoch at which the number of vaccinated individuals reaches the warning level w. The box encloses first and third quartiles of the distribution, the line drawn across the box indicates the median of the distribution. Dashed lines in the plot are drawn from the lower and upper quartile to 0.005 and 0.995-quantile, respectively, covering 99% of the distribution. We compare patterns in the number of susceptible people when we increase the alert level, in a population of $N = 500$ individuals, where $v_0 = 480$ of them have received a 90% effective vaccine. S_w-distribution presents a symmetric shape, which is more concentrated around the median when we consider higher warning levels. Again, due to high value of R_0, reducing w under 200 produces a small quantitative effect on S_w. In consequence, box-plots for $w < 200$ look like those for $w = 200$ or 250. Therefore, we point out that when we choose a warning vaccination level under 350, we cannot guarantee that at wake-up time the institution would be lodging the minimum number of individuals (i.e., $480 - w$) needed to increase vaccine coverage up to the initial value $v_0 = 480$ through vaccine administration.

In the following set of experiments, we evaluate the influence of the potential risk of vaccine failure on S_w. We assume that the initial coverage is $v_0 = 480$. In Figure 5, we represent the expected number of susceptible individuals at wake-up time, $E[S_w]$, as a function of the warning level. Each curve corresponds to a different vaccine described in terms of its vaccine failure probability h. In accordance with box-plot characteristics indicated in Figure 4, $E[S_W]$ decreases with w, no matter how effective the vaccine is. We notice that, for $w < 200$ the influence of the vaccine failure risk in $E[S_w]$ is relatively small. However, for a fixed warning level $w > 200$, the expected number of susceptible individuals decreases when the risk of vaccine failure increases. In particular, in this institution of 500 individuals affected by a diphtheria outbreak where 480 of them were vaccinated prior to the start of the outbreak, numerical results evince that, at the

FIGURE 5 $E[S_w]$ as a function of the warning level when $v_0 = 480$ and $h \in \{0.05, 0.1, 0.2\}$

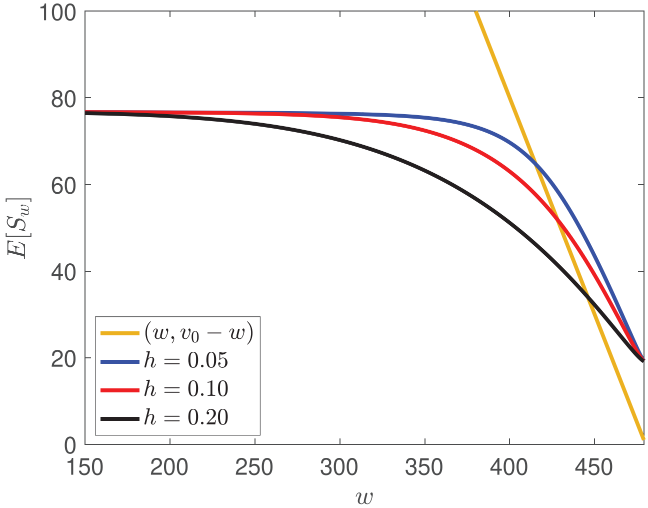
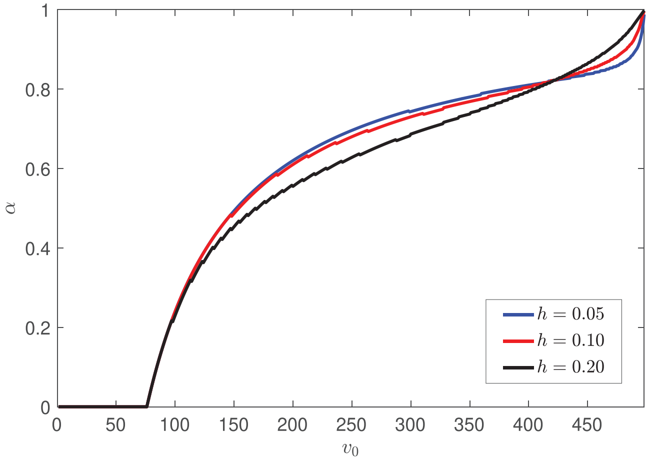


FIGURE 6 Lowest warning level, as a proportion of the initial coverage, satisfying $E[S_w] > v_0 - w$ for several vaccine failure probabilities



moment when 80 vaccinated persons have developed the infection (i.e., $w = 400$), a low effective vaccine with $h = 0.2$ guarantees around 50 susceptible individuals in the population while for a more effective vaccine with $h = 0.05$ the expected value grows up to 70 susceptible individuals.

We observe that we can select an appropriate warning level using a criterion on the expected number of susceptible persons at wake-up time T_w. In that sense, we depict the yellow line corresponding to the straight line $E[S_w] = v_o - w$ which, for every warning level w, gives the minimum quantity of susceptible individuals that should be vaccinated to raise the vaccination coverage to its initial level.

To develop this idea, we introduce α as the lowest proportion of the initial coverage v_0 that guarantees that at wake-up time, $T_{\alpha v_0}$, the mean number of eligible (i.e., susceptible) individuals is large enough to raise the number of vaccinated individuals to the initial level v_0. That is, $\alpha = min\{a \in (0, 1) : E(S_{av_0}) > v_0(1 - a)\}$.

In Figure 6, we represent this lowest proportion as a function of the initial coverage. Each curve corresponds to a different potential risk of vaccine failure h and initial coverage ranges from an unprotected ($v_0 = 0$) to a fully protected ($v_0 = N = 500$) population. In general terms, an increase in initial vaccine coverage implies an increase in the lowest proportion α and consequently in

TABLE 1 Optimal warning level and R_w measures according to vaccine efficacy when $v_0 = 480$ and $i_0 = 1$

h	w^*	$P(R_{w^*} > 0)$	$E[R_{w^*} \mid R_{w^*} > 0]$	$\sigma(R_{w^*} \mid R_{w^*} > 0)$
0.05	417	0.40753	5.86253×10^{13}	1.07798×10^{14}
0.1	429	0.43929	8.11198×10^{13}	1.19392×10^{14}
0.2	448	0.37959	9.47003×10^{13}	1.23915×10^{14}

the warning level. We recall that in accordance with diphtheria and vaccine characteristics, it is possible to determine the appropriate vaccination level that provides herd immunity in the population. In a Markovian stochastic framework, vaccination coverage providing herd immunity can be determined in terms of the exact reproduction number R_{e0}.[30,31] Applying this methodology to our choice of model parameters, we get that an initial coverage of 424 vaccinated individuals reduces viral transmission and prevents major outbreaks in the whole institution. In addition, as was pointed out in Figure 5, for vaccination coverage values higher than 424 less efficient vaccines need larger warning levels to assure that the population will contain, in mean terms, enough eligible individuals to recover the initial vaccine coverage v_0 when the alarm is triggered.

We have suggested a criterion for selecting the warning level w based on checking the expected size of the susceptible group at wake-up time. Though, a choice of a threshold w fulfilling this rule does not guarantee that the event of finding a large enough eligible group will occur in every outbreak. To try to avoid this inconvenience, we can use the information provided by the random variable R_w. We recall that this was defined in Section 3.2 as the elapsed time between the wake-up time and the instant at which the population contains sufficient susceptible individuals to be vaccinated to raise the vaccinated group to its initial size (i.e., the initial coverage v_0).

To illustrate this fact, we state the above criterion clearly. For a fixed initial vaccine coverage, v_0, we choose the warning vaccination level as follows $w^* = min\{w \in [0, v_0) : E[S_w] \geq v_0 - w\}$.

Having in mind the applicability of this choice, next we evaluate some measures related to R_w, when a warning level was fixed according to the above-mentioned criteria. Specifically, for a selected warning level we will compute mean and standard deviation of R_w, and also the probability $P\{R_w > 0\}$, that gives the chances of not being able to launch an immediate vaccination campaign due to an insufficient number of individuals in the eligible group.

Table 1 summarizes numerical characteristics of revaccination time when we vary potential risk of vaccine failure. Again we consider a diphtheria outbreak taking place within an institution of $N = 500$ individuals, where 480 have received a vaccine before the start of the outbreak. According to vaccine and disease parameters, we fix the optimal warning level w^* using the criterion explained in the previous paragraph. Hence, by the time that the number of vaccine protected individuals drops down to w^* individuals, it is expected that the number of susceptible individuals staying in the institution is large enough to increase the total number of vaccine protected individuals to the initial coverage of 480 residents, through a new (and instantaneous) vaccination campaign among the susceptible group. However, the choice of w^* does not guarantee that this new vaccination campaign could be implemented at wake-up time. In that sense, results shown in the Table 1 indicate that, for an $(1-h)100\%$ efficient vaccine and a warning level settled at w^* individuals, it is necessary to wait until the mass of susceptible individuals is large enough in most outbreaks. In addition, entries corresponding to the mean and standard deviation of $(R_{w^*} \mid R_{w^*} > 0)$ indicate that if we cannot revaccinate immediately, then there is a big chance that we will never be able to. Hence, as a consequence of the high transmission potential of diphtheria ($R_0 = 6.5$), it is likely to have to wait a long time to get the number of eligible individuals high enough. Numerical experiments, additional to those reported here, show that the mean and standard deviation of R_w increase as functions of vaccine failure probability h, but decrease for increasing values of the warning level.

Consequently, the criterion to select the appropriate warning level can be refined by fixing a maximum value on $P\{R_w > 0\}$ and/or on $E[R_w]$ regarding the idiosyncrasies of the institution itself.

5 | CONCLUSIONS AND FUTURE WORK

This paper studies a stochastic Susceptible-Infectious-Vaccinated-Susceptible (SIVS) model where a Markov chain represents disease transmission. The CTMC models the changes in the state of the epidemic process that records the number of individuals that are susceptible, infected, or vaccinated at any time $t > 0$. Model hypothesis assume infection reintroduction and imperfect vaccine. Hence, susceptible and vaccinated individuals (when vaccine fails) can get the infection from internal and external contacts. In any case, any individual recovers as a susceptible one, as if he/she had never had the vaccine. We assume that population is herd immunity protected because a sufficient number of individuals, v_0, has been vaccinated prior to the onset of the outbreak. As disease remains present, due to external contacts, eventually every vaccinated individual can get the disease. Consequently, while the epidemic process evolves, the number of vaccinated individuals decreases and herd protection can be lost.

In Ref. 37, we set a level of vaccinated individuals, w, to activate an alert in case the number of vaccinated individuals drops down to the selected level. Our present research focuses on restoring the herd immunity level by scheduling a new vaccination campaign. With this aim in mind and linked to the warning level, we observe the group of individuals eligible for vaccination and introduce the random variables S_w and R_w recording the size of the susceptible group when the alarm is triggered and the time until the size of this group is large enough to increase the vaccinated population to the initial herd level v_0, respectively. We present results giving both analytical formulas and practical numerical methods for calculating moments and generating functions of these variables of interest.

We notice that, the underlying Markov chain X can be identified as a finite quasi-birth-death (QBD) process. These processes are extensively used in modeling stochastic systems and their analysis can be addressed by the matrix-analytics methodology.[45] Most of the theoretical work for QBD concerns stationary distributions and moments of first passage times, but it can be applied to derive other interesting characteristics such as absorption and hitting probabilities.[46,47] In this sense, we point out that the distribution of the random variable S_w can be derived from hitting probabilities of reaching states showing w vaccinated for an auxiliary absorbing process that takes values in $\widehat{W}$, while the random variable R_w can be seen as a first passage time to states in the set $\{(v, i) : 0 \leq v \leq w, 0 \leq i \leq N - v_0 + w - v\}$. Hence results presented in this paper can be derived by the matrix-analytics methodology. Instead of that our approach exploits the structure of the systems of equations to derive the explicit recursive expressions appearing in Theorems 1, 2, 3, and 4.

With illustrative purposes, we consider that a diphtheria outbreak occurs in a herd protected boarding school where 500 pupils live within premises. Institution authorities are aware of health condition of any dweller. In particular, they have information about the number of vaccinated individuals who get the disease, therefore they know if $V(t)$ had reached or not the alarm level w and the time T_w. Analytic and algorithmic results provide information on the distribution of the above-mentioned random variables. Recalling numerical results, for this particular situation where disease transmission is quite high, we observe that as the warning level is less restrictive, the population will contain a larger number of infectious cases when the alarm is triggered and it will be less probable to be able to schedule an immediate vaccination program at wake-up time. Consequently, too low values of w will not guarantee enough individuals in the eligible group for vaccination to restore herd immunity in a reasonable time interval. According to vaccine characteristics and initial coverage, we can select a warning level w that guarantees that $w + E[S_w] \geq v_0$ and refine the search by adding additional criteria depending on the time R_w required for launching a vaccination campaign at the time when the alert is activated.

We point out that a criterion based on S_w and on R_w is also of interest to manage outbreaks of many other vaccine preventable contact diseases. One drawback of our model is the instantaneous revaccination assumption. In practice, giving the cycling of individuals through S and I compartments, the number of susceptible will probably change while the vaccination campaign is running. Another drawback is the assumption of fixed value for failure probability, h, which implies that, within each individual, the vaccine successfully resists challenge by the infection independently and with a fixed probability until the vaccine fails. Assuming more realistic hypothesis increases model complexity, compromises its mathematical tractability, and can pose computational instability. The possibility of studying random variables associated to warning levels in more sophisticated models depends on a balance between the realism of a model and its mathematical simplicity. In this sense, we plan to extend the analysis to epidemic models with latency period or recovery, involving immunization waning effects (see, for instance, Refs. 17, 48–50). Hoping that the study can be developed in a stochastic Markovian framework, where it is possible to identify events leading to a new contagion, recovery, waning immunization, and so forth.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

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