UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE ESTUDIOS ESTADÍSTICOS

TESIS DOCTORAL

Studying the effect of vaccination in epidemic models with stochastic transmission

Estudio del efecto de la vacunación en modelos de epidemias con transmisión estocástica

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

María Gamboa Pérez

Directora

María Jesús López Herrero

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DOCTORADO EN ANÁLISIS DE DATOS

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Dedicado a:

mis padres, Vicen y Regis.

Sin vuestro apoyo

no hubiera sido posible.

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Abstract

Mathematical epidemic models are frequently used in biology for analyzing transmission dynamics of infectious diseases and assessing control measures to interrupt their expansion.

In order to select and develop properly the above mathematical models, it is necessary to take into account the particularities of an epidemic process as type of disease, mode of transmission and population characteristics.

In this thesis we focus on infectious diseases with stochastic transmission including vaccination as a control measure to stop the spread of the pathogen.

To that end, we consider constant and moderate size populations where individuals are homogeneously mixed. We assume that characteristics related to the transmission/recovery of the infectious disease present a common probabilistic behavior for individuals in the population. To assure herd immunity protection, we consider that a percentage of the population is protected against the disease by a vaccine, prior to the start of the outbreak. The administered vaccine is imperfect in the sense that some individuals, who have been previously vaccinated, failed to increase antibody levels and,

in consequence, they could be infected. Pathogenic transmission occurs by direct contact with infected individuals. As population is not isolated, disease spreads from direct contacts with infected individuals inside or outside the population.

In this context, we describe the compartmental stochastic Susceptible-Vaccinated-Infected-Susceptible (SVIS) y Susceptible-Vaccinated-Infected -Recovered (SVIR) models, considering an external source of infection and imperfect vaccine. We represent the evolution of an epidemic process in terms of multidimensional continuous-time Markov chains and we organize state spaces in terms of levels and sub-levels. Such organization will permit us to simplify the study and to analyze the underlying Markov chains as quasi-birth-and-death (QBD) processes.

Under the above model hypothesis, we study the effect of vaccination in the expansion of an epidemic, taking into account different possibilities in the selection of model parameters regarding the transmission of the infectious disease. To attain this objective we analyze the stationary probabilistic behavior of several random variables related to reproduction numbers, incidence measures and time measures, in a post-vaccination context, by applying specific techniques of stochastic processes.

Overall, we show that vaccination plays a fundamental role in the control of an infectious disease. In general, we observe that large vaccine coverage produce less severe epidemics in terms of incidence and speed of transmission of the infectious disease. Vaccine effectiveness also plays an important role in the transmission of the pathogen.

Less effective vaccines could produce faster loss of herd immunity and more incidence of the infectious disease than others more effective. The external source of infections also plays a special role to study the long-term behavior of the epidemic. This hypothesis implies that, for both models, the epidemic process does not end when there are not infected individuals within the population, in contradistinction to the traditional stochastic SIS and SIR models. In that sense, although infection clears, there is an eventual reintroduction of the infectious disease in the population. Consequently, epidemic processes are larger in time and produce more incidence of infectious cases.

Resumen

Los modelos matemáticos epidémiológicos se usan frecuentemente en biología para analizar las dinámicas de transmisión de enfermedades infecciosas y para evaluar medidas de control con el objetivo de frenar su expansión.

Para poder seleccionar y desarrollar adecuadamente estos modelos es necesario tener en cuenta las particularidades propias del proceso epidémico tales como el tipo de enfermedad, modo de transmisión y características de la población.

En esta tesis nos centramos en el estudio de enfermedades de tipo infeccioso con transmisión por contacto directo, que disponen de una vacuna como medida de contención en la propagación del patógeno.

Para ello, consideramos poblaciones de tamaño moderado, que permanece constante a lo largo de un brote y asumiremos que los individuos no tienen preferencia a la hora de relacionarse y que las características referentes a la transmisión de la enfermedad se representan en términos de variables aleatorias, comunes para todos los individuos. La población no está aislada y la transmisión del patógeno se produce mediante contacto directo con cualquier persona infectada, tanto de dentro de la población como fuera de ella. Asumimos que, antes del inicio del brote epidémico, se ha administrado la vacuna

a un porcentaje suficiente de individuos de la población, de forma que se asegure la inmunidad de rebaño. Consideramos que la vacuna administrada es imperfecta en el sentido que algunos individuos vacunados no logran desarrollar anticuerpos frente a la enfermedad y por lo tanto, podrían resultar infectados al contactar con individuos enfermos.

En este contexto describimos los modelos compartimentales estocásticos Susceptible-Vacunado-Infectado-Susceptible (SVIS) y Susceptible-Vacunado-Infectado-Recuperado (SVIR) pero considerando, además, que existe una fuente externa de infección y que la vacuna administrada es imperfecta. En ambos modelos, representamos la evolución del proceso epidémico mediante cadenas de Markov en tiempo continuo multidimensionales y organizamos su espacio de estados en niveles y subniveles. Esta organización nos permite simplificar el estudio y analizar las cadenas de Markov subyacentes como procesos de cuasi-nacimiento y muerte (QBD).

Bajo las hipótesis anteriores, estudiamos el efecto de la vacunación en la expansión de una epidemia teniendo en cuenta diversas posibilidades en la selección de los parámetros característicos relativos a la transmisión de la enfermedad. Para lograr este objetivo analizamos el comportamiento probabilístico, en situación estable, de diversas variables aleatorias tales como números reproductivos, medidas de incidencia y medidas de tiempo, desde el punto de vista post-vacunación, aplicando una metodología enfocada en los procesos estocásticos.

De manera global, mostramos que la vacunación juega un papel fundamental en la contención de la expansión del patógeno. En general, observamos que grandes coberturas vacunales producen epidemias menos severas

en cuanto a incidencia y a velocidad de propagación de la enfermedad. La efectividad de la vacuna también es un aspecto importante a considerar. Vacunas con alta probabilidad de fallo pueden producir más rápidamente una pérdida de la inmunidad de rebaño y mayor incidencia de la enfermedad, que si consideramos vacunas más efectivas. La fuente externa de contagio tiene un papel importante en el comportamiento a largo plazo de la epidemia. Esta hipótesis hace que en ambos modelos, a diferencia de los modelos tradicionales SIS y SIR estocásticos, la erradicación de la enfermedad no se produzca cuando no haya en la población individuos infectados y por lo tanto exista una reintroducción de la enfermedad dando lugar a procesos epidémicos mucho más largos y con una mayor incidencia de individuos contagiados.

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Chapter 1

Introduction

Diseases have afflicted humanity since the earliest days. The Centers for Disease Control and Prevention (CDC) describes an epidemic as an unexpected increase in the number of disease cases in a specific geographical area. If the spread of the disease occurs over a wide geographic area, such as multiple countries or continents, affecting a significant proportion of the population, it is called pandemic. Sometimes the disease is present permanently but limited to a particular region and it is called an endemic outbreak.

This thesis is related to the mathematical modelling of the spread of infectious diseases under the effect of vaccination. In this Chapter, we present an overview of the investigation, giving details about the objectives, the methodology applied that has led us to obtain theoretical and algorithmic results and its organization. We discuss and include up-to-date historical information about the most significant epidemics and pandemics in the history. We also give an introduction to mathematical epidemiology including the development of mathematical models along history. We describe sev-

eral mathematical models and focus on those that consider vaccination as a health control strategy. We provide information about available vaccines and present important insights and concepts related to vaccination. Several measures related to the spread of an infectious disease are described to introduce the quantifiers studied in this investigation.

1.1 Objectives, methodology and thesis organization

1.1.1 Objectives

This thesis aims to draw attention to the effect of vaccination in epidemic models under a stochastic approach. The specific objectives of this project are:

(a) To construct mathematical models to represent the evolution of an epidemic process. In particular, we study the dynamics of the spread of infectious diseases that are transmitted by direct contact, in a population of constant and moderate size. Compared with the existing literature, this research work considers mathematical epidemic models where the underlying population is not isolated and it is partially protected against the disease by an imperfect vaccine. Vaccine was administered, prior to the onset of the outbreak, to a percentage of the population. According to the imperfect vaccine hypothesis, eventually, the number of vaccinated individuals drops down during an epidemic process and the herd immunity could be lost.

(b) To explore the long-term behavior of the infectious process.

(c) To describe and analyze stochastic measures, related to exact reproduction numbers, incidence measures and time measures, in a post-vaccination context, in order to quantify and provide information about:

  (c1) The impact of vaccination on transmission dynamics of the infectious disease in a given population.

  (c2) The potential transmission of the pathogen, through exact reproduction numbers.

  (c3) The scope and severity of an epidemic, trough incidence measures.

  (c4) The speed of transmission of the pathogen, through time measures.

  (c5) The appropriate vaccine coverage that guarantees herd immunity during an outbreak.

  (c6) The possibility of an immediate re-vaccination program and if not possible, the time until it could be launched, through incidence and time measures

  (c7) The appropriate number of susceptible individuals that should be in the population to guarantees that a re-vaccination could be launched immediately.

(d) To carry out a comprehensive sensitivity analysis to measure the robustness of the model and to understand the impact of vaccination.

(e) To illustrate theoretical and algorithmic results by carrying out a set of numerical examples regarding the transmission of the pathogen.

1.1.2 Methodology

The purpose of this Section, is to give an outline of mathematical methods that are followed in the study. Theoretical techniques are focused on the use of the stochastic processes to describe the dynamics of transmission of infectious diseases. This framework is more appropriate than the deterministic one to describe the evolution of the infectious process in small communities, since it takes into account the random nature of an epidemic and differences among individuals regarding epidemic characteristics. In particular, we describe the evolution of an epidemic process in terms of a continuous-time Markov chain (CTMC), with finite state space. We present a specific organization of states that leads to the study of a level-dependent quasi-birth and death process (LD-QBD). In this sense, the transmission dynamics can be analyzed applying matrix methods. In order to carry out objectives (a)-(e), we apply specific techniques such as first step analysis. Gaussian elimination and recursive methods are used to solve system of equations obtained during the analysis of the CTMC.

The first step method proceeds by analyzing or discomposing the possibilities that can arise when sojourn times end and then, appealing the law of total probability, in combination with the Markov property, to establish a system of equations involving the characteristic of interest. Systems of equations obtained in this research work present interesting block matrix structures that led us to obtain theoretical results, using inverse matrix and Gaussian elimination methods and recursive schemes exploiting the special structure of the matrices involved in the CTMC. In more detail, we apply the methodology as follows.

For a given initial state, we establish relationships between probability mass or generating functions or Laplace transforms and the corresponding functions associated to those states accessible from the initial in a single transition. These transitions are associated with the effective events that produce a change in the current state of the epidemic process. The resulting set of recursive equations can be solved using inverse matrix and Gaussian elimination methods.

In this investigation, the incidence measures analyzed are discrete random variables. To compute factorial moments of these measures, we define the related generating functions, conditioned to a specific state, l, as follows

$$\phi_l(z) = E[z^{\mathsf{X}_l}] = \sum_{k=0}^{\infty} z^k P[\mathsf{X}_l = k], \tag{1.1}$$

where X_l, is the incidence measure of interest conditioned to the current state l.

Next, a first step argument, conditioning on the possible transitions out a fixed state, gives a set of linear equations that can be expressed in matrix form. Conditioned factorial moments of order k, m_l^k, can be obtained solving these system of linear equations by applying inverse matrix and Gaussian elimination methods taking into the account applicable boundary conditions and applying the following equality

$$\mathsf{m}_l^k = [\phi_l(z)]^{k)}|_{z=1}, \tag{1.2}$$

where $k)$ denotes the k derivative of the generating function of the random variable of interest.

Time measures, described in this research work, are continuous random variables. We compute conditioned moments of order $k \geq 0$, M_l^k, of these

measures proceeding in a similar way as we make for the incidence measures but defining the Laplace-Stieltjes transforms conditioned to a specific state, l, appearing in Expression (1.3) instead of generating functions in (1.1) and applying Property (1.4) instead of (1.2),

$$\Phi_l(s) = E[e^{-s\mathbf{X}_l}], \tag{1.3}$$

where $\mathbf{X}_l$, is the time measure of interest, conditioned to a fixed state, l, and

$$\mathsf{M}_l^k = E[\mathbf{X}_l^k] = (-1)^k[\Phi_l(z)]^{k)}|_{s=0}. \tag{1.4}$$

This methodology can be extended to higher dimensions to obtain the probabilistic characteristics for the bi-dimensional random variables appearing in Chapter 6.

Random variables depend on model parameters. Variations in their values produce notable changes in the distributions of these quantifiers. To assess the influence of the model parameters on the variation and robustness of the measures of interest, we can perform a sensitivity analysis.

In general, a sensitivity analysis is a technique used to study perturbation effects in the model parameters, on the outputs of the model [258] and to determine which parameter is the most influential. This methodology is very useful for models with many parameters. In this investigation, the perturbation problem is approached through sensitivities and elasticities of the random variable of interest.

For a given model parameter, θ, the elasticity of a general characteristic, Y, is defined as

$$\varepsilon_Y(\theta) = \frac{(\partial Y/\partial\theta)}{(Y/\theta)}. \tag{1.5}$$

In recent years, this methodology has been applied to various subjects of study as demography, ecology [77] and epidemiology [149]. There is a vast literature that addresses this problem, for example in [78], Caswell et al. use matrix calculus to obtain sensitivities and elasticities for moments of several epidemic measures in a continuous-time Markov chain. In [138], Gómez-Corral et al. analyze the perturbation problem through matrix calculus in a LD-QBD process and provide different algorithms to compute elasticities for several random variables related to an epidemic process.

To compute derivatives and elasticities, we mainly rely on matrix calculus [43, 202].

Theoretical and algorithmic results are implemented using R and Matlab software.

1.1.3 Thesis organization

This thesis is organized by chapters. The first one is an introductory Chapter containing a brief description on infectious diseases in history and emerging epidemics that actually, have a relevant scientific, political and social interest. We detail different approaches concerning the mathematical modeling of an infectious process. An exhaustive description of the current vaccines is provided in order to describe different mathematical models that include vaccination as a control health measure. In particular, we describe thoroughly the Susceptible-Infected-Susceptible (SIS) and Susceptible-Infected-Recovered (SIR) models for constant size and isolated populations. Then, we extend this description to models where there is an external source of infection and individuals are partially protected against the disease by an

imperfect vaccine. Finally, we review the existent literature related to numerical characteristics of disease transmission. In particular, we describe in detail reproductive numbers, incidence and time measures, for the SIS and SIR models and their variants.

Chapters 2-4, are based on the published papers [121, 123, 124], respectively. We start by describing the objectives, the specific methodology applied in the investigation and general conclusions. In addition, printed versions of these articles are included. Mathematical model deals with non-isolated, constant and moderate size populations where individuals are mixed homogeneously. Populations are afflicted by an infectious disease that does not confer immunity after recovery. We describe the stochastic Susceptible-Vaccinated-Infected-Susceptible (SVIS) model with infection reintroduction. To assure herd-immunity protection we assume that prior to the start of the epidemic process, a percentage of the population is vaccinated with an imperfect vaccine that fails with a certain probability. We do not consider additional vaccination during the epidemic process and vaccine confers long-last protection.

Specifically, in Chapter 2 we quantify the expansion of an infectious disease through the exact and the population reproduction numbers. For both random variables, we derive theoretical schemes involving their mass probability and generating functions, and moments distributions. We complement theoretical and algorithmic results with several numerical examples. Additional work, related to these measures, is provided in Appendix A that includes: the stationary distribution for the SVIS model, a global sensitivity analysis of the mentioned random variables and some R_p-algorithms.

In Chapter 3, we focus on the imperfect vaccine hypothesis. In this context, eventually, an individual who has been previously vaccinated, can be infected with a fixed probability and the initial number of vaccinated individuals can drop down and the protection conferred by herd-immunity could be lost. In that sense, we fix a threshold on the number of vaccinated individuals. We define the sleeping period and the wake-up time, as the period while the number of vaccinated individuals is over this threshold and the time at which the threshold level is reached, respectively. In addition, an incidence measure is described to inform about the cases of infection occurring during the sleeping period. We study probability mass and generating functions and distribution moments for the incidence measure. For the time measure, Laplace transforms and distribution moments are analyzed. We obtain recursive expressions that permit to derive a global and local sensitivity analysis. Additional work related to these measures is provided in Appendix B.

In Chapter 4, the interest is in providing information about the possibility and the time required to launch a re-vaccination. These aims are obtained analysing the incidence measure that informs about the size of the susceptible population at wake-up time and the required time to have the sufficient number of susceptible individuals, eligible to be vaccinated, in order to elevate the vaccine coverage to the initial level. We analyze the probabilistic behaviour of both random variables analyzing probability mass and generating functions and distribution moments for the discrete random variable and for the continuous one, Laplace transforms and distribution moments are derived. We give theorems and stable recursive schemes to compute them.

We show the applicability of both measures carrying out a numerical analysis and additional work related to these measures are included in Appendix C.

In Chapters 5 and 6, we assume the same population and vaccine hypothesis as in Chapters 2-4 but considering an infectious disease that confers permanent immunity after overcoming the illness. The model involved is the stochastic Susceptible-Vaccinated-Infected-Recovered (SVIR) model, with infection reintroduction and imperfect vaccine.

In more detail, Chapter 5, is based on the published paper [120] and includes the printed version of the study and their scientific impact information, objectives, methodology and conclusions. Our interest is to analyze the speed of transmission of an epidemic process. Specifically, we are concerned with the study of the random variable that quantifies the time to reach a threshold on the number of individuals to become infected. We provide algorithmic recursive schemes for the computation of its Laplace transforms and distribution moments and illustrate numerically the behaviour of this random variable. Complementing this research work, in Appendix D, we describe the random variable that analyze the time until all individuals are infected.

In Chapter 6, we focus on the potential of transmission of an infectious disease by studying analogous measures to the exact reproduction number and population reproduction number but with a novel feature. We distinguish between contagions to susceptible individuals from those to vaccinated. In this sense, we deal with bi-dimensional random variables, and study joint distribution and measures of both characteristics. We complement theoretical and algorithmic results with several numerical examples. This article

is under review. The analysis of the time until all individuals have been infected is included in Appendix E complementing this research work.

1.2 Preliminaries

Epidemics and pandemics have been a threat to the population along the human history. They have killed many people and produced disastrous health impacts and economic disruptions.

One of the most famous epidemic in the history is the bubonic plague or Black Death. It was caused by the bacterium Yersinia pestis and killed more than one third of the European population, about 25 million people, during the fourteenth century [131], and even today this pathogen kills people in many areas of the world [167, 54, 182, 65].

Another example of an infectious disease is the cholera. It is an ancient disease that remains a public health problem in many impoverished locations around the world. Seven pandemics of cholera have been recorded since the first pandemic in 1817 [95, 148, 284]. The disease had a high case-fatality ratio that approached 50% in some areas and spread relentlessly in worldwide pandemics from endemic foci in Asia to the Middle East, Europe, East Africa, and the Americas [130].

Another important infectious disease is the smallpox, which has caused the deaths of millions of people and disfigured many from its probable origin, 3000 to 6000 years ago, to its worldwide eradication in 1978 [127].

Although these are examples of diseases that have been extensively mitigated, in today we find other persistent illnesses. From the 19^{th} century, flu is

one of the most spreading infectious diseases of the world. The most famous and deadly pandemic was the 1918 Spanish flu caused by an influenza A (H1N1) virus [126, 286] that killed more than 50 million people worldwide. The infectious disease affected mostly young and healthy persons and the rapid progression of the illness to fatal multi-organ failure and death, were specific features of this pandemic [277, 199]. In addition, its socioeconomic consequences were huge [206]. But it was not the only flu in the history. In 1957, a new influenza A (H2N2) virus emerged and produced the Asian flu pandemic. It had a speedy transmission and the estimated number of deaths was 1.1 million worldwide [132]. Later, in 1968 a descended from H2N2, an H3N2 strain of the influenza A virus, come out and it resulted in the Hong Kong flu pandemic killing between one and four million people globally [172]. In 2009, a new strain H1N1 swine flu spread fast around the world among humans, and the World Health Organization (WHO) declared it as a pandemic [312]. Currently, influenza cases should be interpreted with caution as the ongoing COVID-19 pandemic has influenced the transmission of infectious diseases. Several hygiene and distancing measures implemented by governments to control SARS-CoV-2 virus transmission have likely played a role in reducing influenza virus propagation. Globally, influenza prevalence remained low in comparison with pre-COVID era, but activity has increased again since February 2022 [312]. The tuberculosis epidemic peaked in the late 18^{th} century in England, in the early 19^{th} century in Western Europe, and in the late of the 19^{th} century in Eastern Europe and North and South America, while in many areas of Asia and Africa have not reached their peak incidence yet. Recent WHO data suggest that the incidence rate may have started to

decline in these regions as well [60]. Poliomyelitis is an acute paralytic disease caused by the polio virus (PV) and has three known serotypes. In 1988, when the Global Polio Eradication Initiative (GPEI) began, polio infected more than $350,000$ children across 125 countries [61]. In 2021, only one of three wild polio virus serotypes, type 1 (WPV1), persists in Afghanistan and Pakistan. Varicella is an easily transmitted disease caused by the varicella zoster virus (VZV). In 1990, globally, 8900 people died due to this disease but in 2013, due to worldwide vaccination programs, the number reduced to 7000, which occurred at a rate of 1 death per 60,000 cases [239]. Rubella, also called German measles, is a communicable viral illness produced by the rubella virus (RV). Prior to the introduction of the rubella vaccine, rubella was endemic worldwide, epidemics occurred at 6- to 9-year intervals [186]. Today, rubella outbreaks continue to occur in some parts of the world, where there is a substantial proportion of the population that are susceptible to get the disease. Another important epidemic of this Modern Era, is the acquired immune deficiency syndrome (AIDS). It is caused by the human immunodeficiency virus (HIV) that was first diagnosed in 1981. Since the beginning of the epidemic, 79.3 million people have been infected with the HIV virus and 36.3 million people have died of HIV. This virus destroys CD4 cells (also called T cells or helper cells), which are critical to the immune system. CD4 cells are responsible for keeping people healthy and protecting them from common diseases and infections. However, not everyone with HIV will go on to develop AIDS. The availability of triple antiretroviral therapy in the mid-1990^s marked the transition from fatal disease to chronic infection. However, AIDS continues to be a global health problem. The rate of new

infections and deaths have shown an increase in recent years in some regions of Asia, the Pacific, the Middle East and North Africa [311, 248]. No effective vaccine has been developed, yet. However, novel promising vaccine platforms are currently under investigation [283]. The diphtheria is a severe vaccine preventable infectious disease caused by a bacteria that affects the mucous membranes of the nose and throat. Usually the diphtheria vaccine is combined with another preventive serums to interrupt several infectious diseases as the tetanus and whooping cough. In November 2017, the largest diphtheria outbreak of this century emerged among Rohingya refugees in Kutupalong camp, Bangladesh. By June 2019, 8640 cases and 45 deaths had been reported [278]. The first known case of severe acute respiratory syndrome (SARS) was detected in November 2002, in Foshan, China. By February 2003, more than 300 cases were reported [93]. It was the first pandemic caused by a coronavirus, it spread over 37 countries and contributed to the deaths of 774 people. Also it produced an economic loss of over US40 billion dollars over a period of 6 months [225]. Ten years later, in 2012, a very aggressive coronavirus was initially reported in Saudi Arabia and the related disease was called as Middle East respiratory syndrome (MERS-CoV). By 2019, 2494 cases were reported, resulting in 858 deaths [44]. The Ebola virus (EV) is also a very aggressive one that causes the Ebola virus disease. It is transmitted by close contact with an infected individual by bodily fluids, secretions, organs and contaminated surfaces and materials [310, 4]. The EV can be lethal and produces, on average, the death of 50% of infected individuals. The 2014 West Africa outbreak was the most devastating and was expanded around several African countries as Guinea, Liberia, Sierra Leone,

Nigeria, Senegal and Mali.

However, all these examples are probably not the last communicable pandemics in history. Actually, we cope with many others infectious diseases that are frequently present in the population as mononucleosis and pertussis and even producing recurrent infections such as conjunctivitis (pink Eye) and impetigo [105]; among others. The WHO and other scientific organizations, are alerting us every day about the appearance of new viruses, a fact which indicates a clear risk of future epidemic outbreaks [234]. Indeed, we are currently immersed in a pandemic produced by a new coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes the coronavirus disease (COVID-19), which is unprecedented in recent years. The whole world is trying to stop its spread and counteract all collateral effects produced by the highly contagious nature of this disease. It causes mild to severe respiratory problems, as fever, cough, pneumonia, and in some cases the death [162]. Recent data show that COVID-19 has spread out very fast and the Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University estimates by 22^{nd} of March of 2022 that there are more that 450.6 million of cases and 6.000.000 of deaths around the world. Vaccination mitigates severe disease and actually we have more than 4335 million of individuals full-vaccinated, that corresponds to the 56.49% of the world population [243].

This current pandemic reveals the importance of vaccination and health protection measures to control an epidemic process. Health protection measures as social-distance, lockdown, isolation, quarantine, hygiene measures, spraying, among others, are adequate when we want to reduce the trans-

mission of an infectious disease [231, 261, 299]. All these measures are very effective but the safest and the most powerful tool to reduce and prevent an outbreak is vaccination [116, 181, 228].

Vaccines are serums that need to be administrated to an individual, before the exposition to the pathogen, to stimulate the body's immune response against diseases.

At the moment, we administrate the following types of vaccines: inactivate, live-attenuated, messenger RNA, subunit, recombinant, polysaccharide, conjugate, toxoid and viral vector vaccines [57, 191, 236]. Inactivate vaccines use the killed form of the pathogen that produces the disease [257]. The flu, hepatitis A, polio and rabies are diseases that we prevent with this types of vaccines. Live attenuated vaccines utilize an attenuated version of the original pathogen that produces an infectious disease [169]. This type of vaccines produces a strong and long-lifelong immunity similar to the natural infection. Measles, rubella, rotavirus, smallpox, chickenpox, yellow fever are diseases that can be mitigated with live-attenuated vaccines. The new type Messenger RNA vaccine [233], produces proteins in order to activate an immune response. As they are not made with any part of the virus, they are safe and there is no risk of causing the disease when they are administered. At the moment, we are using them to protect against the COVID-19. Subunit, recombinant, polysaccharide and conjugate vaccines are very safe, they utilize a specific part of the pathogen to raise a protective immune response and since they cannot replicate in the host, there is no risk of pathogenicity [145]. Hepatitis B, HPV, Pneumococcal disease and Meningococcal disease can be disrupted by these vaccines. Toxoid vaccines use a toxin produced by

the pathogen that produces the infection [210]. The immune system targets that toxin and it will create an immune response to this toxin and not to whole pathogen. These vaccines may need booster doses to achieve an efficient protection to the disease. We use this types of vaccines to mitigate diphtheria and tetanus. Viral vector vaccines modify a different virus as a vector to give protection. These vaccines also have been used for COVID-19 and Ebola diseases; among others [280].

Although all vaccines should be effective in preventing infectious diseases, in some cases they are not perfect at 100% and they can fail. There are three different types of vaccine failure that are commonly considered in the literature [203, 208]: (i) a leaky vaccine prevents the development of disease symptoms, but do not protect against infection and the onward transmission of pathogens [304, 47]; (ii) all-or-nothing vaccine describes a vaccine that has no effect on some individuals but confers complete protection in others [203, 240]; (iii) waning vaccine is the one for which the protection conferred wanes over time [264]. In this thesis, we focus on imperfect vaccines of type (ii) considering that vaccine fails with a fixed probability, h. This failure occurs due to inadequacies of the vaccine or factors inherent in the host [156]. In consequence, a proportion of vaccinated individuals can not develop immunity and can be infected by the pathogen [297]. In real-world situations, to obtain perfect vaccines is not as frequent as expected and it is very important to study its consequences. Thus, a good point of this research work is that we take into account this phenomenon and we incorporate the effect of an imperfect vaccine to the analyzed models.

To control the expansion of an infectious disease in a population, when a

vaccine is available, it is necessary that a proportion of the population (i.e.; vaccine coverage) was vaccinated preventively.

The herd immunity is a concept that is getting attention due to the pandemic of the COVID-19 [242]. Herd immunity, also known as "population immunity", represents the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals (either vaccination or immunity developed through previous infection) exists in a population. In this case, individuals can act as a barrier of infectious disease transmission to other individuals. The point at which the proportion of susceptible individuals in a population falls below the threshold needed for transmission is called herd immunity threshold or herd immunity level and vaccination plays an important role to achieve this value. Reaching optimal vaccination rates is an essential public health strategy to establish herd immunity and to control the spread of an outbreak [229]. This threshold varies for each disease and depends on pathogen characteristics and human behaviour. For example, herd immunity against measles requires about 95% of a population to be vaccinated while for polio the threshold is about 80%. For the current COVID-19 pandemic the herd immunity is uncertain. This fact is due that current serums are leaky vaccines and in consequence, they do not avoid the transmission of the infectious disease.

Sometimes the herd immunity is lost due to the vaccine failures and it is therefore essential to provide health authorities with tools, coming from mathematical models, that enable and facilitate decision-making to manage an epidemic effectively.

Mathematical modeling in epidemics is a crucial tool to analyze the mech-

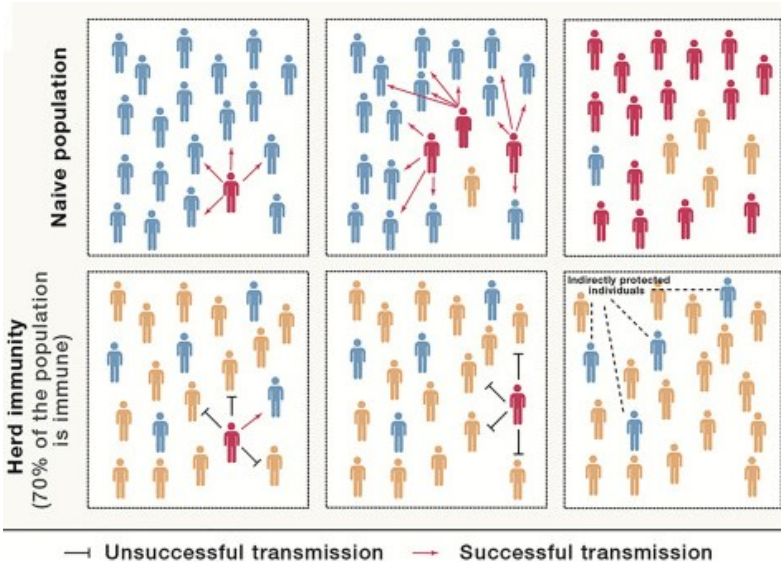

Figure 1.1: Herd Immunity. *Note.* From Randolph, H. E.; Barreiro, L. B. Herd immunity: understanding COVID-19. Immunity 2020, 52(5), 737-741. https://doi.org/10.1016/j.immuni.2020.04.012 [242]

anisms by which diseases spread, to forecast and anticipate the future course of an epidemic process and to evaluate strategies to control an outbreak.

What is considered the first approach to mathematical modelling in epidemics is the work of Bernoulli, in the year 1760. The author proposed a mathematical model to encourage the technique of variolation to prevent smallpox [59]. He applied differential calculus to construct a mathematical model including life-long immunity against the disease. He tried to obtain from mortality tables, in the natural and the infected states, another table where the disease was eradicated [252]. Another relevant precursor of the mathematical modeling was Farr who, in 1840, modeled the evolution of a disease that cattle had. In our days, this model has been applied to the evolution of the acquired immunodeficiency syndrome (AIDS) [110]. Some years later, in London 1854, there was a cholera epidemic and Snow studied the temporal and spatial patterns of cases that were produced. He was able to detect the main source of infection of the outbreak that was in Broad Street water pump [266].

In real-world situations, at the beginning of an epidemic, there is not a large number of infective individuals and transmission depends on the contacts between individuals in the population and this effect should be included in the model. The first authors to study this effect were Galton and Watson in 1874, with a research on the extinction of the "family names" [292]. Some years later, in 1889, Galton redefine the example of Galton-Watson model and the models described are considered the first branching processes [119]. After, in 1930, Steffensen completed these works [269] and Metz, in 1978 [211], provided the derivation of the probabilistic structure of a general

branching process.

The origins of modern theoretical epidemiology owe much to the work of En'ko, Hamer, Ross, Kermack and McKendrick [24]. In 1889, En'ko developed a discrete chain binomial model for the expansion of an epidemic process in a susceptible population [109]. Hamer, in 1906, postulated that the behaviour of an epidemic process depends on the rate of contacts between susceptible and infected individuals. In particular, he assumed that the average number of contacts per individual in unit time sufficient to produce infection, is proportional to the population density. It is called the "mass action" principle of transmission for infectious diseases [144, 67].

Later, in 1908, Ross extended this hypothesis, in a pioneering work, where he studied the transmission by mosquitoes of the malaria [251]. Then, in 1927, Kermack and McKendrick extended and explored, in more detail, the ideas of Hamer and Ross and formulated what is considered the first mathematical model to describe an epidemic process in recent decades. The model was used to describe and count the deaths produced during the Indian plague epidemic, between years 1905 and 1906, and to make predictions using the observed cases [171]. The simple Kermack-McKendrick epidemic model assumes that population is divided into groups according their health status and their sizes are large enough that individuals are mixed homogeneously.

The first epidemiological book describing the beginning of an outbreak was the work of Diekmann and Heesterbeek, in 2000 [98]. The authors appealed to the work initiated by Hamer, focusing on the importance of the contacts between individuals during the first period of the epidemic and assumed that there is a network of contacts of individuals. This network is

described by a graph, where vertices represent members of the population and edges represent contacts between individuals. In addition, authors dealt with concepts as repeated outbreaks, the final size, thresholds and population regulation, that can be useful for evaluating the extent of an outbreak.

The most powerful use of mathematical modeling on public health came with the need for evaluating control strategies for newly emerging and re-emerging infectious diseases [288]. At the end of the twentieth century, the fear of a bio-terrorist attack with smallpox virus took action to use mathematical modeling combining historical data from smallpox epidemics with questions about vaccination in modern societies [178, 114]. Some years after, the epidemic produced by the SARS virus started to employ mathematical models to study infectious disease outbreak data, in real time, to assess the effectiveness of health control measures [287]. In recent years, mathematical modeling come into more widespread use for public health policy making. For example, during the last decades of the AIDS pandemic and lately during the COVID-19 outbreak among others, the development of mathematical models has been very useful to predict the evolution of an infectious disease and to identify the most effective prevention control health strategies.

Above we described a selective account of historical highlights to illustrate the developments of the mathematical epidemic modelling along human history and to introduce the next section, where an exhaustive description of the ongoing epidemic models are described. To give a full account of the history of the mathematical modeling we refer the interested reader to [45, 161, 227, 117].

1.3 Mathematical modeling in epidemics

Our interest in this section, is to explore various types of compartmental mathematical models for describing the evolution of an epidemic process.

Compartmental models are adaptable enough to represent social dynamics and pathogen characteristics. These models divide the population into mutually exclusive compartments, according to their health status regarding the infectious disease. They describe the variation of the number of individuals included at each compartment while the epidemic is in progress. Individuals are assumed to have the same characteristics and they can be assigned from one compartment to other according to their infectious status. These movements depend on the characteristics of the disease and/or community intervention.

Diseases spread by contact through a virus or bacterium. The different health stages related to an infectious disease can be susceptible, infected, exposed and recovered. A susceptible, (S), individual is at risk of developing the disease when getting in touch with an infectious individual. An infectious, (I), individual has developed the illness and is able to infect another individual. In some contagious diseases there is a period, after being infected by the pathogen, while the infected individual can not transmit the illness. During this time span, individuals are called exposed, (E). Some contagious diseases confer long-lasting or temporal immunity after overcome the disease and the individual can not be infected again by the same pathogen during this immunity period. In this case, the individual is called recovered, (R). Taking into account the different stages related to an infectious process, we can describe different compartmental epidemiological mathematical models

[23, 176, 235, 275, 66, 70, 274].

The most studied compartmental models are the Susceptible-Infected-Susceptible (SIS) and the Susceptible-Infected-Recovered (SIR) models.

The SIS model is suitable to model diseases where immunity is not acquired after overcoming the illness and, as a result, over time individuals in the population oscillate between susceptibility and contagion. Conjunctivitis (pink-eye), impetigo and most sexually transmitted illnesses, as human papillomavirus (HPV) and chlamydia, can be modeled using an SIS model [253, 83, 153]. Some viruses, as the human immunodeficiency virus (HIV), produce permanent infection and can be modeled by the Susceptible-Infected (SI) type model. Some other variants of the original SIS model, are developed by combining different stages related to an infectious disease as the Susceptible-Exposed-Infected-Susceptible (SEIS) model, that is employed to model pneumococcal infections [273]. When a vaccine is available, it reduces the incidence of infection by diminishing the proportion of susceptible individuals in the population. In this situation, the Susceptible-Vaccinated-Infected-Susceptible (SVIS) model is suitable to model the propagation of vaccine preventable infectious diseases that do not confer immunity [307].

The SIR models is appropriate for diseases in which permanent immunity is acquired and individuals who have overcome the disease will therefore no longer be susceptible to reinfection. In this case, the human immune system is itself capable of generating antibodies that fight the pathogens causing the disease. MERS, rubella, measles and varicella are epidemics that can be modeled by a SIR model [81, 62, 308, 128]. Many models have been developed from the original SIR-type model. For example, the Susceptible-

Infected-Recovered-Susceptible model (SIRS) is an extension of the general SIR assuming that acquired immunity may disappear after some time. Hence, after losing this temporal immunity, any recovered individual is again susceptible to the disease. Influenza epidemic can be modeled by this type-model [157]. The Susceptible-Exposed-Infectious-Recovered (SEIR) model is appropriated to represent the spread of diseases when there is an exposed period from contact to infection transmission. Ebola and COVID-19 infectious processes can be modeled by an SEIR type model [29, 263, 185, 238]. In case when a vaccine is available, several models have been developed. For example, the Susceptible-Vaccinated-Infected-Recovered (SVIR) that is suitable when the immunity acquired after infection is permanent and the Susceptible-Vaccinated-Infected-Recovered-Susceptible (SVIRS) that is suitable when the immunity acquired is not permanent [300, 30].

There are many mathematical epidemiological models not stated in this work that can be constructed by adding different compartments to the original structure such as: antidote, dead, hospitalized, quarantined , tested and so on. We refer the interested reader to [19, 20, 255, 164] and the references therein, for a detailed description of these models.

Sometimes it is necessary to take into account the specifications of individuals, local interactions and adaptive behavior to study an epidemiological process. In such cases, it is preferable to construct models focused on individuals. These are the so called IBM or individual based models where each individual presents a set of features that change dynamically over time to account for stochastic fluctuations of epidemiological variables [306, 220, 94].

There are mainly two mathematical approaches to represent the evolu-

tion of an epidemic process: the deterministic and the stochastic approaches [10, 25, 90, 147, 2, 75, 300, 213, 293, 267, 305]. The first one constitutes a huge part of the existing studies. In deterministic models, the number of individuals in each model compartment involved in the epidemic, are estimated as functions of discrete time $n = 0, 1, 2...$ or differentiable functions in continuous time $t \geq 0$. Such estimations allow us to derive sets of difference or differential equations governing the process. Consequently they attempt to explain behaviours on the average at the population scale. Solutions of deterministic models are functions of time or space that depend on the initial conditions. These models have been widely used due to their generally simpler analysis and mathematical tractability [154, 56]. They are especially relevant when considering large populations or when stochastic effects can be neglected. Deterministic models assume that the observed dynamics are forced only by internal, deterministic mechanisms. However, real epidemiological systems will always be exposed to influences that are not completely controlled or not viable to model explicitly. In this cases, it is necessary to incorporate these variations in the dynamics. Stochastic noise is often linked to undesirable disturbance for controlling systems. However, it can be beneficial if we use it appropriately. Some models incorporate this stochastic term to the differential equations, to include variation in the dynamics and to stabilize a deterministic dynamical system. These methods are called stabilization by noise (e. g.; Wiener Processes) [103, 158, 272].

Stochastic approach is based on models that employ stochastic processes. These models have the ability to handle unpredictability in the inputs applied and have some inherent randomness. The solution of a stochastic model is a

probability distribution for each one of the random variables describing the evolution of an epidemic process. In consequence, the same set of parameter values and initial conditions produce different outputs.

Both approaches are very important in epidemiology and their main differences rely in their asymptotic behaviour. For instance, Weiss and Dishon, in [294], show that the asymptotic values of the expected number of infected individuals as calculated by the two theories do not necessarily agree and demonstrate that when the deterministic mean tends to zero, the stochastic mean time to extinction remains bounded. Nevertheless, when the deterministic mean time tends to infinity, the mean time to extinction tends to infinity as the total population number grows without bound. Several studies suggest that, the stochastic approach better explains the evolution of an infectious process when underlying populations are not excessively large or in epidemics, where the transmission of the disease, recovery, the variability in demographics or the environment are highly influential [23, 25, 58]. This is the case of small communities as intensive care units in hospitals [118, 40, 289], prisons [159] and schools [270, 37] among others. A large part of the studies concerning stochastic epidemic processes employs Markov chains to represent the evolution of the infectious process.

To describe the evolution of an infectious disease over time in terms of a Markov chain, it is assumed the exponentially of the sojourn times and the independence among the random events that determine transitions among states in state space. Markov chains are widely used in epidemiology. Some classic books, where the reader can find an accurate development of theoretical results, are the monographies by Kemeny and Snell [170]; Karlin and

Taylor [166] and the one by Schinazi [259]. There are mainly two types of mathematical epidemic models based on Markov chains: discrete-time and continuous-time Markov chains. Discrete-time Markov chains (DTMC) study the evolution of an epidemic process at time points [8, 256, 108, 291, 122, 11]. In contrast, continuous-time Markov chains (CTMC) analyze the epidemic behaviour assuming time as a continuum [281, 9, 167]. The underlying mathematical theory involved in a CTMC is widely analyzed by Allen. She has contributed with many textbooks and publications applied to a variety of biological processes such as: epidemic, competition, predation and population genetic processes [15, 16, 9, 10].

1.3.1 The SIS and SIR models

In this thesis we focus on the stochastic SIS and SIR mathematical models to cover infectious diseases that are transmitted by direct contact with a infected individual. Both models differ in the immunity acquired when an infected individual overcome the disease.

As we stated in the previous section, the SIS model is appropriate to describe the transmission dynamics of infectious diseases that do not confer immunity after recovering the illness and the population consists only of susceptible and infected individuals. Individual health state oscillates from susceptible to infected compartments along time. When a susceptible individual comes into direct contact with an infected individual, he/she becomes infected. After an infectious period he/she overcomes the disease and is susceptible again to be infected. In Figure 1.2 we show the movements of individuals in an SIS model.

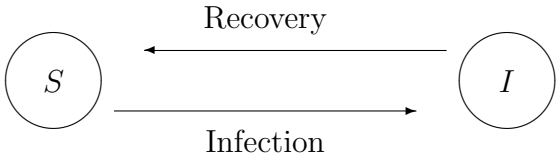

Figure 1.2: Movements of individuals in an SIS model

In what follows, for any time $t \geq 0$, we denote by $S(t)$ and $I(t)$, the number of susceptible and infected individuals at time t, respectively.

For a constant size population where an infectious process is ongoing, the number of susceptible and infected individuals at time t satisfies the following equation

$$S(t) + I(t) = N, \ t \geq 0. \tag{1.6}$$

Assuming "the law of Mass Action" that says that, the rate of interaction between two different subsets of the population is proportional to the product of the numbers in each of the subsets concerned [89], the deterministic SIS model can be formulated in terms of the following system of differential equations, for $t \geq 0$

$$\begin{aligned} S'(t) &= -\frac{\beta}{N} S(t)I(t) + \gamma I(t) \\ I'(t) &= \frac{\beta}{N} S(t)I(t) - \gamma I(t), \end{aligned}$$

where N denotes population size, transmission occurs through direct contacts

(effective contacts) with rate β and any infected individual recovers with rate γ.

Under a stochastic approach and considering a constant and moderate size population where individuals are homogeneous and well-mixed, the evolution of the analogous stochastic model can be described by a birth-death process, assuming the exponentially independence of contact periods and recovery times.

According to the constant size population hypothesis, the Equation (1.6) is also satisfied and the evolution of the epidemic process is modeled in terms of the following one-dimensional CTMC

$$X = \{I(t); t \geq 0\}, \tag{1.7}$$

with birth and death rates given by

$$\begin{aligned} \lambda_i &= \beta i(N-i)/N,\ 1 \leq i \leq N-1, \\ \mu_i &= \gamma i,\ 1 \leq i \leq N, \end{aligned}$$

and state space $S = \{0, 1, ..., N\}$.

In Figure 1.3, we show the transition diagram of the Markov chain X. We point that the state $\{0\}$ is an absorbing one. Since the state space is finite, the extinction is certain and the epidemic will end in a finite expected time. The Markov chain, X, also has a reflecting state in $I(t) = N$ that corresponds to a fully infected population.

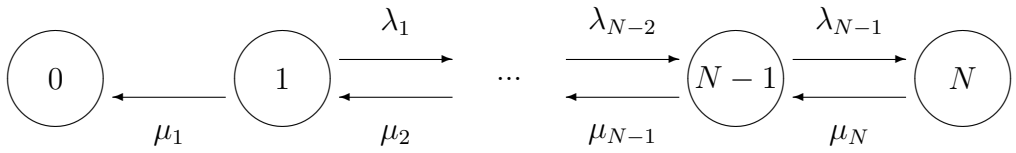

Figure 1.3: Transition diagram of the Markov chain X

Considering an infectious disease that confers permanent immunity, the SIR model is preferable. After an infectious period the infected individual turns into recovered and he/ she never becomes again susceptible to the disease. In Figure 1.4, we show the movements of individuals in an SIR model.

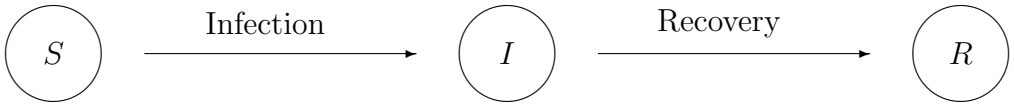

Figure 1.4: Movements of individuals in a SIR model

Let $R(t)$ represents the number of recovered individuals at time $t \geq 0$. According to the constant size hypothesis, the number of susceptible, infected and recovered individuals at time $t \geq 0$, satisfy the following equation

$$N = S(t) + I(t) + R(t), \ t \geq 0. \tag{1.8}$$

Again, applying "the law of Mass Action", the deterministic SIR model can

be formulated in terms of the following system of differential equations for any $t \geq 0$

$$\begin{aligned} S'(t) &= -\frac{\beta}{N} S(t) I(t) \\ I'(t) &= \frac{\beta}{N} S(t) I(t) - \gamma I(t) \\ R'(t) &= \gamma I(t), \end{aligned} \tag{1.9}$$

where model parameters are the same as in the analogous deterministic SIS model.

Under a stochastic approach the spread of the disease can be described by the following bidimensional CTMC:

$$Y = \{(I(t), S(t)) : t \geq 0\}. \tag{1.10}$$

Assuming the initial condition $(I(0), S(0), R(0)) = (m, n, 0)$ we can express the state space as

$$S = \{(i, j) : 0 \leq i \leq m + n, 0 \leq j \leq min(n, m + n - i)\}.$$

For a given state $(i, j) \in S$, the infection and removal rates are respectively

$$\begin{aligned} \lambda_{ij} &= \beta ij/N, \ (i, j) \in S, \\ \mu_i &= \gamma i, \ 1 \leq i \leq m + n. \end{aligned}$$

In Figure 1.5, we show the transition diagram of the Markov chain Y, described in Expression (1.10), when $m = n = 3$.

The states $\{(0, j) \in S, 0 \leq j \leq n\}$ are absorbing ones and the rest are transient states, that are visited at most once. Since the state space is finite

then, the extinction is certain and the epidemic will end in a finite expected time.

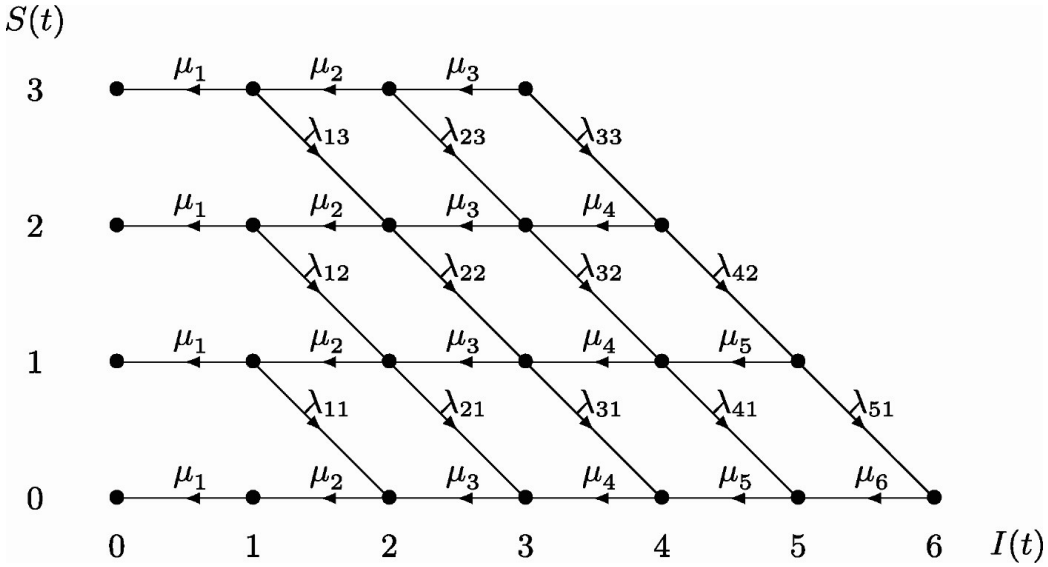

Figure 1.5: Transition diagram of the Markov chain Y. *Note.* From Artalejo, J. R.; Economou, A.; Lopez-Herrero, M. J. Stochastic epidemic models revisited: analysis of some continuous performance measures. Journal of Biological Dynamics 2012, 6(2), 189-211. https://doi.org/10.1080/17513758.2011.552737 [38]

1.3.2 Compartmental models including vaccination as a health control measure

In this thesis, we are interested in compartmental epidemic models that include vaccination as a prophylactic device to stop or control the expansion of an epidemic process. In particular, we consider models of epidemics taking into account various possibilities in the selection of the characteristic

parameters of a vaccine to explore the effect of vaccination.

There is a vast literature dealing with epidemic models that include vaccination and other intervention mechanisms to control and reduce the incidence of an infectious disease. For example, in [88], authors review the effect of information communicated by the public health authorities in determining the outcome of measles vaccination programs for an SIR-type epidemic model. In [142], an SEIR model is developed, authors compare five control policies that can be addressed simultaneously and provide main qualitative properties of the controls. Also a comparison with an SIR model is provided. For the ongoing COVID-19 pandemic, authors in [241], propose a compartmental epidemic model including compartments for susceptible, exposed, infected, quarantined, hospitalized, recovered, deceased and insusceptible individuals in the population taking into the account the use of social distancing, hospitalization and vaccination in order to stop the expansion of the virus. These are some examples of studies that analyze the effect of vaccination on a previous selected compartmental model. Other studies include an specific compartment for vaccinated individuals. For example, in [190], authors propose a compartmental SVIR model to describe the expansion of the influenza virus and they calculate the most efficient critical vaccination coverage to maximize the herd effect. In [97], an extended compartmental SVIR model is described to study the risk of re-emergence of polio and its effect, in a region with low vaccination coverage where unvaccinated people are arriving. In [189], authors describe an SVIS epidemic model applying numerical techniques. In more detail, they investigate the Euler-Maruyama numerical approximated solution to the model and propose

a positivity-preserving numerical method for the compartmental epidemic model described. To explore more literature that includes vaccination as a control measure for the spread of an infectious disease, we refer the interested reader to [69, 25, 147, 2, 300, 181, 228, 301, 290].

According to the several vaccination policies and types of vaccines, mathematical epidemic models assume different inherent characteristics of the vaccine as its efficacy, life-long or waning protection, eligibility, number of doses, vaccine uptake, and so forth.

In our approach, we assume an imperfect vaccine that fails with a fixed probability. Under this assumption, there are several studies that analyze different epidemic models [121, 52, 82, 193, 5]. For example, in [173] and [298], the stationary distribution and stability are studied in SVIR-type models and in [303], the martingale theory is used to estimate the probability of failure of a vaccine. In [143, 271], the authors develop mathematical models assuming imperfect vaccination including an incubation period for infectious diseases that confer permanent immunity. In contrast, for infectious diseases that does not confer immunity, in [1, 31], the authors deal with the threshold dynamics of SIS epidemic models. The effectiveness of a vaccine is widely analyzed in [228], where a mathematical model for the transmission of the SARS-CoV-2 virus is described. The authors propose a mass vaccination strategy to control the transmission of the virus. They quantify the impact of different levels of vaccine efficacy and also other control measures are included in the model as social distance and testing of susceptible individuals. In [301], the authors propose an SVIS model with waning of vaccine-induced immunity and general nonlinear incidence to analyze the optimal vaccine coverage to

eradicate the disease. A time-delayed SVEIR model with a generalized non monotone incidence is considered in [6], where the authors provide a useful application to measles disease. In [187], the authors analyze the effect of vaccine failure on the spreading of a pathogen exploring the dynamics of an SIS epidemic model with three types of imperfect vaccinations on complex networks. A vaccinated compartment is included to indicate if leaky, all-or-nothing and waning vaccines are involved.

A waning protection is considered in [309], where the authors describe the expansion of a cholera epidemic process considering an extended SIR model with additional compartments describing the pathogen population and the number of vaccinated individuals at time t. They assume that susceptible population is vaccinated during the outbreak and also discuss the local and global stability of the endemic equilibrium. In [75], an SIS epidemic model is considered with varying population size and vaccination in presence of environmental noise where vaccinated individuals lose their immunity at a constant rate. In [116], authors examine the effect of various control strategies including vaccination campaigns with a waning vaccine, using systems of differential equations. In [190], the authors consider an SVIS model where vaccinated individuals become again susceptible when vaccine loses its protective properties. The authors call the time individuals spend in the vaccinated class, vaccine-age and they prove that the number of immunized individuals at time $t \geq 0$ depends upon vaccine-age. A life-long vaccine is introduced in [279], for an SEIR model and the stability of the model is discussed using the Lyapunov method. In [179], the authors consider an SVIRS model and suppose the vaccine's effects to be permanent but only

proportionally effective.

Related to the number of doses administrated of a vaccine, in [104], authors find the most efficient critical vaccination coverage assuming that one dose of vaccine suffices and that vaccination instantaneously leads to permanent immunity against infection. However, in [183], the critical vaccination coverage is analyzed with two doses of vaccine.

Vaccines are administered at certain ages, for people in at-risk groups, or for catch-up according to the schedule or even mass vaccination programs with no distinction and not taking into account specific characteristics of individuals. The eligibility criteria to receive a vaccine in a population is also the purpose of several studies. For example, in [175], authors demonstrate for hepatitis B virus disease, that neonatal vaccination influences more the control of transmission than mass vaccination programs. In [113], authors discuss the effect of different criteria related to the selection of individuals to be vaccinated to control the transmission of the measles virus. The vaccine up-take is defined as the proportion of a population that has received a specific vaccine. The difference between this concept and coverage is that, up-take expresses vaccination activity over time, while coverage expresses the resulting protection among a population [313]. When vaccine is not mandatory, this proportion is influenced by a range of factors as the risk of diseases and their effects, information provided to eligible individuals about the available vaccine and social norms among others. This effect is widely analyzed in [74], where authors describe an SIR model with voluntary vaccination and public health system intervention.

To describe above models different population hypotheses are assumed

such as: constant size population [276, 174], non-constant size population [146, 302], demographics variation throughout the epidemic process [265, 140] and keeping the population isolated, among others [207, 298].

Other hypotheses that are assumed in the existent literature, are related to how individuals mix with each other in the population and to the mechanism of transmission of an infectious disease. Usually, models try to work with homogeneous populations [46, 296] but, it is also frequent to work with populations whose individuals are not homogeneously mixed. For example, in [194], several descriptors are studied in small and heterogeneous populations where, in addition, the population is not isolated and there is an external source of infection. The analysis of the transmission of an infectious disease has been expanded assuming heterogeneous contacts [106], infective and susceptible immigrants [18], exposed individuals [197], generally distributed recovery times [137], Markov-modulated interactions [136], vector-borne infections [33], two-species competition [136] and a non-linear incidence rate hypothesis [107], among others.

Next, we describe the SVIS and SVIR models for a constant size population.

1.3.2.1 The SVIS model

Our main interest in this section is to develop deterministic and stochastic SVIS and SVIR models with imperfect vaccine.

We consider a constant size population where individuals are homogeneous and are uniformly mixed. Prior the start of the epidemic, a percentage of the population was immunized preventively to an infectious disease that

does not confers immunity after overcoming the illness. According to the vaccine failure classification described in Section 1.2, we assume an all-or-nothing type vaccine in the sense, that it fails with a fixed probability $h \in (0, 1)$..

Hence, susceptible and, eventually, vaccinated individuals can be infected through direct contact with infected individuals in the population. We are not considering an additional vaccination program during the epidemic process and vaccine induces long-last protection.

Figure 1.6 shows the movements of individuals between compartment in an SVIS model.

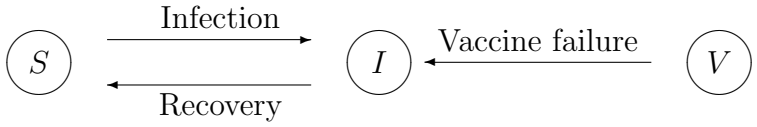

Figure 1.6: Movements of individuals in an SVIS model

At any time $t \geq 0$, we introduce the random variable, $V(t)$, that counts the number of vaccinated individuals at time t.
According to the constant size population hypothesis, the number of susceptible, vaccinated and infected individuals, at time $t \geq 0$, can be calculated from the following equation

$$N = S(t) + V(t) + I(t),\ t \geq 0. \tag{1.11}$$

The deterministic SVIS model with imperfect vaccine is described in terms of the following differential equations, for any $t \geq 0$

$$\begin{aligned} S'(t) &= -\frac{\beta}{N}S(t)I(t) + \gamma I(t) \\ V'(t) &= -\frac{\beta h}{N}V(t)I(t) \\ I'(t) &= \frac{\beta}{N}S(t)I(t) + \frac{\beta h}{N}V(t)I(t) - \gamma I(t), \end{aligned} \tag{1.12}$$

where β and γ, correspond to the effective contact and recovery rates, respectively and are detailed in the following table

Population size	N
Effective contact rate	β
Vaccine failure probability	h
Recovery rate	γ

Table 1.1: Model parameters with vaccination

Figure 1.7 shows the deterministic trajectories of an SVIS model, for a population of 101 individuals, assuming that the initial state of the outbreak is a single infectious, 48 susceptible and 52 vaccinated individuals. We fix the time unit to be the recovery time, therefore the recovery rate is taken as $\gamma = 1$. The effective contact rate is $\beta = 2.5$ and vaccine fails with probability $h = 0.3$. We simulate the evolution during 24 unit times and we record the number of susceptible, vaccinated and infected individuals at time t, during this period.

The blue line corresponds to the number of vaccinated individuals overtime. It presents a decreasing shape due that additional vaccination is not consid-

ered during this period. Black and red lines correspond to the number of susceptible and infected individuals in the population, respectively.

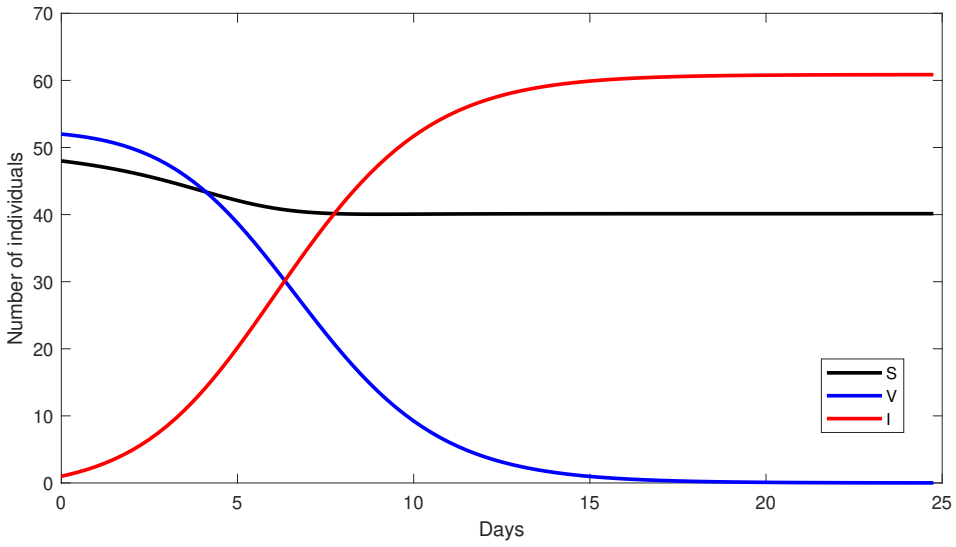

Figure 1.7: Outbreak simulation for 24 days for a deterministic SVIS model

Under a stochastic approach, we consider the same population and vaccine hypothesis as in the deterministic SIVS model. It is assumed that the pathogen is transmitted through direct contacts with an infective individual within the population, following a time-homogeneous Poisson process of rate, β/N. Population is not isolated and in consequence, infections also can be produced through direct contact with an infected individual that is not a community member at rate, ξ.

Once an infected individual overcomes the disease, after independent exponentially distributed times with rate γ, he/she is susceptible again, no matter if he/she was previously vaccinated or not. The length of any infectious average period is, γ^{-1}. The epidemics dynamics are consequence of movements

between separate classes overtime and are described in Figure 1.6.

Under this framework, $V(t)$ and $I(t)$, are random variables that record the number of vaccinated and infected individuals respectively, at time $t \geq 0$. According to the fixed population size hypothesis, we can recover the number of susceptible individuals at time t, from the following equation

$$S(t) = N - V(t) - I(t).$$

The evolution of the epidemic process, at each time point t, is described in terms of the following bi-dimensional Markov chain

$$X = \{(V(t), I(t)), t \geq 0\}. \tag{1.13}$$

The state space of X depends on the initial coverage, v_0. Hence, assuming that at time, $t = 0$, we have v_0 vaccinated individuals, with $0 < v_0 \leq N$, the state space is given by

$$\mathsf{S} = \{(v, i) : 0 \leq v \leq v_0, 0 \leq i \leq N - v\}, \tag{1.14}$$

that contains $(v_0 + 1)\,(N + 1 - v_0/2)$ states.

Assuming that $\xi > 0$ and $h > 0$, the number of vaccinated individuals could drop down from $v = v_0$ to $v = 0$. The stationary distribution concentrates in the set of absorbing states, $\{(0, i) : 0 \leq i \leq N\}$. Consequently, the protection conferred by the vaccine is lost, almost surely, in a finite expected time and, in the long-term, all the population will be susceptible to get the infection. This distribution agrees with the one described in [270] for an SIS-type model with an additional source of infection.

As we are dealing with Markovian models, transition rates are determined by the effective events that cause a change in the current state $(v, i) \in \mathsf{S}$.

Next, we give an exhaustive description of the possible events and in Table 1.3.2.1 we also list their rates.

(S_1) A susceptible individual gets the disease through direct contact with an infected individual within the population.

(S_2) A susceptible individual gets the disease through direct contact with an infected individual who is not a community member.

(S_3) Due to the imperfect vaccine hypothesis, a vaccinated individual is infected by direct contact with an infected individual within the population.

(S_4) Due to the imperfect vaccine hypothesis, a vaccinated individual is infected by direct contact with an infected individual who is not a community member.

(S_5) An infected individual is recovered and becomes again susceptible to be infected.

Effective event	Transition	Rate
(S_1)	$(v,i) \to (v,i+1)$	$\beta i(N-v-i)/N$
(S_2)	$(v,i) \to (v,i+1)$	$\xi(N-v-i)$
(S_3)	$(v,i) \to (v-1,i+1)$	$h\beta iv/N$
(S_4)	$(v,i) \to (v-1,i+1)$	$h\xi v$
(S_5)	$(v,i) \to (v,i-1)$	γi

Table 1.2: Effective events and their transition rates

1.3.2.2 The SVIR model

We describe the deterministic SVIR model with imperfect vaccine considering the same population hypothesis as in the deterministic SVIS model but, assuming that the pathogen confers permanent immunity to individuals after recovery.

In Figure 1.8, we show the movements of individuals in an SVIR model.

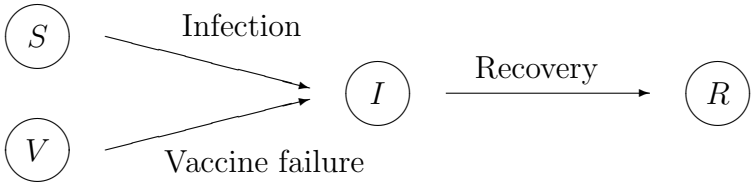

Figure 1.8: Movements of individuals in an SVIR model

Notice that, at time $t \geq 0$ and according to the constant size hypothesis, the number of susceptible, vaccinated, infected and recovered individuals satisfies the following equation

$$N = S(t) + V(t) + I(t) + R(t),\ t \geq 0. \tag{1.15}$$

The deterministic SVIR model with imperfect vaccine can be formulated for $t \geq 0$, in terms of the following differential equations

$$\begin{aligned} S'(t) &= -\frac{\beta}{N} S(t) I(t) \\ V'(t) &= -\frac{\beta h}{N} V(t) I(t) \\ I'(t) &= \frac{\beta}{N} S(t) I(t) + \frac{\beta h}{N} V(t) I(t) - \gamma I(t) \\ R'(t) &= \gamma I(t). \end{aligned}$$

Figure 1.9 shows deterministic trajectories of an SVIR model, for a population of 101 individuals, assuming that the initial state of the epidemics is a single infectious, 40 susceptible, 60 vaccinated and no recovered individuals. The infectious period of an infected individual is on average 2 days and the recovery rate is taken as $\gamma = 0.5$. The effective contact rate is $\beta = 1.5$ and vaccine fails with probability $h = 0.4$. We simulate the evolution during 24 days and we record the number of susceptible, vaccinated, infected and recovered individuals at time t, during this period. Black and blue lines correspond to the number of susceptible and vaccinated individuals along time, respectively. Both present a decreasing shape due to the permanent immunity acquired after recovery and that we do not consider additional vaccination during the epidemic. Green line corresponds to the number of recovered individuals, that show an increasing behaviour.

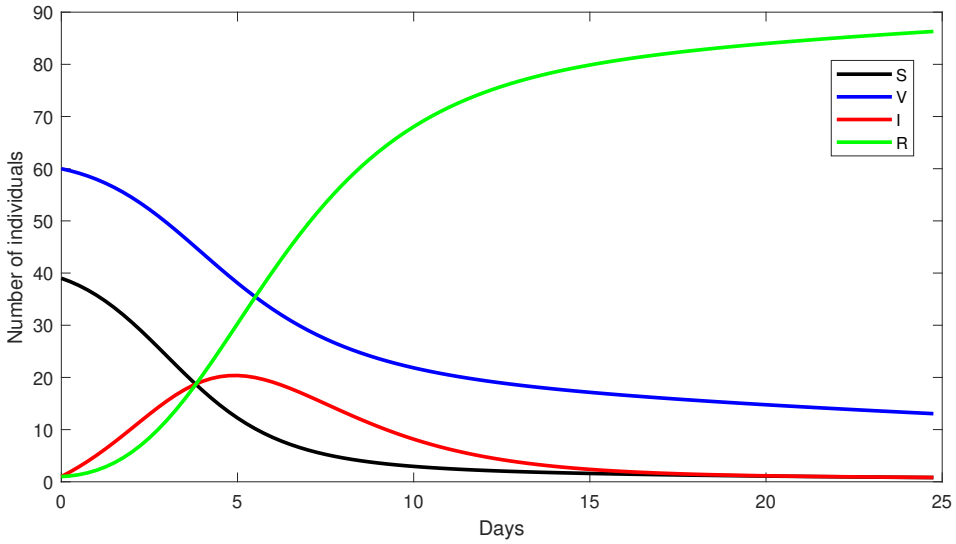

Figure 1.9: Outbreak simulation for 24 days for a deterministic SVIR model

Under a stochastic approach, we assume the same population, vaccine and transmission of the pathogen hypothesis as in the stochastic SVIS model but considering that once an individual is recovered from the disease, he/she acquires permanent immunity and will not be able to become infected again. Model parameters are described in Table 1.3.2.1 and are identical for the stochastic SIVS model described in the previous section. Figure 1.8, represents the movements of individuals for the SVIR model.

Since the size of the population remains constant throughout the epidemic process, the number of recovered individuals at time, $t \geq 0$, can be computed from the following equation

$$R(t) = N - S(t) - V(t) - I(t).$$

Under the above assumptions, the evolution of the epidemic process will be carried out by means of the following three-dimensional CTMC

$$\mathcal{X} = \{(V(t), S(t), I(t)); t \geq 0\}. \tag{1.16}$$

We consider that at the beginning of the outbreak, there are v_0 vaccinated, s_0 susceptible and no recovered individuals. Consequently, the initial state is given by $(V(0), S(0), I(0)) = (v_0, s_0, N - v_0 - s_0)$ for any v_0, $s_0 \geq 0$, with $v_0 + s_0 \leq N$, and the state space of the CMTC, $\mathcal{X}$, is given by

$$\mathcal{S} = \{(v, s, i) : 0 \leq v \leq v_0, 0 \leq s \leq s_0, 0 \leq v + s + i \leq N\}, \tag{1.17}$$

which is finite and contains $(v_0 + 1)(s_0 + 1)(N + 1 - \frac{s_0+v_0}{2})$ states.
There is a unique absorbing state in $\mathcal{S}$: $(0, 0, 0)$ that corresponds to the situation when all individuals have been recovered from the disease.

As we are dealing with a Markovian model, the dynamics of the outbreak over time are represented by transitions between states in $\mathcal{S}$. In Table 1.3, we detail the possible events, their respective rates and transitions between the states of $\mathcal{S}$ involved in the propagation of an infectious disease. For a current state $(v, s, i) \in \mathcal{S}$, these possible events are:

(R_1) A susceptible individual gets infected through contact with an infected individual within the population.

(R_2) A susceptible individual gets infected from the external source of infection.

(R_3) Due to the imperfect vaccine hypothesis, a previously vaccinated individual get the disease through contact with an infected individual within the population.

(R_4) Due to the imperfect vaccine hypothesis, a previously vaccinated individual get the disease through contact with an infected individual that is not a community member.

(R_5) An infected individual is recovered from the disease.

Effective Outgoing Event	Transition	Rate
(R_1)	$(v, s, i) \to (v, s-1, i+1)$	$\beta i(N-v-i)/N$
(R_2)	$(v, s, i) \to (v, s-1, i+1)$	$\xi(N-v-i)$
(R_3)	$(v, s, i) \to (v-1, s, i+1)$	$h\beta iv/N$
(R_4)	$(v, s, i) \to (v-1, s, i+1)$	$h\xi v$
(R_5)	$(v, s, i) \to (v, s, i-1)$	γi

Table 1.3: Possible events and their transition rates.

Throughout this manuscript, attention is focused on the quantification of an epidemic process analyzing several random variables. Thus, next we describe several epidemic measures related to disease transmission and include related bibliography to place our research work.

1.4 Epidemic characteristics of disease transmission

To provide a comprehensive overview of what has been done in the quantification of the spread of an epidemic process, in the following we describe the main epidemic characteristics of disease transmission as reproduction numbers, incidence measures and time measures and we recompile precedent research studies related to above mentioned descriptors.

1.4.1 Reproduction numbers

Reproduction numbers are fundamental measures used to quantify the potential transmission of an epidemic in public health practice. There are several quantities that can be classified as reproduction numbers but the basic reproductive number, R_0, is probably the most widely used descriptor of disease spread and plays a privileged role in epidemiology.

As described by Heesterbeek, in [184, 151], R_0 was created by demographers in 1880 and formalized in 1925 to model the progression of a country's population. However, in recent years, it is mostly found on an epidemiology context, to quantify the transmission potential during the initial period of an outbreak. R_0 is defined as, the average number of infections produced in a fully susceptible population, by a typical infective individual during its entire period of infectiousness in absence of any control measure [150, 96]. Under a deterministic approach and for simple models, it is proven that values of $R_0 < 1$ (i.e.; each individual infects less than one individual, on average) establish that there is a decline in the number of cases and infection does not persists in the population. On the other hand, for values of $R_0 > 1$ the pathogen persists in the population. Commonly it is assumed that pathogens evolve to maximize R_0, and its value provides a direct measure of the control effort required to eliminate the infection [246].

In some situations, the previous epidemic threshold on R_0 does not apply. The basic reproductive number depends on many factors that impact transmission dynamics, including population density, population structure and differences in contact rates across demographic groups, among others. The incorporation of these factors, to the related epidemic model, can imply

assuming different critical values for the basic reproductive number determining the persistence of an infectious disease. For example, in [111], the authors suggest that exogenous reinfection has a drastic effect on the qualitative dynamics of tuberculosis transmission. In particular, exogenous reinfection allows us the possibility of a sub-critical bifurcation at the critical value of the basic reproductive number R_0, and hence the existence of multiple endemic equilibriums for R_0. They suggest that reducing the basic reproductive number to be smaller than one, may not be sufficient to eradicate the disease and an additional reduction in reinfection rate may be required. Another example that illustrate that deterministic assumptions are not always well applied is described in [135]. The authors demonstrate that the heterogeneity in transmission rates is critical for control. They describe several SIR and SIS models assuming that the force of infection is a nonlinear function of density of infectious individuals and they demonstrate that general assumptions for R_0 are also not satisfied for these cases. In [87], the authors assess that, for populations with social or spatial structure, a chronic disease is more likely to invade than an acute disease with the same R_0, because it persists longer within each group and allows, for more hosts, movement between groups. For example, in network models, not only the properties of the individual but also the nature of the network of connections between them, is important in determining the basic reproduction number. These are some of several examples where the basic reproduction number presents inconveniences and we refer the interested reader to [165, 209, 254, 112, 245, 282, 247, 141] and the references therein to get a wide knowledge on the topic.

Under a deterministic approach, there are several methods to calculate R_0

as survival functions, the next-generation methods and Jacobian methods, among others [188].

To compute R_0, applying a methodology based on the survival function, we consider a large population and we denote by $F(\mathsf{a})$ the probability that a new individual remains infected during a time units and by $b(\mathsf{a})$ the average of new infections produced per unit time when the time infected is a [150]. Then, the basic reproductive number is defined as follows

$$R_0 = \int_0^\infty b(\mathsf{a})F(\mathsf{a})d\mathsf{a}.$$

This method is very simple and it can not be applied in some situations. For example, in vector-borne infections, disease is transmitted by infected arthropods and this factor of transmission is not included in the survival function and it should contemplate it.

To solve this inconvenience the next-generation method is preferable because it takes into account more than one transmission element. The next generation method was developed by Diekmann et al. in [100] and popularized by Driessche et al. in [282]. In this method, population is divided into a finite and disjoint number of discrete categories. Then, the so-called next-generation matrix is obtained computing the numbers of newly infected individuals in the various categories in consecutive generations. R_0 is defined as the dominant eigenvalue of the next-generation matrix.

Regarding the Jacobian methods, in [98], Diekmann et al. compute a predictive threshold analyzing the eigenvalues of the Jacobian matrix at the disease-free equilibrium. Around this point, if all the eigenvalues of the Jacobian matrix have a negative real part, the equilibrium is stable and they

use the characteristic polynomial and the Routh–Hurwitz stability conditions to compute the basic reproduction number, R_0. This method is appropriate when the evolution of an infectious process is described in terms of systems of ordinary differential equations. These methods and others are fully described in [99, 282, 102, 188].

The herd immunity level, introduced in Section 1.2 and denoted by, v_c, depends on the basic reproduction number R_0 [115, 72]. The indirect protection will begin to take effect when a population reaches the herd immunity threshold, and it occurs when the proportion of immunized individuals is over the value

$$v_c = 1 - \frac{1}{R_0}. \tag{1.18}$$

The more transmissible a pathogen, the greater its associated basic reproduction number and the greater the proportion of the population that must be immunized to block sustained transmission [152]. The above interpretation of the basic reproduction number and its relation to the herd immunity threshold only is applicable assuming some hypothesis. Specifically, it is assumed that individuals have no preferences in their relationships, develop permanent immunity after recovery and vaccine offers life-long protection. In the real world, these epidemiological and immunological assumptions are not always satisfied and in consequence, the herd immunity level can not be derived from Equation 1.18 [152]. As we stated before, R_0 depends on many factors and, consequently, these will directly or indirectly impact the herd immunity threshold.

In Figure 1.10 we show the herd immunity thresholds for several dis-

eases/outbreaks, as functions of the basic reproduction number. A highly infectious virus, as measles, will have a high R_0 $(14-15)$ and a high proportion of the population must be vaccinated to decrease the transmission of the infectious disease. In contrast, the outbreak of Ebola virus in Guinea 2014, had a low R_0 $(1-2)$ and only the 35% of the population should be vaccinated to control the outbreak. By 2020, most of the studies suggested the R_0 for SARS-CoV-2 pandemic to be between 2 and 3 and it would be necessary to immunize the 60% of the population to attain the herd immunity, in case that permanent immunity was achieved.

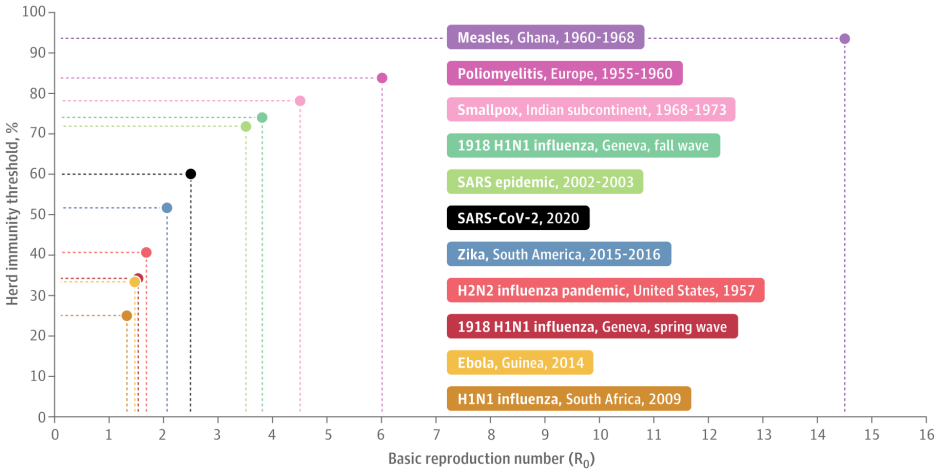

Figure 1.10: Herd Immunity Thresholds by Disease. *Note.* From Omer, S. B.; Yildirim, I.; Forman, H. P. Herd Immunity and Implications for SARS-CoV-2 Control. JAMA 2020, 324 (20), 2095–2096.https://doi.org/10.1001/jama.2020.20892 [229]

We previously mentioned that R_0 works well under a deterministic approach where population group sizes are, as a premise, infinite. In con-

sequence, the probability that two specific individuals have contact equals zero. However, in real-world situations, this behaviour is not true at all. In particular, R_0 quantifies well the initial spread of an epidemic process. It is defined as the invasion time when the index case, who is the first individual who brings the infection to a population, is introduced in a fully susceptible population. The deterministic approach takes into account only average values and neglects that the agent itself diminishes the availability of susceptible individuals (linearization assumption) [98, 102]. This has a bad consequence in the computation of R_0 because there is an overestimation of the number of contacts and secondary infections produced by the typical individual as authors discuss in [102]. Contacts of infectious individuals to individuals, whom have been previously infected, are futile and their should be eliminated [101].

For this reason, it seems relevant to explore alternative measures to R_0. However, the utility of R_0 to quantify the severity and the expansion of an infectious disease still holds. For example, for an SIS model, high values of R_0 are associated with epidemics that persist for long time. In contrast, short epidemics are identified by lower values of the basic reproduction number [42].

The methodology to compute R_0, described above, is preferable under a deterministic approach and assuming that all individuals in the population are equally susceptible to be infected. When a control measure is available, for instance a vaccine, it is preferable to deal with the control reproduction number to quantify the spread of an epidemic [86]. The control reproduction number, denoted by R_c, is the average number of secondary cases due

to a infective individual in a totally susceptible population, in the presence of control measures. The relationship between R_c and R_0 when a proportion f of individuals are vaccinated with a perfect vaccine is very simple. The control reproduction number can be calculated as the product of the basic reproductive number and the fraction of the host population that is susceptible; that is, $R_c = R_0(1-f)$. If the available vaccine is imperfect and there is a proportion h of individuals for which the vaccine has no effect, the relationship between R_0 and R_c is as follows $R_c = R_0(1-(1-h)f)$. If a perfect vaccine is available and assuming that a proportion f of individuals are vaccinated, then disease will not spread if $(1-f)R_0 < 1$. When the vaccine is not perfect and it fails with probability h, the vaccine coverage, v_c^*, necessary to eradicate the infectious disease should satisfies

$$v_c^* > (1-1/R_0)/(1-h).$$

Under a stochastic approach, the literature usually assumes deterministic values for the basic reproduction number. Commonly, for the SIR and SIS models $R_0 = \beta/\gamma$, even that this value is not the real average of secondary infections produced by the index case [71]. For example, in [53], the classical definition for R_0 is well considered in a stochastic SIR model when population is large by the average of the first generation of a Galton-Watson process.

Other studies present a method for incorporating uncertainty in the estimate of the basic reproduction number in a deterministic model of an epidemic. For example in [244], author analyzes an SIR model, with R_0 specified by a probability distribution instead of a single value.

The first paper dealing with the correction of the overestimation that R_0 makes and under a deterministic approach, was written by Diekmann et al.

in [101]. The authors say that, when individuals systematically contact the same individuals, the probability that an infectious individual has contact with an already infected individual is higher than it is when all members of the community contact with each other with the same probability. Thus, the effectivity of the infectious output gets reduced. In particular, the authors assume that each individual has contacts with precisely k other individuals and they give an alternative expression of R_0, taking into the account selective contacts and eliminating the effect of those that are repeated.

Under a stochastic approach, and for SIS and SIR models, Ross in [250] also generalizes the study of transmission to any stage of the epidemic and not only to the instant of invasion, as R_0 makes. The author, combines the basic reproduction number with the probability mass function of secondary infections produced by a typical infected individual, to gain further information and to correct its overestimation.

Other alternatives to the basic reproduction number, in a Markovian framework, are the exact reproduction number, R_{e0} and the population reproduction number, R_p. These descriptors were first described in 2013, by Artalejo and López-Herrero, in [41], for stochastic SIS and SIR models providing exact measures of the number of secondary cases of infection.

The authors described R_{e0} as a random variable that counts the exact number of secondary cases, produced by a typical infective individual during its entire period. The main feature of R_{e0} is that it does not count infections produced to individuals that previously have been infected. These contacts are vain and their effect should be neglected as the authors explain in [51]. In consequence, R_{e0} corrects the effect of the linearization hypothesis, assumed

under a deterministic approach and it does not overestimate the number of secondary cases produced by the index case. In this sense, for small communities and in a stochastic framework, the exact reproduction number is preferable to measure the spread of epidemics.

We recall that, R_0 is defined at the time of invasion, when a typical individual is introduced in a fully-susceptible population, even so, R_{e0} can be defined at any time t, regardless which the compartmental situation is. We point that, R_{e0} is a random variable and it is not an average value, as R_0 is. In consequence, additional probabilistic information can be obtained via generating functions, probability mass functions, moments distributions, among others. When an epidemic process is ongoing and assuming that invasion starts at $t = 0$ with an unique infectious individual, the expected value $\bar{R}_{e0} = E[R_{e0}|I(0) = 1]$ is the exact measure of the disease spread of the traditional R_0.

The population reproduction number, R_p, also was introduced in [41], by Artalejo and López-Herrero, to measure the disease of spread by the whole infective population. Since individuals are not marked to investigate their infections to other individuals, R_p is described as a global measure of the disease spread. In addition, authors analyze these exact reproduction numbers and compare them to the traditional R_0. They also provide algorithmic recursive schemes for the computation of the generating functions, mass probability functions and factorial moments of R_{e0} and R_p applying first-step arguments and iterative methods to solve the set of linear equations involved.

In recent years, the exact reproduction number is getting more attention and several studies analyze this descriptor assuming different epidemiologi-

cal and immunology hypotheses. For example, in [33], Artalejo analyzes the dynamics for a vector-borne infection overtime, in intensive care units and calculate factorial moments distributions for the exacta reproduction number, R_{e0}. Economou et al. in [106], studied the exact reproductive number for the spread of a respiratory disease and infections caused by nosocomial pathogens in intensive care units, for a stochastic SIS epidemic model with heterogeneous contacts. Almaraz et al. in [18], describe the R_{e0} for epidemic models with infective and susceptible immigrants. In [197], Lopez-Herrero extended the work initiated in [41], and she introduced a latency period in the model to quantify the spread of an infective process, assuming a generic incidence rate in a finite and homogeneous population.

Gómez-Corral et al. described these descriptors for infection periods that are not necessarily exponentially distributed in [137]. For the same infectious agent than in [33], López-García et al. in [195], analyzed the R_{e0}, for a unified SIS model, to allow one to move from more compartment-based models for highly homogeneous scenarios to agent-based type models with highly heterogeneous settings.

As we stated in this section, reproduction numbers are very useful to quantify the potential transmission of an outbreak but they are also very practical to evaluate the plausibility of some incidence measures and the uniqueness of their solutions [196].

1.4.2 Incidence measures

Incidence measures quantify the extent and spread of an infectious disease. In addition, these descriptors are useful for assessing the possibility of inter-

vention and to check its impact, in controlling the expansion of the pathogen. Incidence and prevalence are two concepts that are appropriate to use jointly.

In epidemiology, "prevalence" is the number of cases of a disease in a specific population at a particular time point or over a specified period of time. "Incidence" is the rate of new cases of a disease occurring, in a specific population, over a particular period of time. Prevalence tells us the size of the infected group and, in some circumstances, it gives information about the size of the susceptible group. Alternatively, incidence describes the rate of spread [84].

There is a large variety of epidemic descriptors related to incidence measures. Some of them give information about the size of each compartment at a certain time or during a period of time (i.e.; the number of individuals susceptible to infection, the number of infected individuals who are able to transmit the pathogen...). Other descriptors focus on provide information about the epidemic size, counting the total number of transitions to a selected state during a period of time (i.e.; the total number of cases of infection and the number of recovered individuals during an epidemic outbreak, the number of infections produced during a period of time, the total number of infections produced to a marked individual during an epidemic process...). Another measures study the peak prevalence of an infectious disease, during a period of time (i.e.; the maximum number of simultaneously infected individuals during an outbreak, the maximum number of infections produced to a marked individual during an epidemic process...).

The final size of an epidemic is one of the most important incidence measures. It can be defined, informally, as the total number of people expe-

riencing infection during the outbreak. For example, in the classic SIR model described in Section 1.3.1, the final size of an epidemic corresponds with the number of individuals that have been infected during the epidemic process. In contrast, in the classic SIS model, this size corresponds to the number of infections produced during an outbreak.

In the early literature, assuming a deterministic approach, equations involved in the calculation of the the final size of an epidemic are directly related to the basic reproduction number, R_0. The well-known Kermack-McKendrik equation for the final size of an epidemic and for the classic SIR model, was formulated in 1927, and it is the solution of the following equation

$$Z = 1 - e^{-R_0 Z}, \tag{1.19}$$

where Z denotes the estimate of an epidemic's expected final size [171] and infectious periods are assumed exponentially distributed. But, some years later was demonstrated that Equation (1.19), is also valid in remarkably general circumstances.

For example, in 1980, Anderson and Watsons, in [22], proved that the final size equation (1.19), remains true if infectious periods are gamma distributed. In 2000, Diekmann and Heesterbeek, extended this assumption to cover an arbitrary distribution of infectious periods [98]. In [200], Ma et al. showed that same Equation, is invariant to models that include a stage during which infectives are isolated and/or a latent stage and/or multiple infectious stages. In addition, the above equation is unchanged when transmission rates of infectious individuals, are arbitrarily distributed.

The final size of an epidemic is influenced by the human behaviour and this effect has been widely analyzed. For example, in [68], Brauer et al.

studied how having knowledge about the severity of an infectious disease affects the transmission when epidemic is produced by a serious infectious disease. In this situations, individuals can modify their social habits to avoid the infection. In consequence, a contact rate that decreases in time can be considered and the epidemic size decreases considerably. As an application of his methodology, final sizes were calculated for the Sierra Leona and Guinea outbreaks, in 2014. For both epidemics, authors demonstrated knowing the severity of the Ebola virus produced more realistic and smaller estimated values of the final epidemic size than estimates that did not do. Gart, in 1968, [125] extended the original Equation (1.19) to the situation where the initial population of susceptible individuals is divided into two classes with different infection rates. A recent work that deals with a similar situation was conducted by Magal et al. in [201]. The authors divided the population in two classes, the super spreader individuals (highly contagious and capable of spreading disease to an unusually large number of people) and the non-super spreader individuals. The authors studied the final size of the epidemic for each sub-population and focused on the role of super spreaders, in the context of the SARS outbreak in Singapore, in 2003. Another studies suggested that homogeneous mixing population assumptions predicts an unrealistically large final size of an epidemic. Many researches have included detailed accounts for heterogeneities in contact structure, to obtain results in a more realistic scenario. We refer the interested reader to [27, 288, 215, 177] to extend the knowledge about the impact of host heterogeneity on the structure of the final size equation under a deterministic approach.

Ball, in 1985, [48] generalized Gart's result to stochastic epidemics mod-

els, where individuals vary in their susceptibility to the disease, though the exact values of the susceptibilities are not known. The author proved that assuming an average infection rate, for the transmission of an infectious disease, offers increased outcomes of spread of disease under both deterministic and stochastic form.

Under a stochastic approach, it can be obtained the probability distribution of the final size. There is a large number of methodologies to calculate the probability mass function. In 1953, Bailey in [46], analyzed a stochastic SIR epidemic model and calculated the probability mass distribution of the total number of infected individuals solving a set of doubly recurrent relations. Later, in 1955, Whittle [296] showed that this probability mass function can be obtained by solving a set of single recurrent relations. In addition, author provided a stochastic equivalent to Kermack-McKendrick total size equation (1.19). Another methodologies were considered by House et al. in [160], where authors proposed a technique, based on Monte Carlo simulations and on Sellke's method (full method is described in [260]), to simulate the final size for outbreaks with arbitrary recovery period distributions. Moreover, several methods involving Markov chains were detailed in [160], for evaluating the probability mass function of the final size, for homogeneous finite populations and also for heterogeneous and large populations. In [63], Black and Ross presented a new method to calculate the final size distribution applicable to homogeneously mixing Markovian models. The authors used the called degree-of-advancement (DA) representation of the stochastic process, which considers the epidemic process as a random walk ending in an absorbing state, and obtained the final size of the outbreak from

a probability tree. There are additional methods to determine the probability mass function of the final size of an epidemic involving transforms, matrix and spectral approach, approximations and asymptotic results. We refer the interested reader to [167, 222, 204, 212, 27, 50, 32, 51, 71, 219] to explore alternative methodologies.

Under a stochastic Markovian approach, several incidence measures were described. For example, for the SIS model, an infection reintroduction is considered by Stone et al. in [270]. The authors analyzed the maximum number of infectives, the total number of infections produced by an infectious individual during an outbreak, the individual's probability of becoming infected, the mean number of individuals infected and the number of infections per individual among others for an SIS model. In [37], Artalejo et al. provided factorial moments and probability mass functions for the final size of an epidemic until its eradication and also during a fixed period, for SIR an SIS models. Theoretical analysis relies on generating functions and forward-elimination-backward-substitution arguments, providing updated information about the severity of the outbreak, at each time $t \geq 0$. This is a distinguished feature in comparison with the existing literature because they analyze the size of an epidemic even, in transient regime.

In this context, in [36], same authors studied the maximum number of simultaneous infected individuals in an SIS model. This descriptor is useful to measure the severity of an outbreak and it denotes the "peak size" of the epidemic curve. It also provides substantial information about the necessary resources on demand, during an epidemic. In [42], the authors analyze the number of infected on a least one occasion, during an outbreak,

for an SIS model. In addition, mass probability, generating functions and factorial moments for the number of infections per individual are investigated. López-García et al. in [194], studied the final size and the maximum number of individuals simultaneously infected during an outbreak assuming heterogeneous mixed population and small networks. The author proposed a structure by levels and sub-levels of the state space of the Markov chain involved that permits to study the propagation dynamics in a matrix form. Efficient algorithms to compute the distributions of the total and the maximum size of the epidemic are provided. In [21], Amador et al. considered an SEIR model with non-linear incidence rate and limited resources to study the total number of cases of infection and also the maximum number of simultaneous infective individuals in an outbreak.

To complement the literature, we refer the interested reader to [49, 51, 163, 219], where authors described several incidence measures for more refined and pragmatic models, including household, multi-population and rumours, are described. To explore incidence measures, in the framework of queuing theory, we refer to [221, 262, 35, 39, 34], where several descriptors are applied to assess an optimal number of customers to avoid congested systems.

For these cases, among others, it is important to provide information about the propagation dynamics in terms of the length of an epidemic.

1.4.3 Time measures

Time measures are essential in characterizing the expansion of an infectious disease. They are useful to assess if incidence rates and case numbers, have

changed over time and to measure the length and persistence of an epidemic process. They are also practical to quantify the persistence of the infection and the velocity of transmission.

Health control strategies depend not only on their intrinsic efficacy, but also on the time needed for their implementation. For example, for diseases that occur seasonally, health experts can anticipate their appearance and implement control and prevention strategies in advance to avoid severe outbreaks. In this section, we present some time measures as time to extinction, time to reach a number of infections, time to infection and recovery time of a selected individual; among others.

Probably the extinction time is one of the most studied measure in epidemic modelling. Under a deterministic approach and assuming the constant size population hypothesis, this measure is not very practical. By definition, the endpoint of an epidemic process is ambiguous since the information about the size of each compartment, is represented by percentages that never reach zero. In consequence, a threshold as the basic reproduction number, R_0, is required, to determine if extinction may occur.

Some studies provided approximations of the stochastic versions applying a deterministic approach. For example, in [216, 217], the author demonstrated for SI, SIS, SIR, and SIRS models, that these approximations are valid for sufficiently large population sizes. Conditions for validity of the approximations are given for each of the models analyzed and also for the corresponding deterministic models. It is noted that, some deterministic models are unacceptable approximations of the stochastic models, for a large range of realistic parameter values. In [26], the authors provided asymptotic

approximations for the extinction time, for large population sizes, which vary according to the values of R_0 and the number of initial infectives. In [237], author provided a further approximation for large population sizes. In [13] and [12], Allen and the rest of the authors analyzed relationships between deterministic and stochastic thresholds for disease extinction in continuous and discrete-time epidemic models. In a deterministic framework, the literature is limited [205, 3]. A study conducted by Aliee et al. [7], focused on the computation of the distribution in predicted extinction times, which had not been done elsewhere. The authors, developed a basic scheme to study the peri-elimination phase, for an infectious disease, using a simplified SIS model. They used solutions of the corresponding forward Kolmogorov equations, to predict the point of infection extinction in deterministic solutions and extended this framework, to estimate the extinction time of more complicated infection dynamics.

Under a stochastic approach, the time to disease eradication has been widely studied. Norden, in [226], analyzed the distribution of the extinction times for a stochastic logistic process and showed that it is a gamma-type distribution. The author provided explicit expressions for the mean time to extinction given an initial state. Highers moments were computed using backward Kolmogorov equations. Furthermore, a consideration of the process, conditioned on non-extinction, is showed to be an effective way of obtaining a large t (time) description of the unconditioned process. In [216], Nåsell analyzed the extinction time for the SIS model assuming constant and finite population and demonstrate that, if the epidemic process starts in the quasi-stationary state, the time to extinction follows an exponential

distribution, with mean $1/(\gamma q_1)$, where q_1 is the quasi-stationary probability of having a single infective individual. In [11], Allen et al. analyzed numerically, the distribution of the extinction time for several epidemic models and in [133], Goel et al. applied a Laplace transform method to obtain moments of the distribution of the extinction time for several epidemic models. Similar studies were addresses by Oppenheim et al. [230] for a model on chemical reactions, by Cavender, in [79], for birth-and-death processes, by Bartholomew [55] for social diffusion process and by kryscio et al. in [180] who combined and extended previous results to obtain an approximation to the mean time to extinction, for the standard SIS epidemic model. When a single initial infective individual is in the population, closed expressions for expected values and standard deviations of the extinction time were calculated by Newman et al. [223]. A spectral decomposition is applied to study time to extinction by Keilson et al., in [168]. Assuming an isolated population, heterogeneous contacts and an SIS model, Economou et. al [106] analyzed the time until extinction using an appropriate labeling of the states of the involved CTMC. The length of this outbreak was described as a phase-type random variable and its Laplace transform and moments were computed applying a forward elimination backward substitution method. An extension of this work is conducted by Gómez-Corral et. al in [139], where authors analyzed first-passage times to higher levels of the labeled state space and supplied a numerical analysis of an epidemic model for the transmission of varicella-zoster virus within a nursing home.

For stochastic SIR and SIS models, theoretical and computational results, regarding extinction time or the time to reach a specific state, are included in

[42, 38]. We recall that, for the general SIS and SIR models on isolated populations, the epidemic process ends when the number of infective individuals reaches 0. In contrast, when infectious diseases can be recurrent, it is useful to provide alternative measures as an indicator of the disease spread as the time until reach a number of infections. The time to reach a number of infections has been widely analyzed. For example, in [270], Stone et al. consider a stochastic SIS model with an external source of infection and investigate the time to reach 0 infectives, conditioned the current number of infected individuals. The authors also computed expressions for the moments applying generating functions and demonstrated that after reached 0 infected individuals in the population, the process will remain in this state for a period of time that is exponentially distributed with mean $1/(\xi N)$. Artalejo et al. [42] studied the time to reach an individual run of infections for a birth-and-death model and the time that the epidemic needs to reach certain critical levels when dealing with an SIR model. In [20], Amador et al. incorporated an additional compartment for quarantined individuals to an SIS model with limited carrying capacity. The focus is on the analysis of the length of an outbreak and on the time until the quarantined compartment is full for the first time. The authors applied matrix-analytic methods to characterize the arising phase-type random variables and their investigation revealed the importance to quarantine individuals as a strategy for controlling an epidemic process.

Chapter 2

Measuring Infection Transmission in a Stochastic SVI Model with Infection Reintroduction and Imperfect Vaccine

This Chapter is oriented to quantify the potential transmission of an infectious disease that does not confer immunity, trough reproduction numbers, taking into the account vaccination to control its spread. The underlying mathematical model is the SVIS model described in Section 1.3.2.1.

The title of the Chapter matches the title of the published paper [121]. We point out that notation SVI, appearing on the publishing paper, corresponds to the above mentioned SVIS model.

A printed version of [121] is included at the end of Chapter 2, along with scientific information regarding the academic journal where manuscript is published.

2.1 Background

In this research work, we consider the stochastic SIS-type model with an additional compartment of vaccinated individuals and external source of infection, SVI, described in Section 1.3.2.1, where the evolution of the infectious disease, at each time point t, is represented in terms of a bidimensional CTMC.

We focus on the study of the potential transmission of the infectious disease for the SIS-type model with external source of infection in a post-vaccination context. We derive analytical and algorithmic results involving the exact and population reproduction numbers (R_{e0}, R_p) which were described in [41] and in Section 1.4.1.

2.2 Objectives

In this research work we carry out the objectives (a), (b), $(c.1)$, $(c.2)$, $(c.5)$, (d) and (e) described in Section 1.1.1. In more detail:

We construct the stochastic SVI model and we explore the long-term behaviour of the epidemic process, that are objectives, (a) and (b).

We study the effect of vaccination on the spread of an infectious disease and its potential transmission by describing the exact reproduction number, R_{e0} and the population reproduction number, R_p in order to carry out purposes $(c.1)$ and $(c.2)$.

Objectives (d) and (e) are reached by providing a comprehensive sensitivity analysis taking into the account several possibilities in the selection of the model parameters and showing several numerical examples.

Finally, we applied these measures to set an appropriate vaccine coverage that guarantees herd immunity during an epidemic that is the objective ($c.5$).

This investigation is a first approach to investigate the optimal policies to control an epidemic process that will be described in the Chapter 3.

2.3 Methodology

In this investigation we apply the methodology described in Section 1.1.2.

In more detail, we analyze the behaviour of the Markov chain involved by applying the specific techniques of the stochastic processes.

To compute probability mass functions and moments of the discrete random variables, R_{e0} and R_p, we apply first-step arguments, conditioning on the possible transitions out a fixed state, to derive a set of linear equations involving mass and generating functions and moments of the random variable of interest. We solve these linear system of equations applying matrix and Gaussian elimination methods.

2.4 Conclusions

We obtain that the infinitesimal generator of the CTMC has a bi-diagonal structure that guarantee that matrices involved in the theoretical results are, at most, tri-diagonal and diagonally dominant. In consequence, the linear systems involved can be solved efficiently applying matrix methods and a simplified form of the Gaussian elimination algorithms.

The speed of these schemes depends on the population size and model param-

eters and we only present numerical results for moderate sizes populations. The numerical analysis shows that probability mass functions, present long right tails. Consequently, to avoid prolonged computations we use a stopping criterion that consists on iterate the algorithms provided, until the 95% of the mass points are accumulated.

Regarding to the probabilistic behaviour of R_{e0} and R_p, we appreciate the following:

We obtain decreasing values of the number of secondary cases produced by the index case, for increasing values of the external contact rate, ξ. It means that, when we deal with long external contact rates, there are an increasing number of infection cases produced by individuals that do not are in the population. In consequence, the marked individual has less opportunities to spread the pathogen compared with the external source of infection. In contrast, increasing values of the internal contact rate, β, produce increasing values of the number of secondary cases produced by the index case. The effect of the vaccine failure is greater for longer internal contact rates for both random variables. In particular, there are more cases of infection for longer probabilities of vaccine failure. This is an expected behaviour because when a vaccine fails with more probability, there are more possibilities that the marked individual (the entire population) spreads the pathogen to vaccinated individuals. The vaccine coverage has a big impact on the propagation of the infectious disease. For increasing values of the initial number of vaccinated individuals we obtain decreasing values of R_{e0} and R_p. This reveals the importance of vaccination in the control of an epidemic process. In addition, we use R_{e0} and R_p to obtain the minimum level of initial vaccinated individu-

als and we obtain that, when the internal contact rate increases it is necessary to rise the vaccine coverage to assure herd immunity in the population.

2.5 Publication

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REGULAR ARTICLE

Measuring Infection Transmission in a Stochastic SIV Model with Infection Reintroduction and Imperfect Vaccine

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Abstract

An additional compartment of vaccinated individuals is considered in a SIS stochastic epidemic model with infection reintroduction. The quantification of the spread of the disease is modeled by a continuous time Markov chain. A well-known measure of the initial transmission potential is the basic reproduction number R_0, which determines the herd immunity threshold or the critical proportion of immune individuals required to stop the spread of a disease when a vaccine offers a complete protection. Due to repeated contacts between the typical infective and previously infected individuals, R_0 overestimates the average number of secondary infections and leads to, perhaps unnecessary, high immunization coverage. Assuming that the vaccine is imperfect, alternative measures to R_0 are defined in order to study the influence of the initial coverage and vaccine efficacy on the transmission of the epidemic.

Keywords Stochastic Markovian epidemic · Imperfect vaccine · Basic reproduction number

Mathematics Subject Classification 92D30 · 60J28 · 60J22

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1 Introduction

Mathematical modeling is an essential tool to represent the progress of an epidemic through a population. It is commonly accepted that the work of Kermack and McKendrick (1927) is the prototype of almost all epidemiological models based on a classification of individuals by their epidemic status. Since then, many other compartmental models have been developed to investigate a diverse range of communicable diseases to obtain a better knowledge of their transmission mechanisms (Anderson and Britton 2000; Kretzschmar et al. 2001; Aguiar et al. 2010; Artalejo and Lopez-Herrero 2014; Liu et al. 2018).

A common assumption is that the communicable disease spreads in a community of constant size. The population can be closed in the sense that infectious individuals can infect only other individuals within the population under study during the epidemic's time span. However, assuming reintroduction of the disease through contact with infected individuals from other areas could represent a more realistic scenario (Marchette and Wierman 2004; Stone et al. 2007; Amador 2016).

After infection, it is assumed that patients recover due to their own immune system which acts as a body's defense force against germs and other invading substances. Hence, to reduce the incidence of an infectious disease requires improving sanitary and living conditions. In that sense, we cannot ignore the impact of vaccination on this reduction, especially in the developing world. Vaccines activate the immune system's capacity of producing antibodies to fight diseases without exposing it to diseases-producing pathogens. If a vaccinated person comes into contact with the disease for which she/he has been vaccinated, her/his immune system recognizes the invading germs and immediately produces the antibodies that will kill foreign invaders. Generally, vaccines provide immunity similar to that acquired from the natural infection, and duration of protection varies depending on diseases and also on vaccine strains. Lifelong immunity is not always provided by vaccination and usually several doses of vaccine may be required. Furthermore, the immune response may wane over time and it is necessary to administrate new doses of vaccine to increase or restore immunity.

As it is an effective method of disease control, recent epidemiological models (Kribs-Zaleta and Martcheva 2002; Arino et al. 2003, 2010; Ball and Sirl 2013; Samanta 2015; Ball and Sirl 2018; Li and Zhang 2019) have added a vaccination compartment and vaccination strategies into their mathematical model. Some papers discussing the impact of vaccination on the spread of an epidemic assume complete protection (Iannelli et al. 2005; Alexander et al. 2006; Ball et al. 2007; Lin et al. 2014; Eckalbar and Eckalbar 2015; Guo 2017) but even vaccine efficacy, as measured by observational studies, is not 100% (e.g., measles: 90−95%, mumps: 72−88% or rubella: 95−98%) and depends on internal or individual factors, as well as on the dose and strain of the vaccine virus (Demicheli et al. 2012). In scientific literature, vaccine efficacy and effectiveness are often used interchangeably. Vaccine efficacy represents the reduction in the risk of infection at individual level under optimal condition (e.g., randomized controlled trials) while

vaccine effectiveness compares rates of the transmission of the disease between vaccinated and unvaccinated individuals once the vaccine is approved for use in the general population.

The SIS model with imperfect vaccine has been studied from a deterministic point of view in the papers by Moghadas (2004) and Safan and Rihan (2014), under nonlinear incidence in Xiao and Tang (2010) and Yang et al. (2015), and with inclusion of a latency period as well as psychological effects in both susceptible and vaccinated individuals in Cheng et al. (2015). A SIV model with stochastic perturbations is discussed in Liu et al. (2018) and López-García (2016).

The above-mentioned studies deal with large populations, but transmission patterns become quantitatively different when a small population is involved. Firstly, individual variations of infectivity, recovery periods and vaccine protection, even for a homogeneous social group, should be taken into account. Moreover, when the susceptible population becomes depleted the extent of the epidemic is interrupted and, for closed populations, the extinction of the disease is possible (Keeling and Ross 2008).

The aim of this paper is to quantify the spread of an infectious disease that does not confer immunity, within a population that is partially protected against the disease by a vaccine. A continuous time Markov chain (*CTMC*) model represents changes in the composition of infected and vaccinated classes. Two random variables will quantify the transmission of the epidemic process with reintroduction: R_{e0}, the number of infectious cases caused directly by the first infected individual, and R_p, which is the number of infectious cases caused by any infectious spreader. These random variables act as stochastic counterparts to the basic reproduction number, R_0, and more specifically the control reproduction number, R_c, when there is an available vaccine.

In the literature, the term herd-immunity threshold refers to the critical proportion of immune individuals that is needed to interrupt epidemic transmission in a population. There is a simple relationship between herd-immunity coverage and the basic reproduction number. If a perfect vaccine is available and a fraction f of the population is vaccinated, then the disease will not spread if $(1-f)R_0 < 1$. In general terms, we can represent the quality of a vaccine by a measure of the vaccine imperfection $h \in [0,1]$, with $h = 0$ indicating a perfect vaccine, and $h = 1$ a useless vaccine. For imperfect but not useless vaccines, the critical vaccination coverage level to eradicate the infection is related to the proportion $(1 - 1/R_0)/(1-h)$. In any case, herd immunity depends on estimates of R_0, and is the result of a reduction in viral transmission caused by removing vaccinated individuals from the susceptible class. We will investigate the spread of the disease directly, at any time, by updating the current population state, and we will apply our alternative measures to control disease spread by fixing an adequate vaccine coverage level.

The structure of the paper is as follows. In Sect. 2, we describe the SIV stochastic model with infection reintroduction and summarize results for its long term behavior in terms of the reintroduction parameter. Section 3 introduces the proposed random variables, R_{e0} and R_p, as measures of the infection transmission in a partially vaccinated population. Theoretical and algorithmic results will provide probability mass functions and moments for R_{e0} and R_p, depending on the initial vaccine coverage and

effectiveness. Section 4 illustrates the applicability of the algorithmic results and presents several qualitative facts regarding the infection transmission. Finally, we present some concluding remarks and tentative future research lines.

2 Model Description

We consider a homogeneous and uniformly mixing population of constant size, N, where individuals are affected by a contagious disease. This disease is transmitted by direct contact with an infected individual. The population is not isolated, so we assume that there is an additional source of infection due to external contacts. We suppose that some individuals in the population have been protected against the disease with an available vaccine that confers immunity, but it is not a perfect vaccine and some contacts between vaccinated and infectious individuals produce an effective contagion. Once a vaccinated individual gets the infection, he no longer belongs to the class of individuals that have been vaccinated and he belongs to the infective class while he is infectious. Recovered individuals become susceptible to the disease, no matter if they were previously vaccinated or not. Consequently, individuals in the population are classified into three separate classes, namely susceptible, vaccinated and infected. Vaccination was implemented at $t = 0$ and no vaccination will take place after this epoch.

In general terms, the underlying mathematical model involves a SIV model, where movement of individuals among the three epidemiological classes is shown in Fig. 1, with S denoting the class of susceptible individuals, I denoting the class of infected individuals, and V denoting the class of vaccinated individuals.

At any time $t > 0$, the state of the epidemic is described by random variables $S(t)$, $V(t)$, $I(t)$, that record the number of susceptible, vaccinated and infective individuals, respectively, at time t. According to the constant size hypothesis we have

$$S(t) + V(t) + I(t) = N.$$

We represent the evolution of the disease in terms of a two-dimensional CTMC: $X = \{(V(t), I(t)), t \geq 0\}$. Assuming that initially the population contains v_0 vaccinated individuals, with $0 \leq v_0 \leq N$, the state space of X is $\mathsf{S} = \{(v, i) : 0 \leq v \leq v_0, 0 \leq i \leq N, 0 \leq v + i \leq N\}$ that contains $(v_0 + 1)\big(N + 1 - v_0/2\big)$ states. Notice that once $v = 0$ the vaccination compartment is empty and the underlying model is the standard SIS epidemic one.

Next, we describe the dynamics of the Markov chain, X, in full details. See Table 1 for a summary of parameters used. The exhaustive description of the events and their transition rates is presented in Table 2. Finally, a diagram showing transitions from a general state $(v, i) \in \mathsf{S}$ is depicted in Fig. 2.

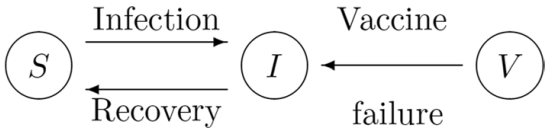


Fig. 1 SIV compartmental diagram

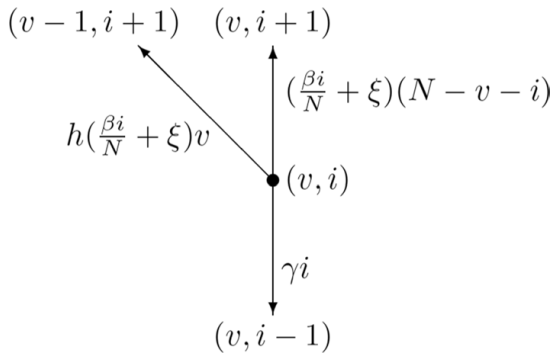
Table 1 Parameters of the model

Population size	N
Disease internal transmission rate	β
Disease external transmission rate	ξ
Probability of vaccine failure	h
Recovery rate	γ

Table 2 Effective events and their transition rates

Effective event	Transition	Rate
Susceptible-infected internal contagion	$(v, i) \to (v, i+1)$	$\beta i(N - v - i)/N$
Susceptible-infected external contagion	$(v, i) \to (v, i+1)$	$\xi(N - v - i)$
Vaccinated-infected internal contagion	$(v, i) \to (v-1, i+1)$	$h\beta iv/N$
Vaccinated-infected external contagion	$(v, i) \to (v-1, i+1)$	$h\xi v$
Recovery and loss of immunity	$(v, i) \to (v, i-1)$	γi

Fig. 2 Transitions among states



To understand the dynamics of the model it is necessary to describe the events that cause a change in the current model state (v, i). There are five possible effective events that are listed in Table 2.

E_1. A susceptible individual gets the infection from an infective individual within the population.
E_2. A susceptible individual gets the infection from an external source of infection.
E_3. Due to vaccine failure, a vaccinated individual becomes infected from an infective individual within the population.
E_4. Due to vaccine failure, a vaccinated individual becomes infected from an external source of infection.
E_5. An infective individual is recovered and becomes susceptible.

Sojourn times at each state in S are independent and exponential random variables, with rate

$$q_{v,i} = \left(\frac{\beta i}{N} + \xi\right)(N - v - i) + h\left(\frac{\beta i}{N} + \xi\right)v + \gamma i. \tag{1}$$

To describe $\mathbf{Q}$, the infinitesimal generator of the Markov chain X, we partition the state space in levels regarding the number of vaccinated individuals, that is $\mathsf{S} = \cup_{v=0}^{v_0} L(v)$, where level $L(v) = \{(v, i) \in \mathsf{S} : 0 \leq i \leq N - v\}$, for $0 \leq v \leq v_0$, which contains $(N + 1 - v)$ states. Then, we can express the infinitesimal generator of X in the following non-null block form

$$\mathbf{Q} = \begin{pmatrix} \mathbf{Q_{0,0}} & & & \\ \mathbf{Q_{1,0}} & \mathbf{Q_{1,1}} & & \\ & \mathbf{Q_{2,1}} & \mathbf{Q_{2,2}} & \\ & & \ddots & \ddots \\ & & \mathbf{Q_{v_0,v_0-1}} & \mathbf{Q_{v_0,v_0}} \end{pmatrix},$$

where $\mathbf{Q_{v,v^*}}$, for $0 \leq v, v^* \leq v_0$, are matrices of dimension $(N + 1 - v) \times (N + 1 - v^*)$. The blocks $\mathbf{Q_{v,v-1}}$, for $1 \leq v \leq v_0$, correspond to transitions due to vaccine failures, and the blocks $\mathbf{Q_{v,v}}$, for $0 \leq v \leq v_0$, correspond to transitions within level $L(v)$ that are due either to infections of susceptible or recoveries. Non-null sub-matrices are described as follows

$$\mathbf{Q_{v,v-1}} = \begin{pmatrix} 0 & h\xi v & & & \\ & 0 & h\left(\frac{\beta}{N} + \xi\right)v & & \\ & & \ddots & \ddots & \\ & & & 0 & h\left(\frac{\beta(N-v)}{N} + \xi\right)v \\ & & & & \end{pmatrix}$$

and

$$\mathbf{Q_{v,v}} = \begin{pmatrix} -q_{v,0} & \xi(N-v) & & & \\ \gamma & -q_{v,1} & \left(\frac{\beta}{N} + \xi\right)(N-v-1) & & \\ & \ddots & \ddots & \ddots & \\ & (N-v-1)\gamma & -q_{v,N-v-1} & \frac{\beta(N-v-1)}{N} + \xi & \\ & & (N-v)\gamma & -q_{v,N-v} & \end{pmatrix}.$$

The above block bidiagonal structure of $\mathbf{Q}$ guarantees that square matrices appearing in the forthcoming theoretical results are, at most, tridiagonal and diagonally dominant. Thus, they are non-singular, and linear systems involving these matrices can be solved efficiently by a simplified form of the Gaussian elimination algorithm (Golub and van Loan 1996).

2.1 Stationary Behavior

As we are dealing with a finite state CTMC, the long-term behavior of X depends on the structure of communicating classes of absorbing states. In that sense, we notice that the reintroduction parameter (that is, the external transmission rate ξ) plays an important role in the classification of the states in S. If we assume that the population is isolated and contagions are produced only by internal contacts; i.e., $\xi = 0$, then states with 0 infective individuals are absorbing. This fact and the finiteness of the state space guarantee that the process will become absorbed into any of the non-communicating classes of absorbing states with probability one. Hence, the epidemic extinction is certain and outbreaks involve a single epidemic episode that will last a finite expected time.

On the other hand, when $\xi > 0$, the state space of the finite CTMC X contains a single absorbing set given by $L(0) = \{(0, i) : 0 \leq i \leq N\}$. Thus, once the process enters into $L(0)$ it can move across these states but it can not leave the absorbing set. Hence the stationary distribution assigns mass to every state with no vaccinated individuals. Which means that, in the model with external source of infection, occasionally the disease is faded away (i.e., $I = 0$) for a short time, but the infection is reintroduced at a later time. More specifically, the theoretical long-term distribution of the number of infective individuals agrees with the stationary distribution provided in Stone et al. (2007), Section 2.6.

Figures 3 and 4 show typical trajectories for the CTMC X, starting from a single individual infected in a population of 25 individuals, 5 of which are vaccinated. We simulate 500 transitions among states and keep track of the time at which a transition occurs. Each line in Figs. 3 and 4 represents the sequence of time points and the number of individuals (infected, vaccinated or susceptible) recorded at these time epochs. The paths in Fig. 3 correspond to an isolated population and we observe that, approximately, after 2 time units the epidemic transmission will cease. In Fig. 4, the reintroduction parameter is $\xi = 0.01$. The path for vaccinated individuals

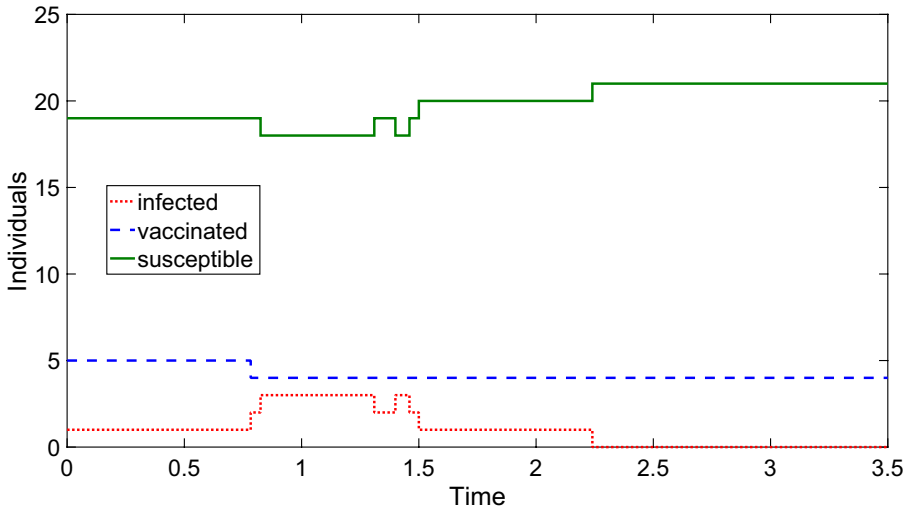


Fig. 3 Simulated trajectories of X when $N = 25$, $\beta = 2.5$, $\xi = 0$, $h = 0.3$ and $\gamma = 1.0$

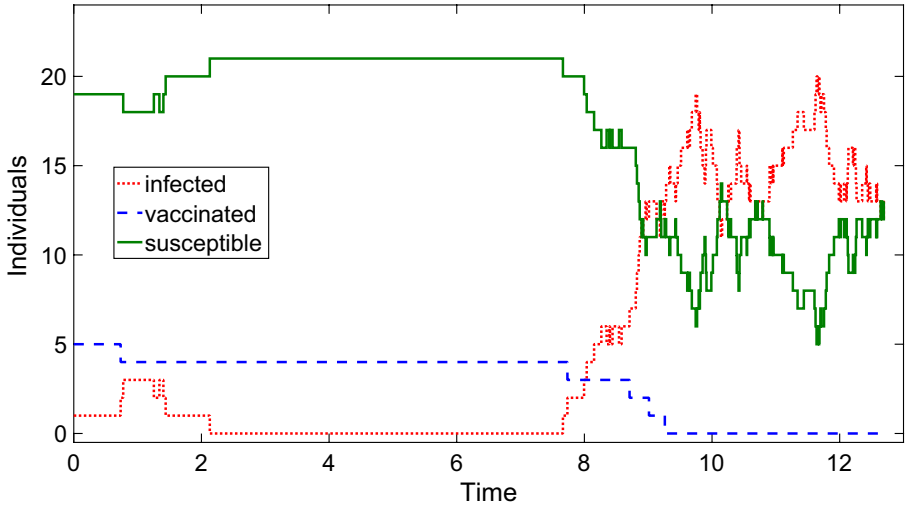


Fig. 4 Simulated trajectories of X when $N = 25$, $\beta = 2.5$, $\xi = 0.01$, $h = 0.3$ and $\gamma = 1.0$

shows that vaccine protection has faded away in about 10 time units, while the paths for the infected and susceptible populations settle towards the stationary endemic scenario.

3 Disease Spread

This section deals with a probabilistic characterization of the offspring distribution of secondary infections of an epidemic process, at a particular time. We will consider two random variables to measure the spread of the infection, when a first case of disease is identified in a population.

In epidemiology, the individual who first brings the disease into a group is called the *index case* and we will start focusing on the number of infections coming from the index case during its entire infectious period. Secondly, we will study all of the secondary cases produced by the whole set of currently infectious individuals prior to the first recovery. The above mentioned measures are the stochastic analogues to the well-known basic reproduction number R_0 and, more specifically, to the control reproduction number R_c, defined as the average number of secondary cases due to each infective individual in the presence of control measures. In the case of vaccination R_0 and R_c satisfy the simple expression $R_c = R_0(1 - (1 - h)f)$, where h is the proportion of vaccinated individuals for which the vaccine has no effect (hence, $1 - h$ quantifies the vaccine effectiveness), and f represents the vaccine coverage as the initial fraction of the target population that has received the vaccine (Alexander et al. 2004; Magpantay 2014).

The Markovian chain, describing the evolution of the epidemic in the compartmental model, will play an essential role to develop theoretical results. The evaluation of the probability mass distribution of the number of secondary infections produced by a selected individual was firstly introduced by Ross (2011) and, in an independent way, by Artalejo and Lopez-Herrero (2013). Both papers consider finite

SIS and SIR compartmental models and present probabilities of the offspring distribution as the solution of systems of linear equations. Their results generalize the study of the infection transmission from the instant of the invasion to any stage of the disease progression and show that, for populations of moderate size, the basic reproduction number can overestimate the potential transmission of the epidemic process.

The analysis of the transmission of an epidemic process has been extended to epidemic models with vector-borne infections (Artalejo 2014), heterogeneous contacts (Economou et al. 2015; López-García 2016), infective and susceptible immigrants (Almaraz et al. 2016), latency periods (Lopez-Herrero 2017), generally distributed infectious periods (Gómez-Corral and López-Garcia 2017), Markov-modulated interactions (Almaraz and Gómez-Corral 2018) or to models for two-species competition (Gómez-Corral and López-Garcia 2015).

Our results will reveal the influence of the vaccine, coverage and effectiveness, and the reintroduction parameter on the transmission potential of the disease. Hence, in the subsequent sections we proceed with theoretical discussions leading to probabilistic results.

3.1 The Exact Transmission Variable R_{e0}

In this section we study the potential transmission of an infective process by studying the random variable R_{e0}, defined as the number of infective individuals that arise from contagions caused directly by the index case, that is, the first individual in the population able to spread the disease. The objective is to characterize the distribution of the random variable R_{e0} and to observe the influence of the initial group of vaccinated individuals (i.e., vaccine coverage) on the transmission.

This analysis is directly related to the infectious period of the index case. During this period, the underlying Markov chain X evolves in $\widehat{S}$, the subset of states showing at least one infectious individual. For practical purposes $\widehat{S}$ will be partitioned in levels, according to the current number of vaccinated individuals, as follows:

$$\widehat{S} = \bigcup_{v=0}^{v_0} \widehat{L}(v) = \bigcup_{v=0}^{v_0} \{(v,i) : 1 \le i \le N - v\}.$$

First, we introduce appropriate notations for the generating and probability mass functions, and for the factorial moments of R_{e0} conditioned to a specific state $(v,i) \in \widehat{S}$.

$$\begin{aligned}
\varphi_{v,i}(z) &= E\left[z^{R_{e0}} | (V(0) = v, I(0) = i)\right] \\
&= \sum_{k=0}^{\infty} z^k P\left(\left\{R_{e0} = k | (V(0) = v, I(0) = i)\right\}\right), \text{ for } |z| \le 1, \\
x_{v,i}^k &= P\left(\left\{R_{e0} = k | (V(0) = v, I(0) = i)\right\}\right), \text{ for } k \ge 0, \\
m_{v,i}^k &= \begin{cases} 1 & \text{if } k = 0, \\ E\left[R_{e0}\left(R_{e0} - 1\right) \cdots \left(R_{e0} - k + 1\right) | (V(0) = v, I(0) = i)\right] & \text{if } k > 0. \end{cases}
\end{aligned}$$

In the rest of the section we will develop algorithmic schemes for determining $\varphi_{v,i}(z)$, $x^k_{v,i}$ and the moments $m^k_{v,i}$. Firstly, we mark the index case. The homogeneous mixing assumption guarantees all-to-all interactions with no preferences in relationship among individuals. Therefore, individuals are all the same and we split transitions in Table 2, associated to contagions, by distinguishing whether or not a new infection comes from the index case. That is, we partition contagion rates in the following way

$$\left(\frac{\beta i}{N}+\xi\right)(N-v-i) = \frac{\beta}{N}(N-v-i) + \left(\frac{\beta(i-1)}{N}+\xi\right)(N-v-i),$$
$$h\left(\frac{\beta i}{N}+\xi\right)v = h\frac{\beta}{N}v + h\left(\frac{\beta(i-1)}{N}+\xi\right)v.$$

Then, for $(v,i)\in\widehat{S}$, we define new rates $\alpha^*_{v,i}$, $\widetilde{\alpha}_{v,i}$, β^*_v and $\widetilde{\beta}_{v,i}$ as follows.

$$\alpha^*_{v,i} = \frac{\beta}{N}(N-v-i), \tag{2}$$

$$\widetilde{\alpha}_{v,i} = \left(\frac{\beta(i-1)}{N}+\xi\right)(N-v-i), \tag{3}$$

$$\beta^*_v = h\frac{\beta}{N}v, \tag{4}$$

$$\widetilde{\beta}_{v,i} = h\left(\frac{\beta(i-1)}{N}+\xi\right)v. \tag{5}$$

A first-step argument, conditioning on the possible transitions out of a fixed state $(v,i)\in\widehat{S}$, shows that generating functions $\varphi_{v,i}(z)$ satisfy the following set of linear equations:

$$\begin{aligned}\varphi_{v,i}(z) =& \frac{\gamma}{q_{v,i}} + (1-\delta_{v,0})\left(\frac{\beta^*_v}{q_{v,i}} z\varphi_{v-1,i+1}(z) + \frac{\widetilde{\beta}_{v,i}}{q_{v,i}}\varphi_{v-1,i+1}(z)\right)\\ &+ (1-\delta_{i,1})\frac{\gamma(i-1)}{q_{v,i}}\varphi_{v,i-1}(z)\\ &+ (1-\delta_{i,N-v})\left(\frac{\alpha^*_{v,i}}{q_{v,i}} z\varphi_{v,i+1}(z) + \frac{\widetilde{\alpha}_{v,i}}{q_{v,i}}\varphi_{v,i+1}(z)\right),\end{aligned} \tag{6}$$

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

Equation (6) is the basis to get the mass function of the conditional random variable $R_{e0}|(V(0)=v, I(0)=i)$ by numerical inversion, which can be done with the help of a Fast Fourier Transform (*FFT*) algorithm (Tijms 2003). As mass

functions will be obtained through a direct recursive scheme, we do not go further on this point and we proceed to get factorial moments $m^k_{v,i}$, for $k \geq 1$.

By differentiating Eq. (6) with respect to z repeatedly k times ($k \geq 1$) and evaluating at $z = 1$, we obtain the equations involving factorial moments conditioned to states $(v, i) \in \widehat{S}$.

$$\begin{aligned} m^k_{v,i} = {} & (1-\delta_{v,0})\left(\frac{\beta^*_v}{q_{v,i}} m^k_{v-1,i+1} + \frac{\widetilde{\beta}_{v,i}}{q_{v,i}} m^k_{v-1,i+1}\right) + (1-\delta_{i,1})\frac{\gamma(i-1)}{q_{v,i}} m^k_{v,i-1} \\ & + (1-\delta_{i,N-v})\left(\frac{\alpha^*_{v,i}}{q_{v,i}} m^k_{v,i+1} + \frac{\widetilde{\alpha}_{v,i}}{q_{v,i}} m^k_{v,i+1}\right) \\ & + (1-\delta_{v,0})k\frac{\beta^*_v}{q_{v,i}} m^{k-1}_{v-1,i+1} + (1-\delta_{i,N-v})k\frac{\alpha^*_{v,i}}{q_{v,i}} m^{k-1}_{v,i+1}. \end{aligned} \tag{7}$$

Using relationships appearing in (2)–(5), we can write a useful and simplified version of (7),

$$\begin{aligned} q_{v,i} m^k_{v,i} = {} & (1-\delta_{v,0})h\left(\frac{\beta i}{N} + \xi\right) v m^k_{v-1,i+1} + (1-\delta_{i,1})\gamma(i-1) m^k_{v,i-1} \\ & + (1-\delta_{i,N-v})\left(\frac{\beta i}{N} + \xi\right)(N-v-i) m^k_{v,i+1} \\ & + (1-\delta_{v,0})k\beta^*_v m^{k-1}_{v-1,i+1} + (1-\delta_{i,N-v})k\alpha^*_{v,i} m^{k-1}_{v,i+1}. \end{aligned} \tag{8}$$

We notice that Eq. (8) provides conditional moments of order k based on conditional moments of one order less.

Moreover, at any level $0 \leq v \leq v_0$, the system of equations described in (8), for $1 \leq i \leq N - v$ and $k \geq 0$, can be written in matrix form as follows

$$\mathbf{m^0_v} = \mathbf{e_v}, \tag{9}$$

$$\mathbf{A_v m^k_v} = -\left(\left(1-\delta_{v,0}\right)(\mathbf{D_v \widehat{m}^k_{v-1}} + \mathbf{D}_{\beta\mathbf{v}}\mathbf{\widehat{m}^{k-1}_{v-1}}) + k\mathbf{D}_{\alpha\mathbf{v}}\mathbf{\widetilde{m}^{k-1}_v}\right), \tag{10}$$

where the auxiliary matrices and vectors involved in (9)–(10) are defined below.

For $0 \leq v \leq v_0$, $\mathbf{e_v}$ is an all-ones vector of dimension $(N - v)$ and $\mathbf{A_v}$ will denote the square $(N - v)$ matrix with non null entries

$$A_v(i,j) = \begin{cases} (i-1)\gamma & \text{if } j = i-1,\ 2 \leq i \leq N-v, \\ -q_{v,i} & \text{if } j = i,\ 1 \leq i \leq N-v, \\ \left(\frac{\beta i}{N} + \xi\right)(N-v-i) & \text{if } j = i+1,\ 1 \leq i \leq N-v-1. \end{cases}$$

In addition, $\mathbf{D_v}$, $\mathbf{D}_{\beta\mathbf{v}}$ and $\mathbf{D}_{\alpha\mathbf{v}}$ represent $(N - v)$ diagonal matrices, defined as follows:

$$\mathbf{D_v} = Diag\left(h\left(\frac{\beta i}{N} + \xi\right) v : 1 \le i \le N - v\right),$$
$$\mathbf{D}_{\beta\mathbf{v}} = Diag\left(\beta_v^* : 1 \le i \le N - v\right),$$
$$\mathbf{D}_{\alpha\mathbf{v}} = Diag\left(\alpha_{v,i}^* : 1 \le i \le N - v\right).$$

Finally, for $k \ge 0$ and $0 \le v \le v_0$, $\mathbf{m_v^k}$ and $\widetilde{\mathbf{m}}_\mathbf{v}^\mathbf{k}$ are $(N - v)$-dimensional vectors defined as

$$\mathbf{m_v^k} = \left(m_{v,1}^k, ..., m_{v,N-v}^k\right)^T,$$
$$\widetilde{\mathbf{m}}_\mathbf{v}^\mathbf{k} = \left(m_{v,2}^k, ..., m_{v,N-v}^k, 0\right)^T,$$

and $\widehat{\mathbf{m}}_\mathbf{v}^\mathbf{k}$ is an $(N - v - 1)$-dimensional vector given by $\widehat{\mathbf{m}}_\mathbf{v}^\mathbf{k} = \left(m_{v,2}^k, ..., m_{v,N-v}^k\right)^T$, where notation T denotes transposition.

Given an integer k, factorial moments are recursively determined with the help of the algorithmic scheme shown in Algorithm 1.

Algorithm 1 R_{e0} factorial moments

For any $k > 0$, factorial moments $\mathbf{m_v^k} = \left(m_{v,1}^k, ..., m_{v,N-v}^k\right)^T$, with $0 \le v \le v_0$, are computed as follows:

Step 1. Set $j = 0$.

Step 1a. For $0 \le v \le v_0$, set $\mathbf{m_v^0} = \mathbf{e_v}$.

Step 2. Set $j = 1$.

Step 2a. Set $v = 0$, and

$$\mathbf{w_0^j} = -j\mathbf{D}_{\alpha\mathbf{0}}\widetilde{\mathbf{m}}_\mathbf{0}^{\mathbf{j-1}}.$$

Step 2b. Compute $\mathbf{m_0^j} = \mathbf{A_0^{-1}}\mathbf{w_0^j}$. Set $v = 1$. If $v_0 = 0$, go to Step 3.

Step 2c. Set

$$\mathbf{w_v^j} = -\left(\mathbf{D_v}\widehat{\mathbf{m}}_{\mathbf{v-1}}^\mathbf{j} + \mathbf{D}_{\beta\mathbf{v}}\widehat{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{j-1}} + k\mathbf{D}_{\alpha\mathbf{v}}\widetilde{\mathbf{m}}_\mathbf{v}^{\mathbf{j-1}}\right).$$

Step 2d. Compute $\mathbf{m_v^j} = \mathbf{A_v^{-1}}\mathbf{w_v^j}$. Set $v = v + 1$. If $v \le v_0$, go to Step 2c.

Step 3. Set $j = j + 1$. If $j \le k$, go to Step 2a.

Remark 1 Notice that the random variable R_{e0} measures the exact number of secondary infective individuals arising directly from the index case and, in contradistinction with R_0 or R_c that are defined at the time of the invasion, R_{e0} can be checked at all times. If we set $t = 0$ for the time at which the invasion starts the initial situation is $V(0) = v_0$ and $I(0) = 1$, and $\overline{R}_{e0} = E\left[R_{e0}\middle|V(0) = v_0, I(0) = 1\right]$ provides the exact amount of expected disease transmission, considering vaccine characteristics such as coverage and effectiveness.

Let us proceed to the analytic derivation of the probabilities $x_{v,i}^k$ that the index case will originate $k \ge 0$ new infections, given that the current situation is $(v, i) \in \widehat{S}$.

A new appeal to the first-step methodology, by observing transitions out of the state (v, i), provides the following set of recursive equations:

$$\begin{aligned} q_{v,i}x_{v,i}^{k} &= \delta_{k,0}\gamma + (1-\delta_{k,0})\Big((1-\delta_{v,0})\beta_{v}^{*}x_{v-1,i+1}^{k-1} + (1-\delta_{i,N-v})\alpha_{v,i}^{*}x_{v,i+1}^{k-1}\Big) \\ &+ (1-\delta_{v,0})\widetilde{\beta}_{v,i}x_{v-1,i+1}^{k} \\ &+ (i-1)\gamma x_{v,i-1}^{k} + (1-\delta_{i,N-v})\widetilde{\alpha}_{v,i}x_{v,i+1}^{k}. \end{aligned} \tag{11}$$

For $k \geq 0$ and $0 \leq v \leq v_0$, Eq. (11) for states in $L(v)$ can be written in matrix form in the following way:

$$\begin{aligned} \mathbf{B_v}\mathbf{x_v^0} &= -\gamma\mathbf{e_v} - (1-\delta_{v,0})\mathbf{C_v}\widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{0}}, \\ \mathbf{B_v}\mathbf{x_v^k} &= -(1-\delta_{v,0})\big(\mathbf{C_v}\widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{k}} + \mathbf{D}_{\beta\mathbf{v}}\widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{k-1}}\big) - \mathbf{D}_{\alpha\mathbf{v}}\widetilde{\mathbf{x}}_{\mathbf{v}}^{\mathbf{k-1}}, k > 0, \end{aligned} \tag{12}$$

where notations $\mathbf{e_v}$, $\mathbf{D}_{\beta\mathbf{v}}$ and $\mathbf{D}_{\alpha\mathbf{v}}$ represent the same algebraic structures as defined in the lines following Eqs. (9, 10).

The remaining algebraic structures appearing in matrix expressions (12) are described next: $\mathbf{B_v}$ and $\mathbf{C_v}$ are $(N-v)$ square matrices with entries

$$B_v(i,j) = \begin{cases} (i-1)\gamma & \text{if } j = i-1, 2 \leq i \leq N-v, \\ -q_{v,i} & \text{if } j = i, 1 \leq i \leq N-v, \\ \widetilde{\alpha}_{v,i} & \text{if } j = i+1, 1 \leq i \leq N-v-1, \\ 0 & \text{otherwise,} \end{cases}$$

$$\mathbf{C_v} = Diag\Big(\widetilde{\beta}_{v,i} \,:\, 1 \leq i \leq N-v\Big),$$

and the vectors $\mathbf{x_v^k}$, $\widehat{\mathbf{x}}_{\mathbf{v}}^{\mathbf{k}}$ and $\widetilde{\mathbf{x}}_{\mathbf{v}}^{\mathbf{k}}$, containing probabilities $x_{v,i}^{k}$, are

$$\begin{aligned} \mathbf{x_v^k} &= \Big(x_{v,1}^{k}, ..., x_{v,N-v}^{k}\Big)^{T}, \\ \widehat{\mathbf{x}}_{\mathbf{v}}^{\mathbf{k}} &= \Big(x_{v,2}^{k}, ..., x_{v,N-v}^{k}\Big)^{T}, \\ \widetilde{\mathbf{x}}_{\mathbf{v}}^{\mathbf{k}} &= \Big(x_{v,2}^{k}, ..., x_{v,N-v}^{k}, 0\Big)^{T}. \end{aligned}$$

Notice that $P(\{R_{e0} < \infty | V(0) = v, I(0) = i\}) = 1$ for $(v, i) \in \widehat{S}$, because $\widehat{S}$ is a finite union of disjoints sets, and in a finite population the number of infective individuals arising from contagions caused by the index case is necessarily finite. Consequently, $\sum_{k=0}^{\infty} x_{v,i}^{k} = 1$, for $(v, i) \in \widehat{S}$.

For every number of contagions $k \geq 0$ the equations in (12) are solved recursively with the help of Algorithm 2. In order to determine mass distribution functions, a stopping criteria should be provided to avoid longer computation runs. In fact, numerical results appearing in Sect. 4 come from applying both recursive Algorithms 1 and 2. More specifically, those results dealing with R_{e0}-distributions for a

given initial coverage value, v_0, are obtained from iterating Algorithm 2 until 95% of the values of the distribution of $(R_{e0}\big|V(0) = v_0, I(0) = 1)$ is accumulated.

Algorithm 2 R_{e0} probabilities

For a fixed integer $k \geq 0$, the set of conditional probabilities $x_{v,i}^k$, for $(v,i) \in \widehat{S}$, can be computed according to the following scheme:

Step 1. Set $v = 0$.

Step 1a. Set $j = 0$ and compute $\mathbf{x_0^0} = -\gamma \mathbf{B_0^{-1}} \mathbf{e_0}$.

Step 1b. Set $j = j + 1$. While $j \leq k$, compute $\mathbf{x_0^j} = -\mathbf{B_0^{-1}} \mathbf{D}_{\alpha \mathbf{0}} \widetilde{\mathbf{x}}_{\mathbf{0}}^{\mathbf{j-1}}$.

Step 2. Set $v = 1$. If $v_0 = 0$, stop.

Step 2a. Set $j = 0$ and compute $\mathbf{x_v^0} = -\mathbf{B_v^{-1}} \left(\gamma \mathbf{e_v} + \mathbf{C_v} \widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{0}}\right)$.

Step 2b. Set $j = j + 1$. While $j \leq k$, compute

$$\mathbf{x_v^j} = -\mathbf{B_v^{-1}} \left(\mathbf{C_v} \widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{j}} + \mathbf{D}_{\beta \mathbf{v}} \widehat{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{j-1}} + \mathbf{D}_{\alpha \mathbf{v}} \widetilde{\mathbf{x}}_{\mathbf{v}}^{\mathbf{j-1}}\right).$$

Step 3. Set $v = v + 1$. If $v \leq v_0$, go to step 2a.

3.2 The Population Transmission Variable

Another measure of the expansion of a contagious disease is R_p, which provides the global spread of the disease by counting all the infections that take place within the population, no matter who is the infectious spreader, before the first recovery occurs. R_p is a random variable that can be analyzed either at the beginning of the outbreak or at any later time, by updating the population situation in terms of the current state of the CTMC X.

The aim of this section is to describe the probabilistic behavior of R_p and to study the influence of the model parameters on global infection transmission. In particular, we are interested in comparing R_c, the control reproduction number of this model, with the expected value $\overline{R}_p = E[R_p\big|(V(0) = v_0, I(0) = 1)]$ for different scenarios.

First, we derive theoretical results involving the probability distribution and factorial moments of R_p. As in the preceding section, the central tool for our results will be the first-step methodology. But to avoid repetitive arguments we provide results in a comprehensive manner, leaving out unnecessary details.

Let $\psi_{v,i}(z)$ be the generating function of R_p, given that the current state of X is $(v,i) \in \widehat{S}$, with factorial moments $M_{v,i}^k$ for $k \geq 1$ ($M_{v,i}^0 = 1$). At any point z, with $|z| \leq 1$, generating functions are the solution of the following tridiagonal set of linear equations:

$$\begin{aligned}\psi_{v,i}(z) = &\frac{\gamma i}{q_{v,i}} + (1 - \delta_{v,0}) \frac{h\left(\frac{\beta i}{N} + \xi\right) v}{q_{v,i}} z \psi_{v-1,i+1}(z) \\ &+ (1 - \delta_{i,N-v}) \frac{\left(\frac{\beta i}{N} + \xi\right)(N - v - i)}{q_{v,i}} z \psi_{v,i+1}(z),\end{aligned} \tag{13}$$

for $0 \leq v \leq v_0, 1 \leq i \leq N - v$.

The $k-$th factorial moments of states $(v,i) \in \widehat{S}$ are the solution of a system of linear equations, arising from (13) as usual by taking derivatives with respect to z followed by an evaluation for $z = 1$, that is expressed in matrix form as follows:

$$\mathbf{H_v M_v^k} = -(1-\delta_{v,0})\mathbf{D_v}\left(k\widehat{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k-1}} + \widehat{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k}}\right) - k\widetilde{\mathbf{D}}_{\mathbf{v}}\widetilde{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k-1}}, \tag{14}$$

for $k \geq 1$ and $0 \leq v \leq v_0$. Here $\mathbf{H_v}$ and $\widetilde{\mathbf{D}}_{\mathbf{v}}$ are $(N-v)$ square matrices defined by:

$$H_v(i,j) = \begin{cases} -q_{v,i} & \text{if } j = i, 1 \leq i \leq N-v, \\ \left(\frac{\beta i}{N} + \xi\right)(N-v-i) & \text{if } j = i+1, 1 \leq i \leq N-v-1, \\ 0 & \text{otherwise.} \end{cases}$$

$$\widetilde{\mathbf{D}}_{\mathbf{v}} = Diag\left(\left(\frac{\beta i}{N} + \xi\right)(N-v-i) \,:\, 1 \leq i \leq N-v\right).$$

Vectors $\mathbf{M_v^k}$, $\widehat{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k}}$ and $\widetilde{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k}}$ related to factorial moments are defined as follows

$$\mathbf{M_v^k} = \left(M_{v,1}^k, ..., M_{v,N-v}^k\right)^T,$$
$$\widehat{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k}} = \left(M_{v,2}^k, ..., M_{v,N-v}^k\right)^T,$$
$$\widetilde{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k}} = \left(M_{v,2}^k, ..., M_{v,N-v}^k, 0\right)^T.$$

The distribution of the random variable R_p, conditioned to any state $(v,i) \in \widehat{S}$, can be obtained by inverting transforms with the help of the recursive equations (13) and an FFT algorithm. But, as it was stated in the preceding section, it is possible to find a set of equations whose solution provides directly the point mass function of R_p: $z_{v,i}^k = P(\{R_p = k | V(0) = v, I(0) = i\})$, when $(v,i) \in \widehat{S}$, for $0 \leq k \leq N-1$. Notice that when we observe i infected individuals in the population, then the number of secondary cases taking place before the first recovery is at most $N-i$. So, for any integer k, with $0 \leq k \leq N-1$, $z_{v,i}^k = 0$, whenever $i > N-k$.

Next, we introduce appropriate vectors to derive probabilities $z_{v,i}^k$ when $(v,i) \in \widehat{S}$, that is:

$$\mathbf{z_v^k} = \left(z_{v,1}^k, ..., z_{v,N-v}^k\right)^T,$$
$$\widehat{\mathbf{z}}_{\mathbf{v}}^{\mathbf{k}} = \left(z_{v,2}^k, ..., z_{v,N-v}^k\right)^T,$$
$$\widetilde{\mathbf{z}}_{\mathbf{v}}^{\mathbf{k}} = \left(z_{v,2}^k, ..., z_{v,N-v}^k, 0\right)^T.$$

Finally, for each level v, with $0 \leq v \leq v_0$, R_p point probabilities come from the following recursive equations:

$$\mathbf{D_Q z_v^0} = \mathbf{d}_\gamma, \tag{15}$$

$$\mathbf{D_Q z_v^k} = (1 - \delta_{v,0})\mathbf{D_v \widehat{z}_{v-1}^{k-1}} + \widetilde{\mathbf{D}}_\mathbf{v} \widetilde{\mathbf{z}}_\mathbf{v}^{\mathbf{k-1}}, \text{ for } 1 \leq k \leq N-1, \tag{16}$$

where $\mathbf{D_Q}$ and $\mathbf{d}_\gamma$ are a diagonal matrix and a vector, with respective entries $q_{v,i}$ and γi, for $1 \leq i \leq N - v$.

As in Sect. 3.1, R_p factorial moments and probabilities can be computed from recursive schemes based on Eqs. (14–16), respectively. Their algorithmic descriptions are similar to Algorithms 1–2 and are not stated in the text, but they are the basis for obtaining R_p's numerical results appearing in Sect. 4.

Remark 2 In the paper by Artalejo and Lopez-Herrero (2014), the authors presented closed form expressions for probabilities dealing with the population transmission random variable in stochastic SIS and SIR models. For our SIV model, the mathematics is more involved due to the external transmission parameter and, unfortunately, it is not possible to derive general closed expressions for conditional probabilities $z_{v,i}^k$. However, after some algebra we obtained the closed values of point probabilities in a few specific situations.

$$z_{0,N}^k = P(\{R_p = k | V(0) = 0, I(0) = N\}) = \delta_{k,0}, \text{ for } 0 \leq k \leq N-1.$$

For $0 \leq v \leq v_0$ and $1 \leq i \leq N - v$ we get:

$$\begin{aligned} z_{v,i}^0 &= P(\{R_p = 0 | V(0) = v, I(0) = i\}) = \frac{\gamma i}{q_{v,i}}, \\ z_{v,i}^1 &= P(\{R_p = 1 | V(0) = v, I(0) = i\}) \\ &= (1 - \delta_{i,N}) \frac{\left(\frac{\beta}{N} i + \xi\right)\gamma(i+1)}{q_{v,i}} \left(\frac{hv}{q_{v-1,i+1}} + \frac{(N - v - i)}{q_{v,i+1}}\right). \end{aligned}$$

4 Numerical Illustrations

This section illustrates theoretical and algorithmic results derived in previous sections.

We fix the recovery rate as $\gamma = 1.0$ in all the experiments, so the time unit is taken as to be the expected time that an infected individual takes to recover to become susceptible again.

In the first scenario, we consider a population of $N = 100$ individuals, 20% of which is partially protected against the infection by a vaccine with effectiveness of 97%. We are interested in the random variable R_{e0}, that is the number of secondary infections produced by the index case. Hence, the initial number of infective individuals is $I(0) = i_0 = 1$.

Figures 5 and 6 represent histograms for the distribution of R_{e0} when we vary external or internal contact rates, respectively. Heights indicate the value of the probabilities $x_{20,1}^k = P(\{R_{e0} = k | V(0) = 20, I(0) = 1\})$ and colors appearing in both figures are depicted for a better distinction among considered situations. In more

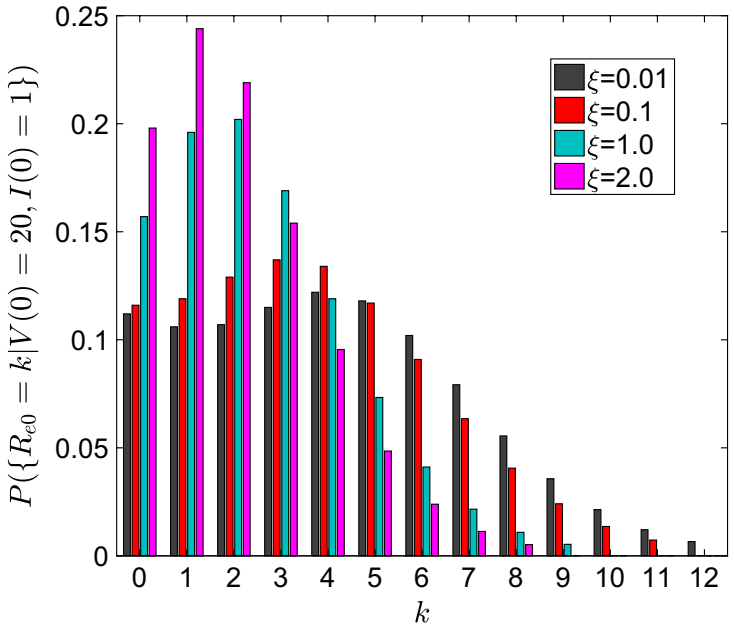


Fig. 5 R_{e0} distribution for several values of ξ, when $N = 100$, $\beta = 10.0$ and $h = 0.03$

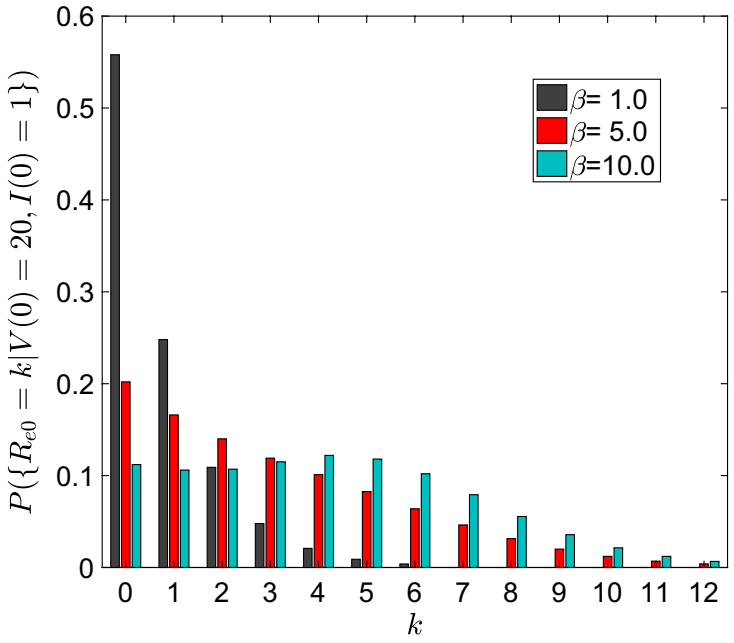


Fig. 6 R_{e0} distribution for several values of β, when $N = 100$, $\xi = 0.01$ and $h = 0.03$

detail, Fig. 5 shows mass functions of R_{e0} when the external transmission rate ξ is 0.01, 0.1, 1.0 and 2.0, for a fixed internal transmission rate $\beta = 10.0$. For each rate ξ, mean values of R_{e0} are 4.2035, 3.7601, 2.5342 and 2.0592, respectively. Moreover, distributions present a strictly positive mode that occurs with a probability that decreases for increasing values of the external rate. This remark is according to the intuition because for a fixed internal contact transmission rate β, when the external

transmission rate increases the index case has less opportunities to spread the disease compared with outsider infection sources.

Figure 6 displays mass functions corresponding to $\beta = 1.0, 5.0$ and 10.0, for an external transmission rate $\xi = 0.01$. We get decreasing shape functions for $\beta = 1.0$ or $\beta = 5.0$ and the chance that the index case produces no secondary infections is 55% and 20%, respectively. However, for $\beta = 10.0$, the R_{e0} distribution is bimodal, with an 11.2% chance that the index case recovers before spreading the infection. In general terms, long internal transmission rates contribute a higher number of secondary cases.

Next we focus on the effect of the vaccine coverage on the expansion of the infection. Figure 7 shows the probability that the index case produces two or more secondary cases of infection, as a function of the external rate β. This quantity can give an idea of what is, for a given infective process, the chance of invading a susceptible-vaccinated population. Each curve corresponds to a different initial vaccine coverage. The remaining parameters of the model are $N = 100$, $\xi = 0.01$, and the vaccine is efficient in 97% of the vaccinated individuals. Probability increases with β, no matter how large the initial coverage v_0 is. For a fixed external transmission rate, the chance of having at least two infections increases when initial coverage decreases. In particular for a small population of 100 individuals affected by a hard measles outbreak, with $R_0 = \beta/\gamma = 18.0$, numerical results evince that a massive vaccination policy with two doses of MMR vaccine (measles, mumps, rubella) guarantees that the probability of having two or more measles infections from the index case is 0.12, while in an unprotected population ($v_0 = 0$) this probability grows up to 0.9.

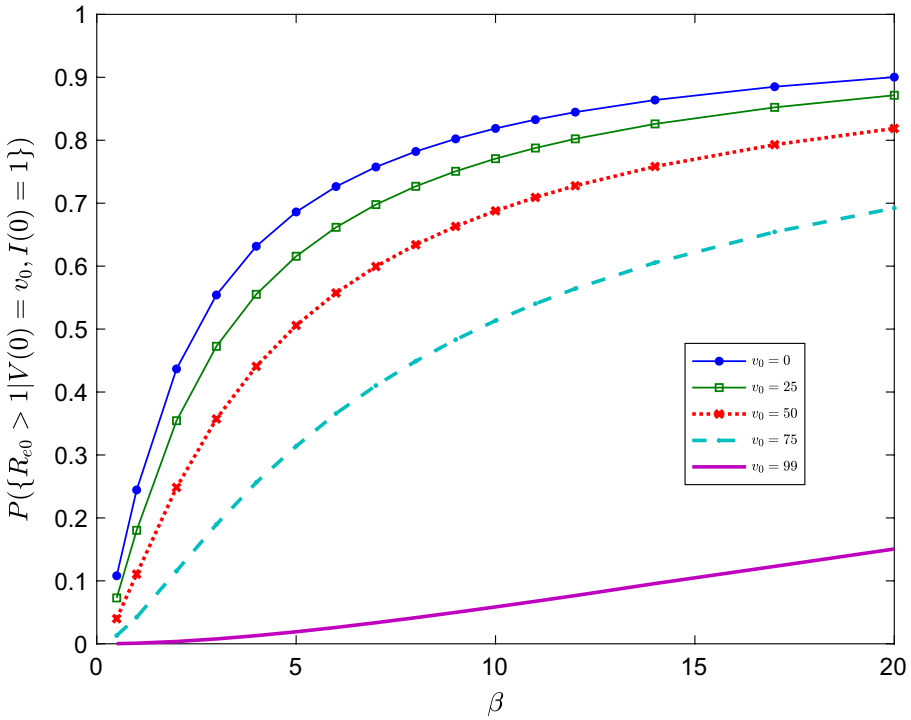


Fig. 7 $P(\{R_{e0} > 1 \big| V(0) = v_0, I(0) = 1\})$ as a function of the internal transmission rate when $N = 100$, $\xi = 0.01$ and $h = 0.03$

Now we deal with the expected number of secondary cases produced by the index case since their introduction in a population where individuals are either susceptible or vaccinated. We observe the influence of the model parameters β, ξ, h and v_0 on the expected value of R_{e0}. Results correspond to a population of $N = 100$ individuals.

Figures 8, 9 and 10 are contour graphs for $\overline{R}_{e0} = E[R_{e0}|V(0) = v_0, I(0) = 1]$, arising when we combine the influence of two parameters of the model. Different colors represent different values for $\overline{R}_{e0}$, as it is indicated by the color code given in each of the Figures.

Figure 8 shows the influence on $\overline{R}_{e0}$ of the internal and external transmission rates, when 20% of the population has received a vaccine which is effective among 97% of the vaccinated individuals. The average of secondary infections, produced by the index case, increases with the internal transmission rate and it decreases when ξ increases, which is in agreement with the comment for Fig. 5. These behaviors are more noticeable for large transmission intensities.

Figure 9 displays $\overline{R}_{e0}$ as a function of the internal transmission rate, β, and the potential risk of vaccine failure, h. We assume in addition that 20% of the population is vaccinated and that the rate of external transmission is $\xi = 0.01$. The expected number of infections caused directly by the index case increases with β. In the early spread of the epidemic, the influence of the vaccine failure risk is relatively small for outbreaks showing internal rates β smaller than 6 compared to those with higher values for β.

Finally, the contour graph shown in Fig. 10 presents the relationship of the internal transmission and vaccine coverage on $\overline{R}_{e0}$. The additional parameters

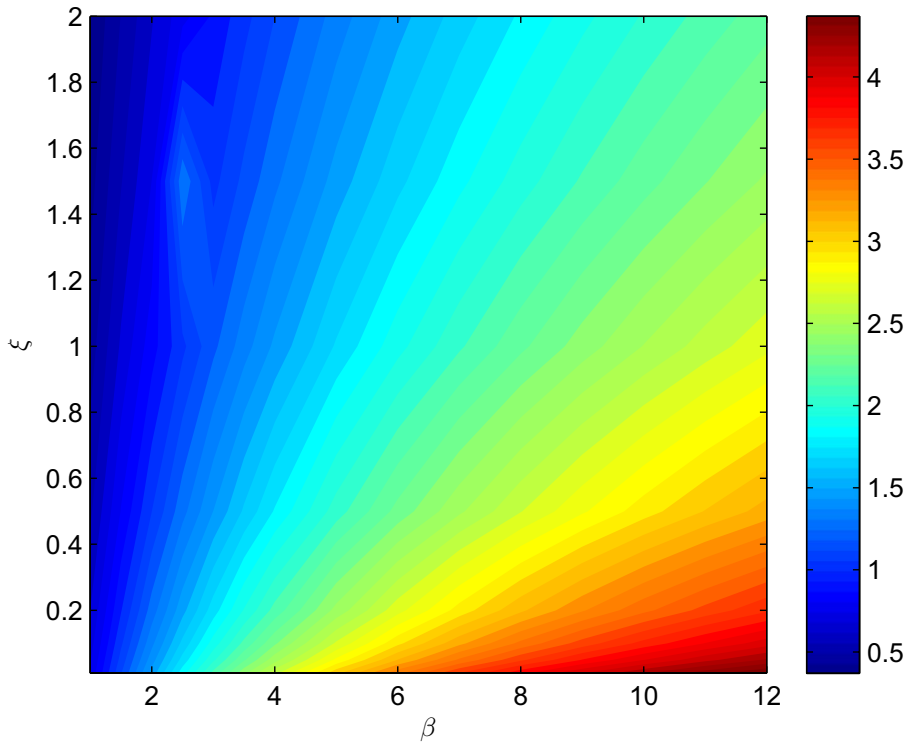


Fig. 8 $\overline{R}_{e0}$ as a function of β and ξ when $N = 100$, $h = 0.03$ and $v_0 = 20$

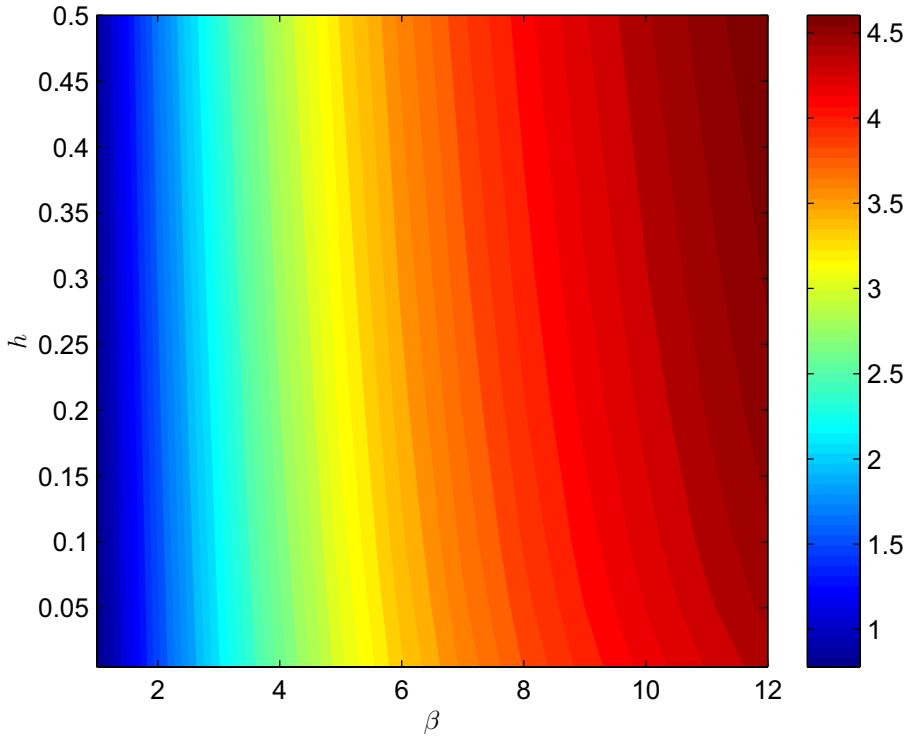


Fig. 9 $\overline{R}_{e0}$ as a function of β and h when $N = 100$, $\xi = 0.01$ and $v_0 = 20$

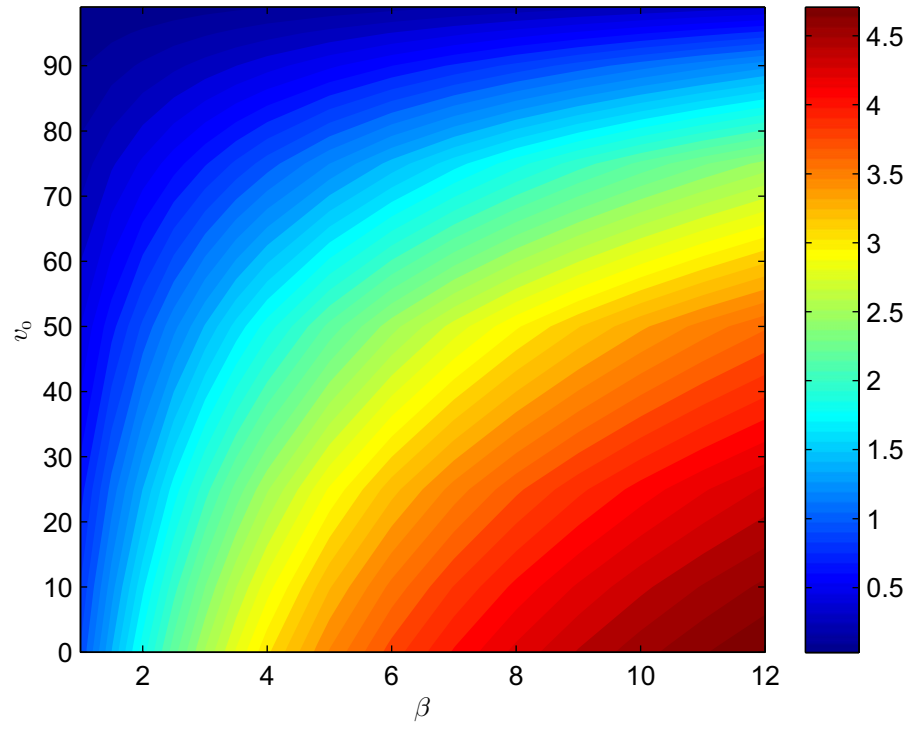


Fig. 10 $\overline{R}_{e0}$ as a function of β and v_0 when $N = 100$, $\xi = 0.01$ and $h = 0.03$

are $N = 100$, $\xi = 0.01$ and 97% for vaccine effectiveness. An increase of vaccine coverage produces a decrease on the initial spread of the infection. For instance, administration of two doses of MMR vaccine is 97% effective against rubella (basic reproduction number $R_0 \approx 6$). So, assuming that $R_0 = \beta/\gamma$, results in Fig. 10 show that the index case transmits an infection like rubella to an average of 3.5 people in an unprotected population, and to less than one person when a massive vaccination policy was launched in the population. To achieve that the infection will not propagate in the population, that is $R_{e0} < 1$, higher immunization coverage is needed as β increases.

The boxplot appearing in Fig. 11 corresponds to the distribution of the number of secondary infections produced by the index case. The box encloses the middle central part of the distribution, lower and upper edges of the box correspond to the lower and upper quartile, respectively, and the line drawn across the box indicates the median of the distribution; finally, whiskers above and below the box cover 95% of the distribution. The objective is to compare the patterns of the epidemic when we increase the vaccination coverage, in a population of $N = 100$ individuals, assuming that a 97%-effective vaccine is available to control an epidemic process with internal and external transmission rates $\beta = 10.0$ and $\xi = 0.1$, respectively. This choice for model parameters corresponds to an infection by varicella-zoster virus (VZV) and the administration of varicella vaccine that is 97% effective in the first year after vaccination. A low vaccine coverage leads to a large number of secondary infections. In general terms, the number of secondary cases produced by the index case decreases when v_0 increases. Notice that changes on the number of secondary infections are not significant while the

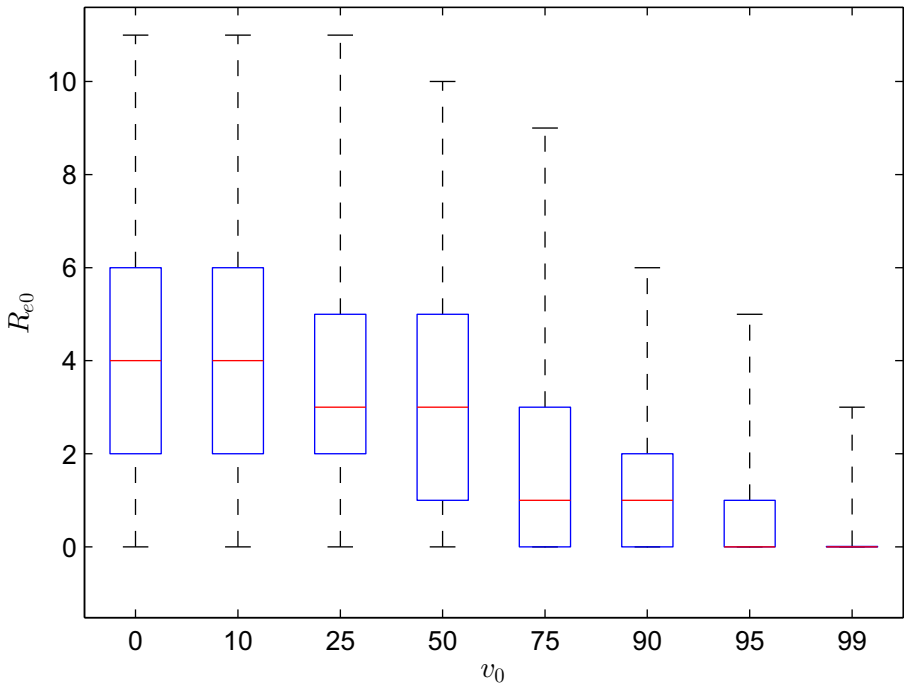


Fig. 11 Boxplot for R_{e0} under several vaccine coverage values when $N = 100$, $\beta = 10.0$, $\xi = 0.1$ and $h = 0.03$

vaccination coverage is under 25. This fact shows the importance of the random variable R_{e0} to fix an appropriate vaccination level.

Next we present some results relative to the global spread of the disease. In Fig. 12, we compare R_c, $\overline{R}_{e0}$ and $\overline{R}_p$ when the internal transmission rate β varies over the interval (0, 20.0). As in previous scenarios, the recovery rate is $\gamma = 1.0$. Vaccine coverage reaches half of the population and presents an effectiveness of 97%. We compare results for populations of $N = 100$ and 1000 individuals, with external transmission rate $\xi = 1/N$. For our parameter selection $R_0 = \beta$ and $R_c = R_0(1 - (1 - h)/2) = 0.515\beta$. Hence, as a function of β, the control reproduction number corresponds to the top line in Fig. 12. We notice that differences between R_c and R_{e0} increase with increasing transmission rates. When $\beta = 20.0$, we find $R_c = 10.30$ and $\overline{R}_{e0} = 4.36$ for $N = 100$, and $\overline{R}_{e0} = 5.67$ for $N = 1000$. These magnitudes show the overestimation of the number of secondary cases of infection produced by the index case, as provided by R_c, and how the expected exact reproduction number $\overline{R}_{e0}$ corrects the effect of the linearization hypothesis commonly assumed in the deterministic literature. Regarding the expected population transmission, $\overline{R}_p$, we conclude that it converges to the control reproduction number as the population size increases. In fact, for $N = 1000$ differences between R_c and $\overline{R}_p$ are smaller than 0.4 when $\beta \in (0, 20.0)$. Hence, the line for $\overline{R}_p$ is graphically indistinguishable from R_c and it is not plotted for $N = 1000$.

Finally, Table 3 shows the minimal vaccination coverage needed to interrupt epidemic transmission; that is, in order to get values smaller than one for the expected number of secondary cases coming from the index case. Notice that if the expected transmission (either from the whole set of infectious or limited to the index case) is less than 1, each infected individual transmits the disease to less than one person, which means that not every case will result in a new individual infection and epidemic transmission will cease. We display results for a population of $N = 1000$

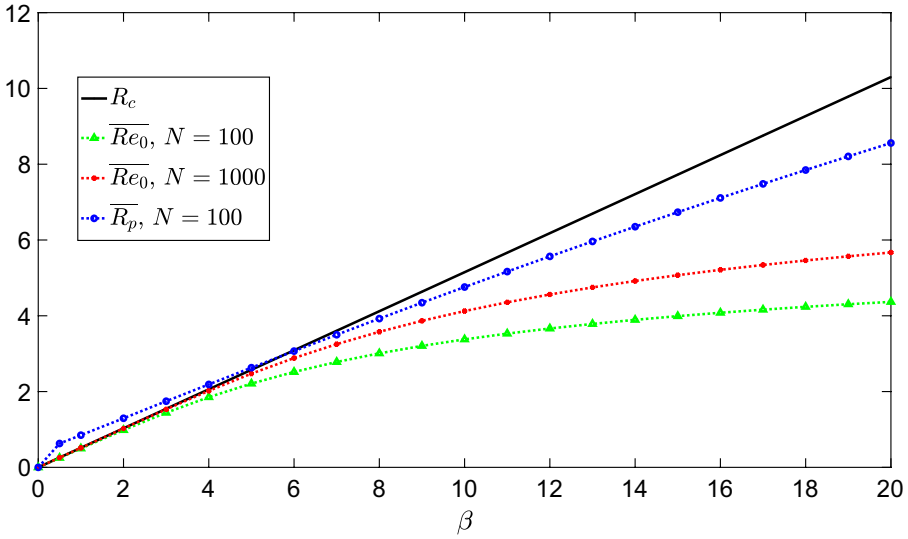


Fig. 12 Comparing R_c, $\overline{R}_{e0}$ and $\overline{R}_p$ versus the internal transmission rate when $\xi = 1/N$, $h = 0.03$ and $v_0 = N/2$

Table 3 Minimum level of vaccination with parameters $N = 1000$ and $\xi = 1/N$

	$h = 0.03$			$h = 0.1$		
β	v_c	v_{e0}	v_p	v_c	v_{e0}	v_p
1	0	0	413	0	0	445
1.5	344	341	556	370	368	695
2	515	513	645	556	554	808
3	687	686	750	741	739	873
4	773	772	809	833	832	915
5	825	823	848	889	888	944
6	859	858	875	926	925	966
7	884	882	896	952	952	982
8	902	902	911	972	972	996
9	916	915	923	988	988	–
10	928	927	933	–	–	–
11	937	936	942	–	–	–
12	945	944	949	–	–	–

individuals, where the external transmission rate is taken as $\xi = 1/N$ and the internal rate β is assumed to be at least 1. We compare two scenarios by considering that the effectiveness of a vaccine is either 97% or 90%. Values represented by v_c give the herd-immunity threshold based on the control reproduction number R_c (i.e., starting from $R_0 = \beta/\gamma$, coverage is chosen as $v_c/N > (R_0 - 1)/(R_0(1 - h))$ in order that $R_c < 1$). Additionally, v_{e0} and v_p are minimal critical levels that guarantee that expected values $\overline{R}_{e0}$ and $\overline{R}_p$, respectively, are less than one. Numerical values come from an iterative application of Algorithm 1 for R_{e0} and its variant for R_p, by raising initial coverage until expected values fulfill the required condition. Any dash symbol in Table 3 means that even a 100% vaccine coverage does not guarantee that the expected number of secondary cases (measured in terms of R_c, $\overline{R}_{e0}$ or $\overline{R}_p$) are less than one. Note that, as $\overline{R}_p$ includes also secondary cases arising from external infectious individuals, the minimal critical level v_p presents higher values, at a fixed transmission rate β, when it is compared with v_c or v_{e0}. On the other hand, when the internal transmission rate β increases, higher immunization coverage is needed to keep the expansion of the epidemic under control.

5 Conclusions

This paper studies infectious disease dynamics in a stochastic framework, where a Markov chain is used to model disease transmission. The continuous time Markov chain models changes in the state of the process defined as the number of individuals that are susceptible, infected or vaccinated. Assuming that susceptible and vaccinated individuals (due to vaccine failures) can get the infection through both internal and external contacts makes the model more realistic than those with only internal contacts.

Deterministic models are very useful in understanding the dynamics of infectious diseases and estimating important epidemiological descriptors as, for instance, the basic reproduction number. In this context, populations are relatively large, and the effect of depletion of susceptibles is minor but leads to reproductive numbers that overestimate the transmission potential of the disease. Our research involves a pair of random variables, R_{e0} and R_p, as alternative measures of the control reproduction number R_c. The stochastic Markovian framework allows us to identify the effective event leading to a new contagion. Consequently, we exclude repeated contacts established between the index case and already infected individuals, thus correcting for the effect of the linearization assumption commonly assumed in the deterministic framework and which produces the overestimation of the reproductive potential of a disease.

Concerning speed, our numerical algorithms provide results depending strongly on the population size and the other parameters of the model. For instance, the derivation of $\overline{R}_{e0}$ through Algorithm 1 involves factorial moments $m^1_{v,i}$ of $(N - v_0/2)(v_0 + 1)$ transient states, which for the particular choice of $N = 1000$ and $v_0 = N/2$ implies 375, 750 such states and requires 118 sec CPU time, in a personal computer of 2.31GHz and 6GB RAM.

Numerical results regarding vaccination coverage levels should be seen as a first approach to investigate optimal policies for controlling the spread of an infectious disease. The aim for future research is to develop health policies based on time horizons and warning levels related to the remaining vaccinated individuals.

This research can be generalized to different models for imperfect vaccine response by considering vaccines that reduce the probability of infection or that confer protection that wanes over time (see, for instance, Ball et al. 2008; Ball and Sirl 2018). Additionally, more sophisticated models could be treated by introducing population structures such as households, and also by including assumptions concerning to epidemics showing latent infectious periods or lifetime immunity after recovery.

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Chapter 3

The Effect of Setting a Warning Vaccination Level on a Stochastic SIVS Model with Imperfect Vaccine

In this paper we extend the work initiated in [121].

The main feature of this investigation is to provide optimal policies to control an epidemic process. In this sense, we introduce a threshold for the number of vaccinated individuals. We focus on two epidemic characteristics: the time until the number of vaccinated individuals descends to the above mentioned threshold and the incidence of infections observed until this epoch.

This research was published in [123] and at the end of the Chapter, we include a printed version of the article adding the academic journal scientific information.

3.1 Background

Considering the epidemic model described in [121] and due to the imperfect vaccine assumption, eventually, the number of vaccinated individuals can be drop down. Thus, the group of vaccinated individuals is gradually disappearing and the herd immunity could be lost. In addition, the external source of infection also contributes to descend the number of immunized individuals even when there is no infective individuals in the population.

To manage this issue, we introduce a threshold for the number of vaccinated individuals and we call it, the warning vaccination level, w. When the critical vaccination level is reached, an alarm is triggered in order to take appropriate action like planning a re-vaccination.

We introduce two concepts related to w: the sleeping period and the wake-up time. Both are necessary to alert health authorities about the possibility of a lost population immunity and to quantify the time to reach the warning vaccination level.

The sleeping period is the interval time starting at the onset of the epidemic and ending when the threshold, w, is reached. The instant when the number of immunized individuals reaches the warning level is called the wake-up time, T_w.

To quantify the incidence of infectious cases during the sleeping period, we define the random variable N_w, that describes the total number of infections involving non-vaccinated individuals in $[0, T_w]$.

3.2 Objectives

In this research work we attain the objectives $(c.1)$, $(c.3)$, $(c.4)$, (d) and (e) described in Section 1.1.1. In more detail:
We describe the random variable, T_w, to measure the speed of transmission in order to carry out purpose $(c.4)$.
We quantify the disease incidence during the interval $(0, T_w]$ by analysing the random variable N_w, that is aim $(c.3)$.
Objectives $(c.1)$, (d) and (e) are reached by carrying out general and local sensitivity analysis. In more detail, these objectives are reached by studying the relative importance of the model parameters for several numerical examples for transmission of HPV virus and using derivatives and elasticities for both random variables.

3.3 Methodology

To study the random variables, T_w and N_w, we exploit the block-structure of the infinitesimal generator of the CTMC and a set of linear equations systems are obtained applying first-step arguments, conditioning on the possible transitions out a fixed state, involving T_w-Laplace transforms, N_w-Generating and N_w-Probability mass functions.
Moments of both measures are derived by applying to these equations properties (1.4) and (1.2) in Section 1.1.2. We solve the linear systems of equations obtained by applying matrix methods.

To assess the influence of the model parameters on the variation and robustness of the random variables, T_w and N_w, we apply the sensitivity analy-

sis described in Section 1.1.2, using derivatives of their conditional moments and elasticities.

3.4 Conclusions

We derive T_w and N_w-Moments and N_w-Probability mass functions by applying recursive algorithms where a stopping criterion is used to avoid long iterative runs. Execution times of these algorithms depend on population size and model parameters and we only present numerical results for moderate size populations.

Regarding the probabilistic behaviour of the random variable, T_w, we notice that as a function of the internal transmission rate, β, expected values have a decreasing behavior. This is reasonable due to increasing values of β produce increases contacts, contagions and, consequently, the time to reach the warning level is shorter. For the external contact rate, ξ, we also obtain this behaviour. When we fix the internal contact rate, β, we obtain that average values of T_w, increase with the recovery rate, γ. In contrast, we obtain shorter expected values of the sleeping period, if individuals are protected by vaccines with high failure probabilities, h. The average time to reach the warning level increases with the initial coverage, v_0. Longer warning levels, w, produce shorter sleeping periods. We point that, any increase in the time to reach the warning level, w, will produce an increase in the number of cases of infection observed during the sleeping period.

For the random variable N_w we obtain that for increasing values of β, the N_w-probability mass functions are displaced to the right. This is a logic

behaviour due to there are more contacts between individuals and in consequence, eventually, more infections can be produced to susceptible individuals. As we expected, we obtain more infections during the sleeping period considering lower warning levels, w.

We carry out a local sensitivity study and, analyzing elasticities, we observe that changes on β and γ produce more noticeable changes on $E[T_w]$ and $\sigma[T_w]$ than the remaining parameters. Regarding measures for N_w the more influential parameters are the internal contact rate and vaccine failure probability.

This research work is a first approach to investigate the possibility of an immediate re-vaccination that is the goal of the next Chapter.

3.5 Publication

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The Effect of Setting a Warning Vaccination Level on a Stochastic SIVS Model with Imperfect Vaccine †

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Abstract: This paper deals with a stochastic Susceptible-Infective-Vaccinated-Susceptible (*SIVS*) model with infection reintroduction. Health policies depend on vaccine coverage, v_0, that guarantees herd immunity levels in the population. Vaccine failures occur when an organism develops a disease despite of being vaccinated against it. After vaccination, a proportion of healthy individuals unsuccessfully tries to increase antibody levels and, consequently these individuals are not immune to the vaccine preventable disease. When an infectious process is in progress, the initial vaccine coverage drops down and herd immunity will be lost. Our objective was to introduce a warning vaccination level and define random measures quantifying the time until the number of vaccinated descends to a warning vaccination level (i.e., the so-called sleeping period), and the epidemic size. A sensitivity analysis was performed to assess the influence of the model parameters on the variation and robustness of the sleeping period and the number of infections observed within it.

Keywords: stochastic Markovian model; warning vaccination level; sensitivity analysis

MSC: 92D30; 60J22; 60J28

1. Introduction

Infectious diseases have a huge impact on human society across the globe and throughout history. At the moment, people all over the world are concerned about the novel corona-virus disease (COVID-19) and its dramatic clinical and nonclinical consequences. This is an example of new emerging diseases (avian influenza, Ebola, SARS, etc.) but old-time significant diseases are still present today (diphtheria, measles, polio, tuberculosis, etc.). The main purpose for public health is to increase knowledge about the spread of a disease within a community, with the goal to establish control measures and surveillance strategies to minimize or to stop viral transmission.

Mathematical models have been used to investigate the dynamics of infectious disease since the first mathematical model of Bernouilli, proposed in 1760 for smallpox inoculation [1]. In general terms, there are mainly two mathematical approaches to represent the evolution of an epidemic process: the deterministic approach whose models rely on differential equations and the stochastic approach based on models that employ stochastic processes (Markov chains, branching and diffusion processes, etc.). Historically, deterministic models have received more attention. Although the 1926 stochastic model by

A.G. Mckendric [2] preceded his well-known deterministic model in the joint work with W.O. Kermack [3], the early model passed practically unnoticed. Both types of models play an important role in epidemiology showing main differences in their asymptotic behavior. According to several authors [4–6], stochastic modeling of epidemics is important in small populations or to model phenomenon where the epidemic outcome depends strongly on the variability in demography, disease transmission or environment.

A possible way to formulate a stochastic model is to directly use its deterministic counterpart [7]. It requires defining random variables depending on individual dynamics. In Markov chain models, the transition probabilities depend on the time between events and the process providing the state of the population at any time satisfy the Markov property. Stochastic differential equations (*SDE*) models are the natural extension of deterministic models, either by adding a noise term to ordinary differential equations or by randomizing in some sense relevant parameters.

Vaccination is a really effective way to prevent infectious diseases. Vaccines train the body's immune system in a way that it can recognize and fight pathogens to which it has not been exposed before. Typically, vaccines are given to healthy people to keep them healthy. Hence, they are medications with the highest standards of safety. However a vaccine failure can occur and a proportion of vaccinated individuals do not develop immunity against its infectious pathogen [8]. The main reasons for this failure are failure of the vaccine delivery system and failure of the immune response due to inadequacies of the vaccine or host factors. People that are immune to an infectious disease can impede the transmission of a disease to vulnerable people, this is called herd protection. An interesting question is to determine the number of people in a population that should be immunized against a disease in order to practically remove disease transmission in the population. This threshold, which is called the immunity threshold, varies among diseases, depending on the reproductive potential of the pathogen. For instance, the measles virus needs a high and sustained level of vaccine coverage to interrupt disease transmission. Recent outbreaks of vaccine preventable diseases have arisen in communities with low vaccine coverage because they do not have herd protection [9].

There is a large number of publications dealing with compartmental models involving vaccination as a strategy for disease control [10–14]. Susceptible-Infected-Susceptible (*SIS*) type models are appropriate for diseases showing repeated infections, where recovery does not confer immunity. Hence, a protective vaccine alleviates, when available, many of these infections and the associated health and economic issues.

Assuming imperfect vaccination, the SIS model has been studied in a deterministic framework in [15,16], assuming nonlinear incidence in [17,18] and including a latency period as well as psychological effects in both susceptible and vaccinated individuals in [19]. A Susceptible-Infective-Vaccinated-Susceptible (*SIVS*) model under stochastic disturbance approach is discussed in [20,21], in a population of varying size [22], or assuming nonlinear incidence in [23].

In this paper, we deal with a stochastic compartmental model, where the propagation of a contagious disease was modeled in terms of a continuous time Markov chain (*CTMC*) [7,24–27]. We assumed that an infectious disease outbreak is taking place within an homogeneous moderately-sized community in which individuals are identical in terms of social mixing and disease contact or recovery characteristics. For community protection, a certain number of individuals were vaccinated against the contagious disease prior to the arrival of the outbreak.

Under the same model assumptions, in [27], the transmission potential of a contagious disease was analyzed by studying R_{e0} and R_p, two stochastic descriptors equivalent to the basic reproduction number, R_0. Like R_0, the above mentioned stochastic measures provide the minimal vaccination coverage needed to interrupt epidemic transmission. As the administered vaccine was not perfect, since the onset of the epidemic, the group of vaccinated people gradually disappears, leaving the whole population unprotected when the number of vaccinated declines to zero.

The purpose of the present paper was to introduce a threshold for the number of vaccinated individuals, say w, that triggers an alarm when the critical vaccination level drops down. We focused on the sleeping period, defined as the interval of time starting at the epidemic onset and ending when the warning level w is reached. More specifically, we analyzed both the length of the sleeping period and disease incidence during this time interval. To measure the strength of the model across parameter changes and to identify which one of them must be estimated accurately, we conducted a sensitivity analysis on performance measures of the random variables defined to study the length of the interval and disease incidence.

The rest of the paper is organized in the following way: Section 2 contains the description of the stochastic SIVS model with imperfect vaccine and infection reintroduction. Section 3 deals with the warning vaccination level w, the wake up time, T_w, and the disease incidence, N_w, during the sleeping period $[0, T_w]$. Theoretical and algorithmic results regarding the distribution of both random variables are provided in terms of the model parameters. Theoretical results in Section 4 come from the application of matrix calculus techniques to a perturbation analysis for performance measures of the random variables introduced in Section 3. In Section 5, we illustrate both theoretical and algorithmic results and present a local sensitivity analysis applied to human papillomavirus (*HPV*). Results and main insights are summarized in Section 6.

2. Model Description

The stochastic SIVS model, used to represent the evolution of a contagious disease within a population, was described in [27]. It refers to a compartmental model where individuals are classified in three groups: namely, susceptible (S), vaccinated (V), and infected (I). The model describes the movement of individuals from one compartment to another as it is shown in Figure 1.

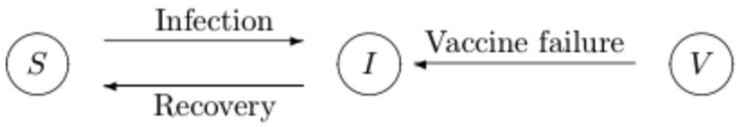

Figure 1. Movements of individuals in a Susceptible-Infective-Vaccinated-Susceptible (*SIVS*) model.

The model tracks the changes in a constant-sized, homogeneous, and uniformly-mixed population suffering from the contagious disease. This population was not isolated. Hence, infection was transmitted due to contacts, whether inside or outside the population, with infected individuals.

To prevent disease spread, health authorities launched a vaccination policy and part of the population received a vaccine that confers immunity. Due to several reasons, the vaccine was not fully effective, a proportion of vaccinated individuals failed to increase antibody levels and was not immune to the vaccine-preventable communicable disease. Therefore, a proportion of contacts between vaccinated and infectious individuals produced new cases of infection. When this occurred, the vaccinated individual loses vaccine protection and becomes an infected individual.

After recovery, any infected individual became susceptible (i.e., unprotected) to the disease, regardless of whether or not he was previously vaccinated. There was no immunity after recovery and consequently any unprotected individual can get the infection several times during an outbreak.

Our mathematical description involved a CTMC that provides the evolution of the disease in terms of the number of individuals present at each compartment at any time t. In this framework, at time $t \geq 0$ we record the number of unprotected susceptible, $S(t)$, vaccinated, $V(t)$, and infected individuals, $I(t)$.

On the other hand, the constant population size hypothesis implies that $S(t) + V(t) + I(t) = N$. Assuming that at $t = 0$ there are v_0 vaccinated individuals, with $0 < v_0 \leq N$, the underlying stochastic model is a bidimensional CTMC

$$X = \{(V(t), I(t)) : t \geq 0\},$$

with state space $\mathbf{S} = \{(v, i) : 0 \leq v \leq v_0, 0 \leq v + i \leq N\}$, that has a cardinality of $(v_0 + 1)(N + 1 - v_0/2)$ states.

As provided in [27], the structure of the infinitesimal generator of X presents a block bidiagonal structure that is helpful for computational purposes.

Regarding the dynamics and evolution of the disease, we summarize model parameters in Table 1 and we describe the effective events that produce a change in the current state of the epidemic process. Therefore, Table 2 enlists events jointly with outer transitions and rates. In more detail, the effective events were the following:

E_1. A susceptible individual gets the infection through a direct contact with an infected individual either within the population or from an external source of infection.

E_2. Since the vaccine was not fully effective, a vaccinated individual becomes infected through a contact with an infectious individual either within the population or from an external source of infection.

E_3. An infectious individual recovers and becomes susceptible.

Table 1. Summary of model parameters.

Size of the population	N
Rate for disease internal transmission	β
Rate for disease external transmission	ξ
Probability of vaccine failure	h
Rate for recovery	γ

Table 2. Outgoing events and their transition rates.

Effective Outgoing Event	Transition	Rate
Susceptible-Infectious contagion	$(v, i) \to (v, i + 1)$	$(\frac{\beta i}{N} + \xi)(N - v - i)$
Vaccinated-Infectious contagion	$(v, i) \to (v - 1, i + 1)$	$h(\frac{\beta i}{N} + \xi)v$
Recovery and loss of immunity	$(v, i) \to (v, i - 1)$	γi

Times spent at each state $(v, i) \in \mathbf{S}$ are independent and exponentially distributed random variables, with rates $q_{v,i}$, depending on the state and on the model parameters, which are as follows

$$q_{v,i} = (\frac{\beta i}{N} + \xi)(N - v - i) + h(\frac{\beta i}{N} + \xi)v + \gamma i. \tag{1}$$

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

$$\begin{aligned} \gamma_i &= (1 - \delta_{i,0})\gamma i, \\ \lambda_{v,i} &= (1 - \delta_{i,N-v})(\frac{\beta i}{N} + \xi)(N - v - i), \\ \eta_{v,i} &= (1 - \delta_{v,0})h(\frac{\beta i}{N} + \xi)v \end{aligned} \tag{2}$$

where the symbol $\delta_{i,j}$ represents the well-known Kronecker delta function, which takes the value 1 if $i = j$ and 0 otherwise.

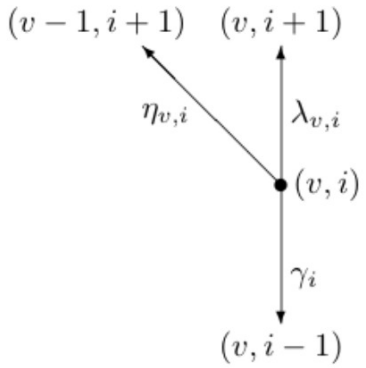

Figure 2. Outer transitions from a generic state.

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 absorbing set of states with no vaccinated individuals $\{(0, i) : 0 \leq i \leq N\}$ and agrees with the stationary distribution of the number of infectious individuals in a SIS model with external source of infection [27,28]. That is, the protection provided by the vaccine fades away almost surely in finite expected time, leaving the whole population unprotected and vulnerable to the disease.

The aim of this paper was to introduce a warning vaccination level, $w < v_0$, that alerts health authorities not only about the danger of a major outbreak but also the need to urge some individuals to get re-vaccinated.

3. The Warning Vaccination Level

In this section, we analyze the random variables T_w and N_w related to the warning vaccination level, w. We assume that, for an initial vaccine coverage v_0, w is an integer such that $0 \leq w \leq v_0$.

At time $t = 0$, v_0 is the number of vaccine protected individuals and the first case of infection is detected. During the outbreak, the number of vaccinated individuals $V(t)$ decreases according to the number of infections that are due to vaccine failure. As soon as the number of vaccine protected individuals drops to w an alert is triggered.

Hence, given a warning level, we first focus on the time at which the alert is activated. We refer to the random variable T_w as the *wake-up time* and we call the random interval $[0, T_w]$ the *sleeping period*. Secondly, we put attention on N_w, the number of cases of infection among unprotected people taking place until the wake-up time, that is, during the sleeping period $[0, T_w]$.

3.1. The Wake-Up Time, T_w

The aim of this section is to analyze the period of time that the infectious process needs to hit the warning level for vaccination.

It is interesting to know how fast the warning level will be reached to take an appropriate action like planning a re-vaccination.

Given a warning level for vaccination w, $0 \leq w \leq v_0$, we are interested in the random variable

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

which indicates how long the number of vaccinated individuals takes to reach the warning level w. Additionally, T_w is called first passage time into the set $\{(w,i) : 0 \leq i \leq N-w\}$. It can be shown that T_w presents a phase-type distribution [29], that involves the exponential of a matrix, which is a sub-matrix of the infinitesimal generator of X. In this paper we proceed by using a different approach based on the first-step methodology.

Let us denote by $\widehat{W} = \{(v,i) \in \mathbf{S} : w \leq v \leq v_0, 0 \leq i \leq N-v\}$. We are going to study the probabilistic behavior of the random variable T_w conditioned to the current situation, that is the set of random variables $\{(T_w \,|V(0) = v, I(0) = i\,)$, for $(v,i) \in \widehat{W}\}$. Therefore, we need to identify Laplace transforms and central moments for these conditioned variables. To ease theoretical derivations, we eliminate the warning level from the notation of transforms and central moments. Hence, for $s \in \mathbb{C}$, with $Re(s) \geq 0$ and $(v,i) \in \widehat{W}$ we define

$$\begin{aligned} \psi_{v,i}(s) &= E[e^{-sT_w} \,|V(0) = v, I(0) = i\,], \\ M^k_{v,i} &= E[T^k_w \,|V(0) = v, I(0) = i\,] = (-1)^k \frac{\partial^k [\psi_{v,i}(s)]}{\partial s^k}|_{s=0}. \end{aligned}$$

When we condition to the initial situation of the outbreak, we can state some basic results.

$$P(T_w = 0 \,|V(0) = w, I(0) = i\,) = 1, \text{for } 0 \leq i \leq N-w. \tag{3}$$

$$P(T_w < \infty \,|V(0) = v, I(0) = i\,) = 1, \text{for } (v,i) \in \widehat{W}. \tag{4}$$

Result (3) is trivially true from the definition of T_w by noticing that the warning level agrees with the initial number of vaccinated individuals. Result (4) comes from the long-term behavior of the CTMC X. On one hand, $\widehat{W}$ is a finite set of transient states. On the other hand, the mean time to absorption, in the set $\{(0,i) : 0 \leq i \leq N\}$, is finite. Hence, any level of vaccination will be reached in a finite time almost surely.

Moreover, we notice that Equation (4) gives that

$$\psi_{v,i}(0) = M^0_{v,i} = 1, \text{for } (v,i) \in \widehat{W}. \tag{5}$$

Additionally, from Equation (3), we get that

$$\psi_{w,i}(s) = 1, \text{ for } 0 \leq i \leq N-w, \tag{6}$$

at any point $s \in \mathbb{C}$, with $Re(s) \geq 0$.

In fact, the result in Equation (6) will be the starting point to determine the remaining set of Laplace transforms for a given number of vaccinated individuals v, with $w < v \leq v_0$.

Let us assume that the initial situation of the outbreak is $V(0) = v$, and $I(0) = i$, with $w+1 \leq v \leq v_0$ and $0 \leq i \leq N-v$. A first step argument conditioning on the exponentially distributed time to the first transition, out of the state (v,i), gives the following relationship

$$\psi_{v,i}(s) = \frac{\gamma_i}{s+q_{v,i}}\psi_{v,i-1}(s) + \frac{\lambda_{v,i}}{s+q_{v,i}}\psi_{v,i+1}(s) + \frac{\eta_{v,i}}{s+q_{v,i}}\psi_{v-1,i+1}(s).$$

That is equivalent to

$$-\gamma_i\psi_{v,i-1}(s) + (s+q_{v,i})\psi_{v,i}(s) - \lambda_{v,i}\psi_{v,i+1}(s) = \eta_{v,i}\psi_{v-1,i+1}(s). \tag{7}$$

Remark 1. *Notice that, at any point s, the right hand side term of Equation (7) just depends on model parameters and on Laplace transforms of one level less of vaccination. Therefore, it is possible to get the numerical value of any Laplace transform $\psi_{v,i}(s)$ in a recursive way starting from the boundary result (6), in the natural order for v. With the help of numerical methods for Laplace transforms inversion (see [30,31]) it is possible to calculate probability distribution functions. Although the numerical inversion is indeed possible, it is many times computationally not feasible. In our model, the recursive solution of Equation (7) could be particularly useful to get computational results.*

Apart from the above observation, Equation (7) is the basis to get the central moments of the wake up time random variable: T_w.

Firstly, we need to introduce some notation. For any number of vaccinated, v, with $w \leq v \leq v_0$ and any integer $k \geq 0$, we denote

$$\begin{aligned} \mathbf{M_v^k} &= (M_{v,0}^k, \cdots, M_{v,N-v}^k)', \\ \widetilde{\mathbf{M}}_{\mathbf{v}}^{\mathbf{k}} &= (M_{v,1}^k, \cdots, M_{v,N-v}^k)' \end{aligned}$$

where notation $'$ stands for transpose vectors.

In what follows $\mathbf{1}_j$ and $\mathbf{0}_j$ will represent $j-$dimensional all-ones and all-zeroes vectors, respectively.

The following theorem provides central moments as the solution of a system of linear equations.

Theorem 1. *Given a fixed warning vaccination level w, with $0 \leq w \leq v_0$, and an integer k, $k \geq 0$, the central moments of order k, are the solution of the following system of linear equations:*

$$\mathbf{M_v^0} = \mathbf{1}_{N-v+1}, \text{ for } w \leq v \leq v_0, \tag{8}$$

$$\mathbf{M_w^k} = \mathbf{0}_{N-w+1}, \text{ for } k \geq 1, \tag{9}$$

$$\mathbf{R_v M_v^k} = k\mathbf{M_v^{k-1}} + \mathbf{D_v}\widetilde{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k}}, \text{ for } k \geq 1 \text{ and } w < v \leq v_0. \tag{10}$$

where $\mathbf{R_v}$ and $\mathbf{D_v}$ are $(N - v + 1)$ square matrices whose non-null entries are

$$\mathbf{R_v}(i,j) = \begin{cases} -\gamma_i, & \text{if } j = i-1 \text{ and } 1 \leq i \leq N-v \\ q_{v,i}, & \text{if } j = i \text{ and } 0 \leq i \leq N-v \\ -\lambda_{v,i}, & \text{if } j = i+1 \text{ and } 0 \leq i \leq N-v-1 \end{cases}$$

and $\mathbf{D_v}(i,j) = \eta_{v,i}$, for $j = i$ and $0 \leq i \leq N - v$.

Proof. First we notice that Equation (8) summarizes the result appearing in Equation (5). By differentiating repeatedly k times Equation (6) with respect to s, and setting $s = 0$, we get the result appearing in Equation (9).

For any initial situation (v, i), such that $w + 1 \leq v \leq v_0$ and $0 \leq i \leq N - v$, to obtain higher order central moments, we take $k \geq 1$ derivatives on Equation (7) with respect to s and, after evaluation in $s = 0$, we get

$$-\gamma_i M_{v,i-1}^k + q_{v,i} M_{v,i}^k - \lambda_{v,i} M_{v,i+1}^k = k M_{v,i}^{k-1} + \eta_{v,i} M_{v-1,i+1}^k. \tag{11}$$

This system of equations can be written in matrix form as appears in Equation (10). □

Theorem 1 provides a recursive scheme for the computation of any central moment $M_{v,i}^{k}$, for $k \geq 0$ and $(v,i) \in \widehat{W}$. It is summarized in the following algorithmic scheme (Algorithm 1).

Algorithm 1 T_w- central moments.

For any integer k, $0 \leq k \leq N-w$, central moments of order k for the random variable T_w are determined from the following scheme:

Step 1: Set $j=0$.

Step 1a: For $w \leq v \leq v_0$, set $\mathbf{M_v^0} = \mathbf{1}_{N-v+1}$.

Step 2: Set $j=1$.

Step 2a: Set $v=w$ and $\mathbf{M_v^j} = \mathbf{0}_{N-v+1}$. If $w=v_0$ go to Step 3.

Step 2b: Set $v=v+1$. While $v \leq v_0$ compute

$$\mathbf{M_v^j} = (\mathbf{R_v})^{-1}(j\mathbf{M_v^{j-1}} + \mathbf{D_v}\widetilde{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{j}}).$$

Step 3: Set $j=j+1$. While $j \leq k$, go to Step 2a.

3.2. Epidemic Transmission during the Sleeping Period $[0,T_w]$: Number of Infectious Cases

In this section, we investigate the epidemic transmission until the number of individuals in the vaccinated compartment drops to the warning level, w. More precisely, we observe the number of cases of infection that take place in the time interval $[0,T_w]$. We recall that a vaccinated individual, once infected and subsequently recovered becomes susceptible to the infection. Hence, the epidemic final size in the time interval $[0,T_w]$ amounts to (v_0-w) infections due to vaccine failure plus the number of infections related to susceptible individuals (i.e., unprotected people).

We introduce a random variable, N_w, that provides the number of infections of unprotected individuals that take place during $[0,T_w]$. As T_w was analyzed conditioned on the population description at $t=0$, we study a conditional version of N_w, that is $(N_w|V(0)=v, I(0)=i)$, for $(v,i) \in \widehat{W}$.

First, we notice that when the warning level is chosen equal to the vaccine coverage at $t=0$ no infections of susceptible can occur, that is

$$P(N_w = 0|V(0)=w, I(0)=i) = 1, \text{ for } 0 \leq i \leq N-w. \tag{12}$$

Equation (12) shows that, for this particular initial condition, N_w is a random variable of finite support; however, in general, this property is not satisfied when the warning level is fixed below the initial vaccination level. Instead of that there is an unbounded set of outcomes for the number of infections of susceptible individuals taking place in the sleeping period $[0,T_w]$. Nevertheless, from the long-term behavior of the CTMC X and the result shown in Equation (4) we get

$$P(N_w < \infty|V(0)=v, I(0)=i) = 1, \text{ for } (v,i) \in \widehat{W}. \tag{13}$$

We recall that any outbreak of the infectious process is detected as soon as the first infection occurs. Consequently, we assume that at time $t=0$ the population is composed of v_0 vaccinated, a single infectious individual and $(N-v_0-1)$ susceptible.

Let us fix a warning vaccination level w, with $0 \leq w \leq v_0$. To study the probabilistic behavior of $(N_w|V(0)=v_0, I(0)=1)$ we introduce a set of auxiliary variables where, in order to ease theoretical derivations, the warning level has been removed from the notation. Hence, for any $(v,i) \in \widehat{W}$, we denote

$$N_{v,i} \equiv (N_w|V(0)=v, I(0)=i).$$

Probabilistic behavior of any random variable $N_{v,i}$, with $(v,i) \in \widehat{W}$, is analyzed from its mass probability and generating functions, and factorial moments. Notation for probabilities, generating functions and factorial moments is as follows:

$$\begin{aligned} x_{v,i}^k &= P(N_{v,i} = k), \text{ for } k \geq 0, \\ \phi_{v,i}(z) &= E[z^{N_{v,i}}] = \sum_{k=0}^{\infty} z^k P[N_{v,i} = k], \text{ for } z \in \mathbb{C}, |z| \leq 1, \\ m_{v,i}^k &= \frac{\partial^k [\phi_{v,i}(z)]}{\partial z^k}|_{z=1}, \text{ for } k \geq 0. \end{aligned} \tag{14}$$

Observe that, due to the result shown in Equation (13), the factorial moments of order zero are

$$m_{v,i}^0 = \phi_{v,i}(1) = 1, \tag{15}$$

and we have that $m_{v,i}^k = E[N_{v,i}(N_{v,i}-1)\cdots(N_{v,i}-k+1)]$, for $k \geq 1$.

As a consequence of the Markovian property and of Equation (12) we obtain some trivial results when the number of vaccinated individuals reaches the warning level.

$$x_{w,i}^k = \delta_{0,k}, \text{ for } 0 \leq i \leq N-w, \tag{16}$$

$$\phi_{w,i}(z) = 1, \text{ for } 0 \leq i \leq N-w \text{ and } |z| \leq 1, \tag{17}$$

$$m_{w,i}^k = \delta_{0,k}, \text{ for } 0 \leq i \leq N-w \text{ and } k \geq 0. \tag{18}$$

Let us begin by exploring generating functions. As we did with the analysis of T_w, we use a first step argument conditioning on the first effective event leading to an outer transition from a state $(v,i) \in \widehat{W}$ to get the relationship

$$\phi_{v,i}(z) = \frac{\gamma_i}{q_{v,i}}\phi_{v,i-1}(z) + \frac{\lambda_{v,i}}{q_{v,i}} z\phi_{v,i+1} + \frac{\eta_{v,i}}{q_{v,i}}\phi_{v-1,i+1}(z).$$

That is equivalent to

$$-\gamma_i\phi_{v,i-1}(z) + q_{v,i}\phi_{v,i}(z) - \lambda_{v,i}z\phi_{v,i+1}(z) = \eta_{v,i}\phi_{v-1,i+1}(z). \tag{19}$$

Equation (19) is the starting point in the derivation of factorial moments of the random variables $N_{v,i}$, for $(v,i) \in \widehat{W}$. We follow the lines stated in the previous section and, for any integer $k \geq 0$, we obtain factorial moments of order k as the solution of a system of linear equations. First, we introduce some notation for vectors involving moments $m_{v,i}^k$ that will appear in the Theorem 2 that summarizes the complete set of results for computing any factorial moment

$$\begin{aligned} \mathbf{m_v^k} &= (m_{v,0}^k, \cdots, m_{v,N-v}^k)', \\ \widehat{\mathbf{m}}_\mathbf{v}^\mathbf{k} &= (m_{v,1}^k, \cdots, m_{v,N-v}^k, 0)', \\ \widetilde{\mathbf{m}}_\mathbf{v}^\mathbf{k} &= (m_{v,1}^k, \cdots, m_{v,N-v}^k)'. \end{aligned}$$

Theorem 2. *Given $k \geq 0$, factorial moments of order k in the set $\{m_{v,i}^k : (v,i) \in \widehat{W}\}$ are recursively computed from the following equations:*

$$\begin{aligned} \mathbf{m_v^0} &= \mathbf{1}_{N-v+1}, \text{ for } w \leq v \leq v_0, && (20)\\ \mathbf{m_w^k} &= \mathbf{0}_{N-w+1}, \text{ for } k \geq 1, && (21)\\ \mathbf{R_v m_v^k} &= k\mathbf{L_v}\widehat{\mathbf{m}}_\mathbf{v}^{\mathbf{k-1}} + \mathbf{D_v}\widetilde{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{k}}, \text{ for } k \geq 1 \text{ and } w < v \leq v_0, && (22) \end{aligned}$$

where matrices $\mathbf{R_v}$ and $\mathbf{D_v}$ are defined in Theorem 1 and $\mathbf{L_v}$ is a diagonal matrix of dimension $N - v + 1$, with non-null elements $\lambda_{v,i}$, for $0 \leq i \leq N - v$.

Proof. We start from the explicit results shown in Equations (15) and (18), which can be expressed in matrix form as appears in Equations (20) and (21) in the statement of this theorem.

Remaining moments will arise by taking $k \geq 1$ derivatives regarding z, followed by an evaluation at $z = 1$, in Equation (19). In that sense, for any initial state (v,i), with $w+1 \leq v \leq v_0$ and $0 \leq i \leq N - v$, we get

$$-\gamma_i m_{v,i-1}^k + q_{v,i} m_{v,i}^k - \lambda_{v,i} m_{v,i+1}^k = k\lambda_{v,i} m_{v,i+1}^{k-1} + \eta_{v,i} m_{v-1,i+1}^k, \quad (23)$$

which can be expressed in matrix form as it is shown in Equation (22).

Notice that the right hand side of Equation (23) depends on moments of one order less and moments related to one vaccinated individual less. Hence, we can solve the system of equations given in (22) in a recursive way starting from the explicit results that appear at Equations (20) and (21). □

Remark 2. *Another algorithm can be written for the recursive computation of factorial moments. The scheme is similar to the one shown in the Algorithm 1 with the natural changes in notation and substituting computation in Step 2b by*

$$\mathbf{m_v^j} = (\mathbf{R_v})^{-1}(j\mathbf{L_v}\widehat{\mathbf{m}}_\mathbf{v}^{\mathbf{j-1}} + \mathbf{D_v}\widetilde{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{j}}).$$

For any initial situation $(v,i) \in \widehat{W}$, the distribution of $N_{v,i}$, the number of infections taking place in the interval $[0, T_w]$, could be computed recursively by inverting generating functions $\phi_{v,i}(z)$ with the help of the Equations (17) and (19), and applying a *fast Fourier transform* (FFT) algorithm [32]. Instead of that, in Theorem 3, we derive a system of equations whose solution provides directly the mass probability function of $N_{v,i}$, introduced in expression (14).

As in the preceding sections, first, we set out some adequate notation. Let define a new set of vectors associated to the probability of having $k \geq 0$ infections of unprotected individuals during the sleeping interval $[0, T_w]$

$$\begin{aligned} \mathbf{x_v^k} &= (x_{v,0}^k, \cdots, x_{v,N-v}^k)', \\ \widehat{\mathbf{x}}_\mathbf{v}^\mathbf{k} &= (x_{v,1}^k, \cdots, x_{v,N-v}^k, 0)', \\ \widetilde{\mathbf{x}}_\mathbf{v}^\mathbf{k} &= (x_{v,1}^k, \cdots, x_{v,N-v}^k)'. \end{aligned}$$

Theorem 3. *For any initial state $(v,i) \in \widehat{W}$, the distribution of the conditional random variables $N_{v,i}$ is given by the probabilities $\{x_{v,i}^k, k \geq 0\}$, which are determined from the following equations:*

$$\begin{aligned} \mathbf{x_w^k} &= \delta_{0,k}\mathbf{1}_{N-w+1}, && (24)\\ \mathbf{R_v^* x_v^k} &= (1-\delta_{0,k})\mathbf{L_v}\widehat{\mathbf{x}}_\mathbf{v}^{\mathbf{k-1}} + \mathbf{D_v}\widetilde{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{k}}, \text{ for } w < v \leq v_0, && (25) \end{aligned}$$

where matrices $\mathbf{L_v}$ *and* $\mathbf{D_v}$ *are defined in Theorem 2 and* $\mathbf{R_v^*}$ *is a square* $(N-v+1)$ *matrix whose non-null entries are*

$$\mathbf{R_v^*}(i,j) = \begin{cases} -\gamma_i, & \text{if } 1 \leq i \leq N-v \text{ and } j = i-1 \\ q_{v,i}, & \text{if } 0 \leq i \leq N-v \text{ and } j = i. \end{cases}$$

Proof. First, we observe that the result in Equation (24) is the matrix version of Equation (16). For a vaccination level v, such that $v \geq w$, we proceed by using the first step methodology. Again, by conditioning on the first possible transition out of the state (v,i), for $0 \leq i \leq N-v$, we are able to derive the following linear equation

$$x_{v,i}^k = \frac{\gamma_i}{q_{v,i}} x_{v,i-1}^k + (1-\delta_{0,k}) \frac{\lambda_{v,i}}{q_{v,i}} x_{v,i+1}^{k-1} + \frac{\eta_{v,i}}{q_{v,i}} x_{v-1,i+1}^k,$$

which is equivalent to

$$-\gamma_i x_{v,i-1} + q_{v,i} x_{v,i}^k = (1-\delta_{0,k}) \lambda_{v,i} x_{v,i+1}^{k-1} + \eta_{v,i} x_{v-1,i+1}^k. \tag{26}$$

For $0 \leq i \leq N-v$, Equation (26) can be expressed in matrix form as appears in Equation (25). □

Recalling the result stated in Equation (13), we get that $\sum_{k=0}^{\infty} x_{v,i}^k = 1$, for $(v,i) \in \widehat{W}$. For every number of cases of infection in the susceptible compartment, $k \geq 0$, the system of equations in (24) and (25) are solved recursively with the help of Algorithm 2. To compute the mass distribution function up to the mass point k, a stopping criterion should be provided to avoid too long iterative runs. In particular, numerical results shown in Section 5 come directly from Algorithm 2 until 99% of the probability mass of $N_{v,i}$ is accumulated.

Algorithm 2 N_w- distribution.

Given an integer $k \geq 0$, the set of conditional probabilities $\{x_{v,i}^k, (v,i) \in \widehat{W}\}$ can be determined through the following iterative scheme:
Step 1: Set $v = w$.
  Step 1a: Set $j = 0$ and $\mathbf{x_w^0} = \mathbf{1}_{N-w+1}$.
  Step 1b: Set $j = j+1$. While $j \leq k$, set $\mathbf{x_w^j} = \mathbf{0}_{N-w+1}$.
Step 2: Set $v = w+1$. If $v_0 = w$, stop.
  Step 2a: Set $j = 0$ and compute $\mathbf{x_v^0} = (\mathbf{R_v^*})^{-1} \mathbf{D_v} \widetilde{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{0}}$.
  Step 2b: Set $j = j+1$. While $j \leq k$, compute

$$\mathbf{x_v^j} = (\mathbf{R_v^*})^{-1} (\mathbf{L_v} \widehat{\mathbf{x}}_{\mathbf{v}}^{\mathbf{j-1}} + \mathbf{D_v} \widetilde{\mathbf{x}}_{\mathbf{v-1}}^{\mathbf{j}}).$$

Step 3: Set $v = v+1$. If $v \leq v_0$, go to Step 2a.

4. Local Sensitivity Analysis

Related to the Markov chain that represents the evolution of the disease, in this section we use matrix calculus to conduct a perturbation or local sensitivity analysis of the steady-state results, presented in the Section 3. There is a large body of literature on the perturbation analysis of Markov chains [33], which involves problems related to measuring the difference between two transition matrices [34,35] and also local sensitivity, which is the problem of quantifying the effect of changes in the parameters defining transition probabilities on the behavior of the Markov chain. This second line of problems involves

differentiation and it can be solved using the approach suggested by Caswell for absorbing chains [36] or the extension for non-absorbing structured Markov processes as in [37,38].

The study of sensitivities is of interest in modeling natural phenomena where the estimates of the model parameters come from a set of data (see [39] and the references therein). A local sensitivity analysis is a really helpful methodology to quantify the impact of a small variation of model parameters on the performance measures of interest and also to determine which parameter is of most influence. This methodology is especially relevant for models with many parameters, where this type of analysis is useful to disentangle the effect of each rate over these measures.

In this section, the perturbation problem is approached via derivatives and elasticities (i.e., proportional sensitivities). In that sense, the discussion that follows depends on the derivatives of conditional moments $M^k_{v,i}$ and $m^k_{v,i}$, for $k \geq 1$ and $(v,i) \in \widehat{W}$, with respect to the model parameters. For simplicity we denote $\boldsymbol{\theta} = (\theta_1, \theta_2, \theta_3, \theta_4)' = (\beta, \xi, \gamma, h)'$.

Since we do not have closed form expressions for the moments of T_w and N_w, we cannot derive analytical expressions for sensitivities. However, we take advantage of the matrix-form results, shown in Theorems 1 and 2, to derive recursive equations involving sensitivity and elasticity of the moments of the wake-up time, T_w, and the epidemic incidence during the sleeping period, N_w.

This analysis reveals how parameter variations, close to the baseline input values, influence model behavior. For instance, the sensitivity index defined as the partial derivative $\partial M^k_{v,i}/\partial\theta_j$ gives the rate of change of the moment $M^k_{v,i}$ in response to a change in the parameter θ_j, while the remaining parameters hold constant. The sensitivity analysis provides a prospective study giving outcomes for changes on $M^k_{v,i}$ if the parameter θ_j were to change.

We deal firstly with the moments of the wake-up random variable T_w. By conditioning to the initial situation $(v,i) \in \widehat{W}$, a relationship for partial derivatives of $M^k_{v,i}$ can be obtained from expression (11), which is as follows:

$$\begin{aligned} -\gamma_i \frac{\partial M^k_{v,i-1}}{\partial\theta_j} + q_{v,i}\frac{\partial M^k_{v,i}}{\partial\theta_j} - \lambda_{v,i}\frac{\partial M^k_{v,i+1}}{\partial\theta_j} &= k\frac{\partial M^{k-1}_{v,i}}{\partial\theta_j} + \eta_{v,i}\frac{\partial M^k_{v-1,i+1}}{\partial\theta_j} \\ &+ \frac{\partial\eta_{v,i}}{\partial\theta_j}M^k_{v-1,i+1} + \frac{\partial\gamma_i}{\partial\theta_j}M^k_{v,i-1} - \frac{\partial q_{v,i}}{\partial\theta_j}M^k_{v,i} + \frac{\partial\lambda_{v,i}}{\partial\theta_j}M^k_{v,i+1}. \end{aligned} \tag{27}$$

From relationship (27), we can derive recursive schemes providing numerical values of $\partial M^k_{v,i}/\partial\theta_j$, for any parameter θ_j with $1 \leq j \leq 4$. In fact, if we denote by $A^k_{v,i}(\theta_j) = \frac{\partial M^k_{v,i}}{\partial\theta_j}$ and, for $k \geq 1$ and $w < v \leq v_0$, define the vectors of derivatives as

$$\begin{aligned} \mathbf{A^k_v}(\theta_j) &= (A^k_{v,0}(\theta_j), \cdots, A^k_{v,N-v}(\theta_j))', \\ \widetilde{\mathbf{A}}^k_{\mathbf{v}}(\theta_j) &= (A^k_{v,1}(\theta_j), \cdots, A^k_{v,N-v}(\theta_j))', \end{aligned}$$

then the Equation (27) can be expressed in matrix form as follows, with the help of the matrices involved in Theorem 1

$$\mathbf{R_v A^k_v}(\theta_j) = k\mathbf{A^{k-1}_v}(\theta_j) + \mathbf{D_v}\widetilde{\mathbf{A}}^k_{\mathbf{v-1}}(\theta_j) + \frac{\partial\mathbf{D_v}}{\partial\theta_j}\widetilde{M}^k_{v-1} - \frac{\partial\mathbf{R_v}}{\partial\theta_j}M^k_v, \tag{28}$$

where $\frac{\partial\mathbf{D_v}}{\partial\theta_j}$ and $\frac{\partial\mathbf{R_v}}{\partial\theta_j}$ are the gradient matrices, respect to a scalar θ_j, of $\mathbf{D_v}$ and $\mathbf{R_v}$, respectively.

However, changes in an outcome conditional moment are caused by changes in the vector of parameters $\boldsymbol{\theta}$. Thus, sensitivity analysis in conditional moments requires more than a single derivative $\frac{\partial M^k_{v,i}}{\partial\theta_j}$.

In fact, we have to solve the corresponding Equation (28) once for each parameter. We need an approach to differentiate matrix valued functions of vector arguments, whose usefulness is more relevant for model with a large number of parameters. Matrix calculus permits us to collect various partial derivatives with respect to a vector into vectors and matrices of derivatives, simplifying solving systems of differential equations. A revision on notation and properties of matrix calculus can be found in the paper by Magnus and Neudecker [40].

Starting from Equation (10) in Theorem 1, by applying some basic rules and properties of calculating differentials, we get that

$$\begin{aligned}\frac{d\mathbf{M_v^k}}{d\boldsymbol{\theta}'} &= -((\mathbf{R_v})^{-1}(k\mathbf{M_v^k}+\mathbf{D_v}\widetilde{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k}})'\otimes(\mathbf{R_v})^{-1})\frac{dvec\mathbf{R_v}}{d\boldsymbol{\theta}'} \\ &+ (\mathbf{R_v})^{-1}(k\frac{d\mathbf{M_v^{k-1}}}{d\boldsymbol{\theta}'}+\mathbf{D_v}\frac{d\widetilde{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k}}}{d\boldsymbol{\theta}'})+((\widetilde{\mathbf{M}}_{\mathbf{v-1}}^{\mathbf{k}})'\otimes(\mathbf{R_v})^{-1})\frac{dvec\mathbf{D_v}}{d\boldsymbol{\theta}'}.\end{aligned} \tag{29}$$

where $\frac{d\mathbf{M_v^k}}{d\boldsymbol{\theta}'}$ is the Jacobian matrix with entries given by $\frac{dM_{v,i}^k}{d\theta_j}$, $\otimes$ represents Kronecker product and $vecA$ transforms matrix $\mathbf{A}$ into a vector by stacking the columns of the matrix one underneath the other.

We observe that conditional random variables $(T_w|V(0)=v, I(0)=i)$, for $(v,i)\in\widehat{W}$, are defined as the first passage times to the set $\{(w,j): 0\leq j\leq N-w\}$ which can be seen as an absorbing set of states and, consequently, the above random variables can be regarded as absorption times. Hence, arguments by Caswell (see [36,41]) for sensitivities and elasticities of continuous time absorbing Markov chains can be applied to get the result in Equation (29).

In addition, the structure of the expression appearing in Algorithm 1 can be exploited to derive an algorithm that provides the computation of partial derivatives of the moments $M_{v,i}^k$, with respect to the vector of parameters $\boldsymbol{\theta}=(\theta_1,\cdots,\theta_4)'$. The starting point are the frontier conditions $\frac{d\mathbf{M_v^0}}{d\boldsymbol{\theta}'}=\mathbf{0}_{(N-v+1)\times 4}$, for $w\leq v\leq v_0$, and $\frac{d\mathbf{M_w^k}}{d\boldsymbol{\theta}'}=\mathbf{0}_{(N-w+1)\times 4}$, for $k\geq 1$.

Derivatives involving factorial moments of the conditional random variables $N_{v,i}=(N_w|V(0)=v,I(0)=i)$, for $(v,i)\in\widehat{W}$, can be obtained following a parallel reasoning. We start by taking derivatives on Equation (23), respect to any parameter θ_j:

$$\begin{aligned}&-\gamma_i\frac{\partial m_{v,i-1}^k}{\partial\theta_j}+q_{v,i}\frac{\partial m_{v,i}^k}{\partial\theta_j}-\lambda_{v,i}\frac{\partial m_{v,i+1}^k}{\partial\theta_j}=k\lambda_{v,i}\frac{\partial m_{v,i+1}^{k-1}}{\partial\theta_j}+\eta_{v,i}\frac{\partial m_{v-1,i+1}^k}{\partial\theta_j} \\ &+k\frac{\partial\lambda_{v,i}}{\partial\theta_j}m_{v,i+1}^{k-1}+\frac{\partial\eta_{v,i}}{\partial\theta_j}m_{v-1,i+1}^k+\frac{\partial\gamma_i}{\partial\theta_j}m_{v,i-1}^k-\frac{\partial q_{v,i}}{\partial\theta_j}m_{v,i}^k+\frac{\partial\lambda_{v,i}}{\partial\theta_j}m_{v,i+1}^k.\end{aligned} \tag{30}$$

From Equation (30), we can derive recursive schemes to get partial derivatives of factorial moments, regarding any single parameter. Moreover, a matrix calculus approach gives the following relationship between parameters and moment outcomes.

$$\begin{aligned}\frac{d\mathbf{m_v^k}}{d\boldsymbol{\theta}'} &= -((\mathbf{R_v})^{-1}(k\mathbf{L_v}\widehat{\mathbf{m}}_{\mathbf{v}}^{\mathbf{k-1}}+\mathbf{D_v}\widetilde{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{k}})'\otimes(\mathbf{R_v})^{-1})\frac{dvec\mathbf{R_v}}{d\boldsymbol{\theta}'} \\ &+ (\mathbf{R_v})^{-1}(k\mathbf{L_v}\frac{d\widehat{\mathbf{m}}_{\mathbf{v}}^{\mathbf{k-1}}}{d\boldsymbol{\theta}'}+\mathbf{D_v}\frac{d\widetilde{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{k}}}{d\boldsymbol{\theta}'}) \\ &+ ((k\widehat{\mathbf{m}}_{\mathbf{v}}^{\mathbf{k-1}})'\otimes(\mathbf{R_v})^{-1})\frac{dvec\mathbf{L_v}}{d\boldsymbol{\theta}'}+((\widetilde{\mathbf{m}}_{\mathbf{v-1}}^{\mathbf{k}})'\otimes(\mathbf{R_v})^{-1})\frac{dvec\mathbf{D_v}}{d\boldsymbol{\theta}'}.\end{aligned} \tag{31}$$

Numerical values of the partial derivatives regarding the vector of parameters $\boldsymbol{\theta}$ will result in an iterative manner, starting from boundary conditions $\frac{d\mathbf{m_y^0}}{d\boldsymbol{\theta}'} = \mathbf{0}_{(N-v+1)\times 4}$, for $w \leq v \leq v_0$, and $\frac{d\mathbf{m_w^k}}{d\boldsymbol{\theta}'} = \mathbf{0}_{(N-w+1)\times 4}$, for $k \geq 1$.

In Section 5 we quantify the effect of the model parameters on moments of T_w and N_w. To interpret sensitivities we need to be aware that model parameters are measured in different units. Failure probability h only takes values between 0 and 1. Contact or recovery rates have not such restrictions. Therefore, the sensitivity of a given moment to changes in an epidemic rate is difficult to compare with the sensitivity of the failure probability. To avoid this difficulty, we introduce elasticity indices that measure relative changes in moments when a parameter changes. Hence, in what follows, the elasticity index of a moment m, depending differentiably on a parameter θ, is defined as $\frac{\partial m}{\partial \theta} \times \frac{\theta}{m}$.

5. Sensitivity Analysis

In this section, we present some numerical work for the sleeping time, T_w, and for the epidemic incidence during this period, N_w. Firstly, we present global sensitivity results when the parameters of the model vary over their entire range of interest. Secondly, a local sensitivity analysis is performed to check if results are robust with small changes in the parameters. For illustrative purposes we focus on results related to human papillomavirus.

We consider a population of $N = 100$ individuals where an outbreak of a contagious disease is in progress. We assume that some individuals of the population, v_0, have received a vaccine to be protected against the disease. The outbreak started at the time at which the first infection occurs. Hence, at time $t = 0$, the initial state of the CTMC X is $(v_0, 1)$. Therefore, in the sequel we ease the notation and represent $(T_w|V(0) = v_0, I(0) = 1) = T_w$ and $(N_w|V(0) = v_0, I(0) = 1) = N_w$.

5.1. Global Sensitivity Analysis

Next, we focus on the effect of each parameter of the model on the sleeping period and on the incidence of infections during the sleeping period.

Let us deal first with the sleeping period. Our interest is to observe the influence of the parameters on the expected value and on the standard deviation of T_w. Numerical results for $E[T_w]$ and $\sigma[T_w]$ have been obtained by means of Algorithm 1.

In the first scenario we assume a 90% of vaccine coverage for a population of $N = 100$ individuals. The warning level is fixed at $w = 70$. Consequently, at the start of the outbreak the population contains 90 vaccinated, a single infected, and 9 susceptible individuals. The alarm will be triggered as soon as the number of vaccinated individuals drops to 70 vaccinated.

Figure 3 represents the expected sleeping time as a function of he internal transmission rate β combined with recovery, external transmission rate, and vaccine failure, respectively. Shaded areas have been obtained by considering $E[T_w] \pm \sigma[T_w]$.

We notice that, as a function of the internal transmission rate, the expected value shows a decreasing behavior. This fact can be explained by noticing that an increase in the internal transmission rate β increases contacts, contagions and, consequently, the time to reach the warning level is shortened.

Let us go deeper into each graph to analyze the behavior of T_w regarding the remaining parameters. Figure 3a presents $E[T_w]$ and $\sigma[T_w]$ as a function of β in a scenario with external contact rate $\xi = 0.01$ and vaccine failure $h = 0.1$. The curves correspond to different recovery rates, namely $\gamma = 1.0, 5.0$ and 10.0. We observe that curves for $E[T_w]$ show a monotonic behavior. For a fixed β the expected time increases with the recovery rate. We notice that the slope of the curves decreases for increasing recovery rates. All of these facts agree with the intuition. Higher recovery rates guaranty the existence of a group of susceptible

individuals that are more vulnerable to the disease than the vaccinated ones. In consequence, long recovery rates contribute to a longer sleeping periods. Curves in Figure 3b represent the expected sleeping time in a scenario with recovery rate $\gamma = 1.0$ and vaccine failure $h = 0.1$. Each curve corresponds to internal contact rates $\xi = 0.25, 0.5$ and 1.5. We can observe that $E[T_w]$ decreases for increasing external transmission rates, in agreement with the observation made above on the behavior of the expected time regarding the internal rate β. Figure 3c corresponds to scenarios with external transmission rate $\xi = 0.01$ and recovery rate $\gamma = 1.0$. Curves correspond to the choice on the probability of a vaccine failure as $h = 0.05, 0.1$ and 0.25. We notice that for a fixed internal transmission rate, as could be expected, a less efficient vaccine makes a decrease in the sleeping period. The influence of the vaccine failure on the sleeping period is more noticeable for diseases with smaller transmission rates.

The following set of numerical results focuses on the influence of vaccine coverage and warning level on the sleeping period. We fix the external contact rate as $\xi = 0.01$, the recovery rate as $\gamma = 1.0$, and we consider a vaccine whose failure probability is $h = 0.1$. Figure 4 displays expected values and standard deviation of T_w for different choices on the internal transmission rate, the initial coverage and the warning level.

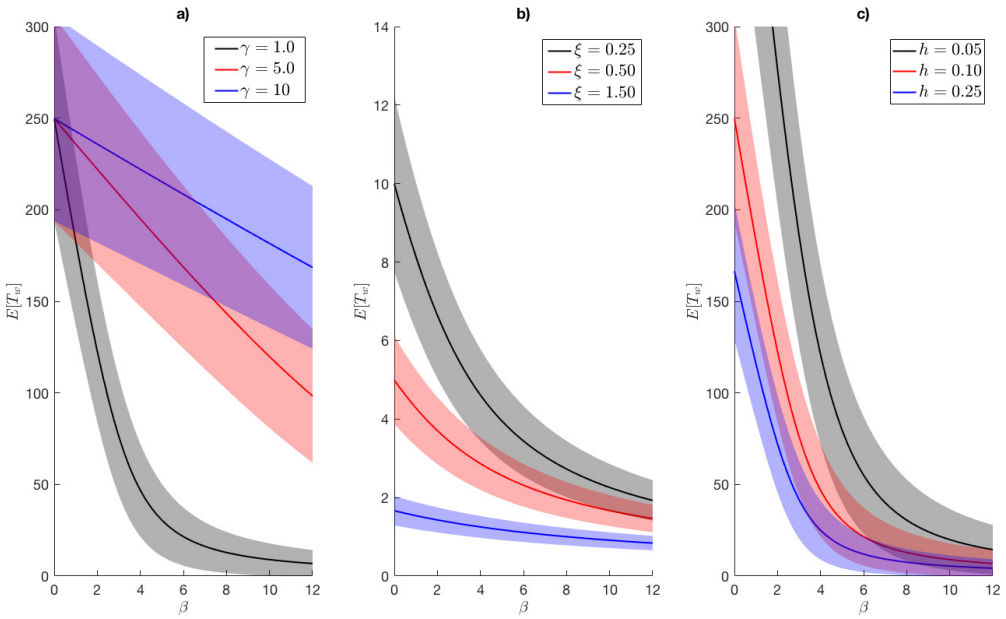

Figure 3. $E[T_w]$ and $\sigma[T_w]$ as a function of β when $N = 100$, $v_0 = 90$, $w = 70$. Curves in (**a**) correspond to $\xi = 0.01$, $h = 0.1$ and $\gamma = 1.0, 5.0, 10.0$. In (**b**), $E[T_w]$ and $\sigma[T_w]$ are represented for $\xi = 0.25, 0.5, 1.5$, $h = 0.1$ and $\gamma = 1.0$. In (**c**), mean and standard deviation are represented for $\xi = 0.01$, $h = 0.05, 0.1, 0.25$ and $\gamma = 1.0$.

Figure 4a presents $E[T_w]$ and $\sigma[T_w]$ as a function of β for three values of the initial coverage, that is, $v_0 = 50, 70$, and 90 individuals. The warning level is fixed as $w = 37$. All curves present a decreasing shape as a function of β. However, for a fixed internal transmission rate we observe that the expected length of the sleeping period increases with the initial coverage. In Figure 4b we assume an initial vaccine coverage of 90 individuals and represent mean and standard deviation of T_w as a function of β, for several warning levels, namely $w = 20, 50$ and 80. As could be expected, under the same internal transmission, higher warning levels give shorter sleeping times. Finally in Figure 4c, the expected and standard deviation are

represented as functions of the warning level, the internal contact rate is $\beta = 1.15$ and we consider an initial number of vaccinated individuals $v_0 = 50, 70$ and 90. Notice that the warning levels are bounded by v_0, that is $0 \leq w \leq v_0$. According to the intuition, expected values and standard deviation decrease for increasing warning levels. When we fix an allowable warning level we observe the same behavior on v_0 described for Figure 4a.

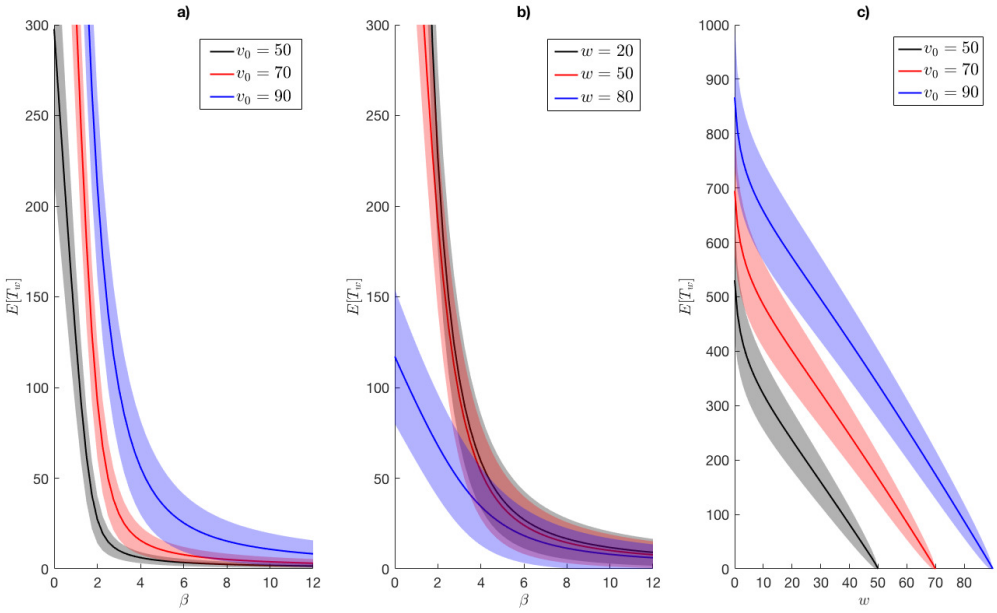

Figure 4. $E[T_w]$ and $\sigma[T_w]$ when $N = 100$, $\xi = 0.01$, $\gamma = 1.0$, and $h = 0.1$. In (**a**), mean and standard deviation are represented as a function of β, for warning level $w = 37$ and vaccine coverage $v_0 = 50, 70, 90$. In (**b**), mean and standard deviation are represented as a function of β, for warning levels $w = 20, 50, 80$ and vaccine coverage $v_0 = 90$. Curves in (**c**) display $E[T_w]$ and $\sigma[T_w]$ as a function of w for $\beta = 1.15$ and vaccine coverage $v_0 = 50, 70, 90$.

Following examples correspond to the disease incidence in the group of susceptible individuals during the sleeping time, N_w. Numerical results dealing with probabilities come by applying Algorithm 2 and results for moments come from a modified version of Algorithm 1. As in the preceding examples, we consider a population of $N = 100$ individuals, with an initial coverage of $v_0 = 90$, the recovery rate is $\gamma = 1.0$, the external transmission rate is $\xi = 0.01$, the vaccine failure is $h = 0.1$ and we fixed the warning level at $w = 70$ vaccinated.

In Figure 5, the distribution of the number of infections of susceptible individuals, taking place during the sleeping time, is plotted for different values of $\beta = 1.15, 5.0$ and 10.0. We can observe that for increasing rates of the internal transmission rate, the distribution of N_w is displaced to the right.

Other experiments, not reported in this paper, show similar patterns when we consider the distribution of N_w for several values either of the probability of vaccine failure or the warning level. In both cases, larger values for h or for w produce a right displacement of the distribution.

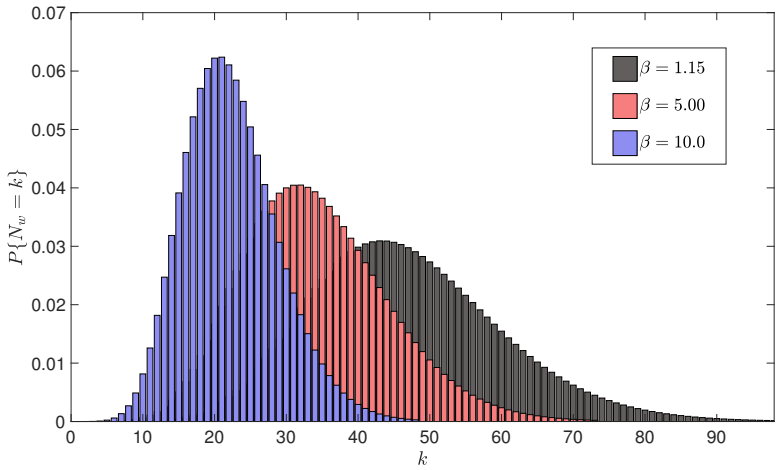

Figure 5. N_w distribution when $N = 100$, $v_0 = 90$, $w = 70$, $\gamma = 1.0$, $\xi = 0.01$, and $h = 0.1$ for several values of β.

To have a better understanding of the distribution of the total number of infections during the sleeping time, we represent in Figure 6 a boxplot graph of the random variable $N_w + (v_0 - w)$. We assume that the initial number of vaccine protected is $v_0 = 90$ and the outbreak starts with a single infected individual, $(v_0, i_0) = (90, 1)$. Our purpose is to compare patterns of the epidemic, when we modify the warning level. The whiskers start at the lowest value of infectious cases, that is $v_0 - w$, and extend to the 99th percentile. We observe that the dispersion of the total incidence, measured in terms of the inter-quartile range, decreases as a function of the warning level and the distribution changes from left-skewed to right-skewed as w increases. As expected, the epidemic process involves more individuals when warning is kept at low levels. Numerical experiments not reported in the paper, when the warning level is $w = 0$, indicate that there is a 0.99 probability that the number of infections until the complete loss of vaccine protection fluctuates in the interval $(90, 6700)$, with median at 3500 cases.

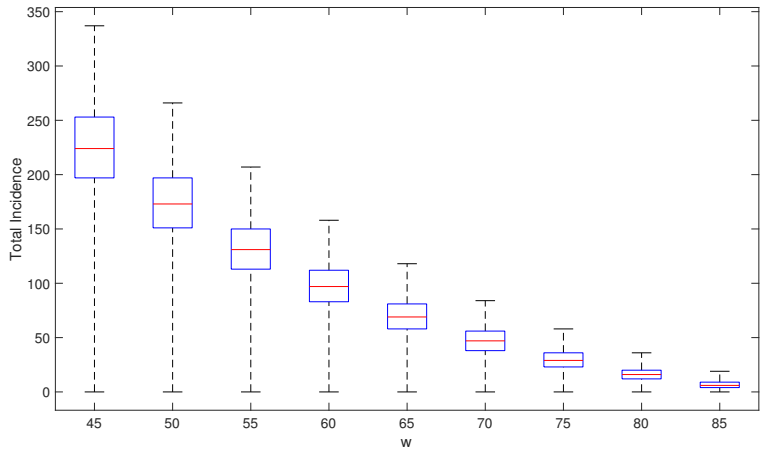

Figure 6. Boxplot for N_w under several warning levels when $N = 100$, $v_0 = 90$, $\beta = 1.15$, $\gamma = 1.0$, $\xi = 0.01$, and $h = 0.1$.

Our knowledge on the N_w distribution can be applied to determine the optimal warning level to guarantee enough resources with a fixed probability. For instance, if we have at hand only 150 treatment units, from Figure 6, we observe that setting the warning level at $w = 55$ vaccinated guaranties that the probability of having at least 150 infections, before the alarm was triggered, is 0.25, while an upper warning level, say $w \geq 65$, guaranties that the probability of having more than 150 infections prior to the alarm activation (i.e., shortage of resources) is less than 0.01.

5.2. Local Sensitivity Analysis Applied to the Spread of Human Papillomavirus Infection

In this section, we present a perturbation analysis on T_w and N_w, to observe the effect of changing contact and recovery rates, and also vaccine efficacy. To this end, we derive elasticities of the mean and standard deviations of the time and incidence of infectious cases until the activation of the alarm. We particularize our results for an infection of human papillomavirus.

The human papillomavirus infection is a viral infection that is transmitted among individuals through a skin-to-skin contact. HPV is the most common sexually transmitted infection [42], in fact, at least 70% of sexually active people gets the HPV once in their lives. Most people get a genital HPV infection through direct sexual contact but, as HPV is a contact disease, it can occur without intercourse.

Although the incidence of the infection is high, most of the infections do not cause symptoms and go away spontaneously. However, the absence of symptoms makes it easy to transfer the virus among individuals. Due to the fact that HPV infects and resides in a latent state in epidermal cells, recurrences are very common. The contagiousness or transmissibility of the HPV virus can be measured by the basic reproductive number R_0, that is usually estimated depending on the underlying mathematical model. The R_0 values have been published for different HPV types and scenarios [42–44] and run from 1.09 to 5.6.

There are four HPV vaccines that protect against HPV types that cause most of HPV cancer. Clinical trials have shown that HPV vaccination induces lifelong protection against new HPV infections. All HPV vaccines have been found to have high efficacy, over 80%, depending on the vaccine used and also on the HPV type [45].

Some of the clinical characteristics of the HPV justify the use of a SIVS mathematical model to represent the evolution and transmission of this disease. HPV is a vaccine preventable disease with very common recurrences. However, we can not ignore that our model is probably far too simplistic to represent the complex dynamic of the HPV transmission. We include it as an application of the methodology.

As in the preceding section, we assume that outbreaks are detected as soon as the first case of infection occurs and that population size remains constant during the epidemic process. The baseline parameter values are summarized in Table 3. The year is the unit of time, the recovery rate γ was fixed as to keep expected recovery times around 300 days, the internal rate β was chosen in order to have a basic reproduction number $R_0 = \beta/\gamma = 2.8$, the external rate is $\xi = 0.01$, and we assume that vaccine efficacy is 90% (i.e.; $h = 0.1$).

Table 3. Baseline parameter values.

Parameter	Value
N	100
v_0	70
β	3.5
ξ	0.01
γ	1.25
h	0.1

Additionally, we assume that vaccine coverage is $v_0 = 70$. We consider three scenarios regarding the warning level, w. Say low, medium, and high warning level condition. More specifically, a low warning level implies that the alert is activated when the number of protected individuals drops to the 10% of the initial coverage; medium and high warning levels are associated to 50% and 90% of the initial coverage, respectively.

Table 4 shows values for mean and standard deviation of T_w and N_w, under low, medium, and high warning conditions. Behavior regarding warning level variations agrees with the one stated in the preceding section.

Table 4. Mean and standard deviation of T_w and N_w for different warning level conditions.

	Low	**Medium**	**High**
$E[T_w]$	43.96852	33.96278	18.33432
$\sigma(T_w)$	16.36562	16.23378	12.76035
$E[N_w]$	777.7604	226.6682	30.08812
$\sigma(N_w)$	130.1556	46.00042	12.74736

Elasticities evaluated at the baseline parameter values appearing in the rest of this section were determined numerically by applying the theoretical results in Section 4. In Table 5 we show elasticities of the sleeping period, T_w, and of the number of cases of infection in unprotected individuals, N_w.

Table 5. T_w and N_w elasticities versus warning condition.

Warning	**Variable**	**Parameter**	**Mean**	**Sd**
Low Condition	T_w	β	−2.611602	+2.778346
		ξ	−0.477366	−0.253497
		h	−1.092157	+1.231468
		γ	+2.088969	−1.470340
	N_w	β	−1.891158	+15.90355
		ξ	−0.029536	+0.539073
		h	−1.006530	−0.939145
		γ	+0.920694	+0.911401
Medium Condition	T_w	β	−2.834902	+1.500176
		ξ	−0.613948	−0.267127
		h	−1.118875	+0.522567
		γ	+2.448851	−0.888822
	N_w	β	−1.676597	+10.02865
		ξ	−0.068708	+0.905739
		h	−1.019953	−0.890020
		γ	+0.745304	+0.705858
High Condition	T_w	β	−2.028866	−0.070704
		ξ	−0.819625	−0.385364
		h	−1.050907	−0.124000
		γ	+1.848492	+0.222181
	N_w	β	−1.031938	+1.412817
		ξ	−0.204952	+0.571329
		h	−0.997156	−0.893880
		γ	+0.236890	+0.301462

In interpreting each elasticity index for $E[T_w]$, in Table 5, we keep all other parameters fixed. We notice that, no matter what the warning conditions are, increasing contact rates (either internal or external) will lead to a decrease in the expected length of the sleeping period. Similarly, reducing vaccine effectivity shortens the sleeping period; however, increasing the recovery rate γ increases $E[T_w]$.

Looking closer to the results for the sleeping period, we appreciate that the more influential parameters are the internal contact rate β and the recovery rate γ. Changes in these parameters have opposite effects. In this sense, either decreasing β or increasing γ by a 1% increases the expected length of the sleeping period by around a 2%, no matter the warning condition.

The stochastic uncertainty of T_w, represented by $\sigma(T_w)$, is more affected by perturbations in β or γ than in h or ξ, whenever we set low or medium warning conditions.

Regardless of the warning condition, sign patterns for $E[N_w]$ agree with the observed for $E[T_w]$. Indicating that any increase in the length of the sleeping period will be accompanied by an increase in the number of cases of infection observed during this interval of time. Elasticities of the expected number of cases of infection show that changes in the internal contact rate β or in the vaccine failure probability h are always among the most significant.

Elasticities for $\sigma(N_w)$ show that standard deviation increases in terms of transmission rates and of recovery rate and decreases for increasing values of the vaccine failure probability. It is noticeable that the volatility of N_w is highly influenced by the internal transmission rate, under low or medium warning conditions. Where an increase of 1% on β produces an increase larger than 10% on the stochastic uncertainty of N_w.

6. Conclusions and Future Work

We analyzed a stochastic SIVS model with imperfect vaccine and infection reintroduction. Disease transmission was modeled by a continuous time Markov chain recording, at any time t, both the number of vaccinated and infectious individuals.

Assuming that v_0 individuals in the population have been vaccinated prior to the onset of the outbreak, we set a level of vaccinated individuals, w, to trigger an alert when the number of vaccinated reaches, w. Our research involves two random variables, T_w and N_w, associated to the warning threshold. T_w, or the wake-up time, gives the epoch, from the onset, at which the alarm is triggered. N_w helps to measure disease incidence until this moment.

For the continuous variable T_w, probability distribution is described in terms of moments, while for N_w we are able to give a complete probabilistic description in terms of its mass distribution function. Algorithmic schemes are provided for getting numerical results. Additionally, the influence of parameter variation on performance measures, related to both variables, was studied using both a global and local sensitivity analysis.

Results are related to outbreaks starting from the initial situation $(v_0, 1)$ but algorithmic procedures provide results for higher initial infected individuals i, with $0 \leq i \leq v_0$.

Given a warning level, w, performance measures for the length and disease incidence of the sleeping period are easily computable. Indeed, they are related to first passage times of the underlying Markov chain describing the evolution of the epidemics. Therefore, our study can be adapted to more involved compartmental models that include natural immunization [46] or a relationship structure among individuals [47]. On the other hand, since vaccine failure tends to leave the population completely unprotected against the disease, our future research will focus on re-vaccination models allowing transitions from the susceptible to the vaccinated compartments. This extension could be used to plan vaccination strategies where the warning level will play a role in the re-vaccination schedule.

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Chapter 4

Measures to Assess a Warning Vaccination Level in a stochastic SIV Model with imperfect vaccine

This Chapter extends the work initiated in [121] and [123].

The main highlight of this research work is to define appropriate measures to evaluate if an immediate re-vaccination could be launched and if it is not possible, to estimate the time until it can be initiated.
We also establish appropriate warning vaccination levels to attain the possibility of launching an immediate re-vaccination.

A printed version of [124], is included in this Chapter, along with scientific information regarding the academic journal where article is published.

4.1 Background

We recall that in [123], we introduced the warning vaccination level, w. Related to this threshold, we defined the sleeping period and the wake-up time, T_w.

As vaccine is administered only to susceptible individuals, it could happen that at the wake-up time, the number of susceptible individuals in the population is not enough to return to the initial level of vaccinated individuals. To inform about the number of individuals eligible to be vaccinated and in consequence, about the possibility of an immediate re-vaccination, we define the random variable, S_w, that records the number of susceptible individuals in the population when the threshold w is reached.
When an immediate re-vaccination campaign is not possible, we measure the time elapsed until it could be launched by analyzing the random variable, R_w. This measure is defined in terms of the wake-up time and provide a tool to manage properly, a re-immunization of the population.

4.2 Objectives

We define the random variables, S_w and R_w to evaluate the possibility of an immediate re-vaccination program and if it is not possible, we measure the time until it could be launched, that is objective $(c.6)$.
In addition, we calculate appropriate warning levels, w, that guarantee to launch a re-vaccination campaign at the instant of time that the threshold for the number of vaccinated individuals is reached, that is objective $(c.7)$.
Aims (d) and (e) are attained taking into the account several possibilities in

the selection of the model parameters representing the evolution of diphtheria outbreaks taking place in a population of moderate size.

4.3 Methodology

We analyze the random variable S_w applying an analogous methodology to the one described for N_w, in [123] and Chapter 3, but considering the discrete auxiliary random variables, $I^w_{v,i}$, defined as the number of infected individuals in the population at the wake-up time, conditioned to a current state. Assuming that prior the beginning of the outbreak the population contains v_0 vaccinated individuals and a single infectious individual, we find a relationship among S_w and the auxiliary variables, which looks as follows:

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

We obtain explicit recursive expressions for generating and probability mass functions and factorial moments for the random variable S_w.

In addition the random variable S_w is used to set the appropriate warning level, w, described in Section 4.2. In more detail, we calculate it as the minimum w that satisfy the following Expression:

$$w \geq v_0 - E[S_w].$$

Regarding the re-vaccination time, R_w, we point out that it is a degenerate random variable with a single mass point corresponding to 0 time units. Hence, we obtain the probability of an immediate re-vaccination in terms of

the random variable S_w, from the following expression

$$P\{R_w = 0\} = P\{S_w \geq v_0 - w\}.$$

If at the wake-up time there are not enough number of susceptible individuals eligible to be vaccinated there is not possibility to schedule an immediate re-vaccination and in that case, the random variable is a continuous one with support in $(0, \infty)$ and it should be analyzed applying a similar methodology to the one described for T_w, in [123].

To illustrate our methodology we represent the evolution of a diphtheria outbreak taking place in a population of moderate size and we analyze the influence of parameter variation on both random variables.

4.4 Conclusions

This investigation is focused on studying the possibility of an immediate re-vaccination, to restore the vaccine coverage to the initial level, analyzing the random variables, S_w and R_w.

We obtain explicit recursive schemes for computing S_w-Probability mass functions and moments for both random variables that are stable even for large populations.

We illustrate theoretical results by considering a boarding school or orphanage institution of 500 individuals where an outbreak of diphtheria is produced. According to the specific characteristics of the infectious disease in [268], we establish the internal contact rate to $\beta = 6.5$ and the recovery rate to $\gamma = 1$. In that situation, for the variable S_w we appreciate that its

distributions are displaced to the right when the warning level increases. Expected values present a decreasing behaviour for increasing values of w, no matter how effective the vaccine is. Such behaviour is also detected for the minimum quantity of susceptible individuals that should be vaccinated, to raise the number of vaccinated individuals to the initial level. When we establish appropriate warning vaccination levels using expected values, $E[S_w]$, we notice that for increasing initial vaccine coverage values we obtain increasing optimal warning levels. This criterion does not always guarantee an immediate re-vaccination in that sense, we analyze numerically, the average time required needed to launch a vaccination campaign, R_w, conditioned to an immediate re-vaccination can not be launched. We observe that if we cannot re-vaccinate immediately, then there is a big chance that we will never be able to as a consequence of the high transmission potential of diphtheria.

4.5 Publication

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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, non-pharmaceutical 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

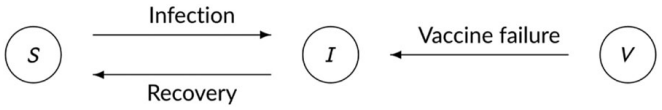

FIGURE 1 Movement of individuals among compartments of the SIVS model

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

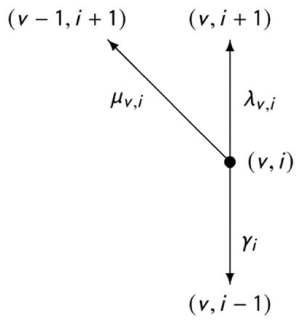

FIGURE 2 Outgoing transitions and rates from a generic state

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 $\{0, 1, 2, \dots, N - w - 1\}$, 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

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

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

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

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

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

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

or equivalently

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

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:

$$C_{v,i} x^k_{v,i} - \lambda_{v,i} C_{v,i-1} x^k_{v,i+1} = D^k_{v,i}, \quad \text{for } 0 \leq i \leq N-v-1, \tag{15}$$

where the constants $C_{v,i}$ and $D^k_{v,i}$ 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

$$C_{v,N-v} x^k_{v,N-v} = D^k_{v,N-v}, \tag{16}$$

which gives the explicit value of the probability $x^k_{v,N-v}$ 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 $x^k_{v,i}$ in terms of probabilities $x^k_{v,i+1}$

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

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, $1 \le k \le N-w$, the set $\{x_{v,i}^k : (v,i) \in \widehat{W}\}$ 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 $x_{v,i}^k$ from Equation (7).
Step 2b: Set $i = i + 1$. While $i \le k$, compute $x_{v,i}^k$ from Equation (7).
Step 2c: Set $k = k + 1$. While $k \le N - w$, 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 $i \le N - v$, compute $C_{v,i}$ from Equation (10).
Step 4: Set $k = k + 1$. If $k > N - w$, go to Step 3.
Step 4a: Compute $D_{v,i}^k$, for $0 \le i \le N - v$, from Equation (11).
Step 4b: Set $i = N - v$ and compute $x_{v,i}^k$ from Equation (8).
Step 4c: Set $i = i - 1$. If $i < 0$, go to Step 4.
Step 4d: Compute $x_{v,i}^k$ from Equation (9).
Step 4e: If $v = v_0$ and $i = 1$, set $P\{S_w = N - w - k\} = x_{v,i}^k$.
Step 4f: Go to Step 4c.

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, $|z| \le 1$, and $(v,i) \in \widehat{W}$, let us define

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

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

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

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

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, $M_{S_w}^k = m_{v,i}^k = 0$, for $k \ge N - w$. 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

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

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

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

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

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

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.

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.*

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,

$$P\{R_{\upsilon,i} = 0\} = 1, \quad \text{for } 0 \le \upsilon \le w, 0 \le i \le N - \upsilon_0. \tag{35}$$

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 $R_{\upsilon,i}$, for $(\upsilon, i) \in \widetilde{W}$.

Let us denote by $f_w(t)$, for $t > 0$, the density function of the continuous part of R_w and we represent by $f_{\upsilon,i}(t)$ the density functions of the continuous random variables $\{R_{\upsilon,i} : 0 \le \upsilon \le w, N - \upsilon_0 + 1 \le i \le N - \upsilon\}$.

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

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

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

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

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

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

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

$$\psi_{\upsilon,i}(z) = \begin{cases} 1, & \text{for } 0 \le i \le N - \upsilon_0, \\ \int_0^\infty e^{-zy} f_{\upsilon,i}(y)dy, & \text{for } N - \upsilon_0 + 1 \le i \le N - \upsilon \end{cases} \tag{40}$$

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

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 $\widetilde{m}^0_{\upsilon,i} = \psi_{\upsilon,i}(0)$ 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 $R_{\upsilon,i}$.

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 $\{R_{w,i} : 1 \le i \le N-w\}$ as follows:*

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

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

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

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 $1 \le i \le N-w$. 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 $1 \le i \le N - v_0$ 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 $z \in \mathbb{C}$, $Re(z) \ge 0$. The Laplace–Stieltjes transforms of the random variables $\{R_{v,i} : (v,i) \in \widetilde{W}\}$ are determined as follows:*

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

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

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

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

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

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

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:

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

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

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

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 $Re(z) \ge 0$, 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:

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

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 $N - v_0 + 2 \le i \le N - 1$

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

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

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

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

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 $0 < v \le w$, 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 $N - v_0 + 1 \le i \le N - v$, 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*

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

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

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

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:*

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

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

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

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.

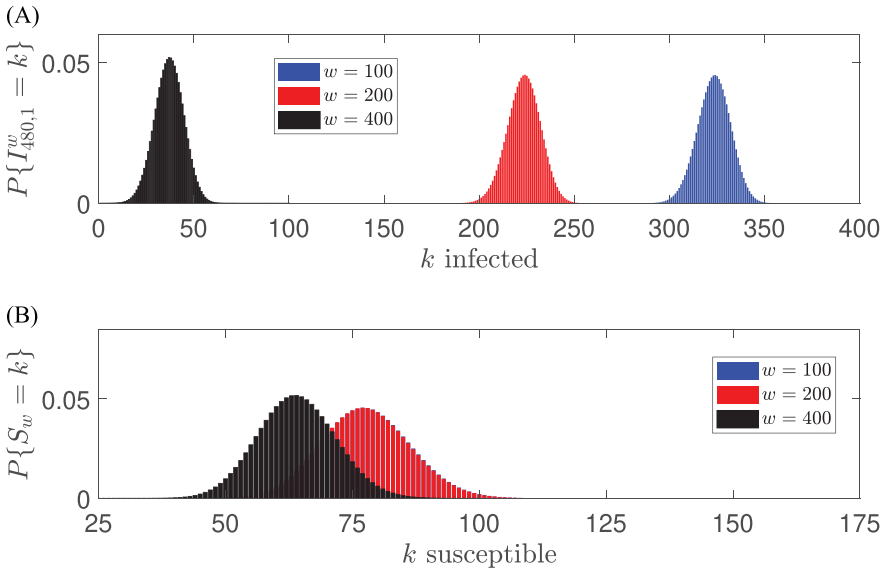

FIGURE 3 Probability mass functions of $I^w_{480,1}$ and of S_w for $w \in \{100, 200, 400\}$, when $h = 0.1$

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 υ_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 ($I^w_{\upsilon_0,1}$, 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 $\upsilon_0 = 480$ 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

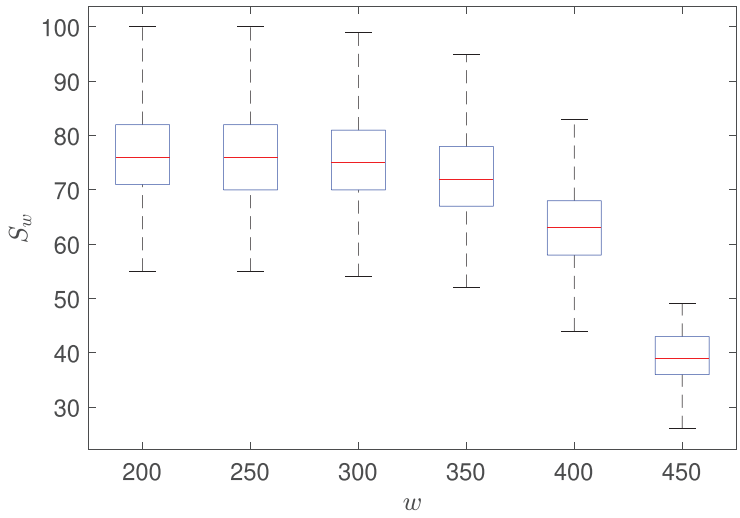

FIGURE 4 Box-plot for S_w under several warning levels when $\upsilon_0 = 480$ and $h = 0.1$

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: $S_w + I^w_{\upsilon_0,1} = N - w$, 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 $\upsilon_0 = 480$ 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 $\upsilon_0 = 480$ 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 $\upsilon_0 = 480$. 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

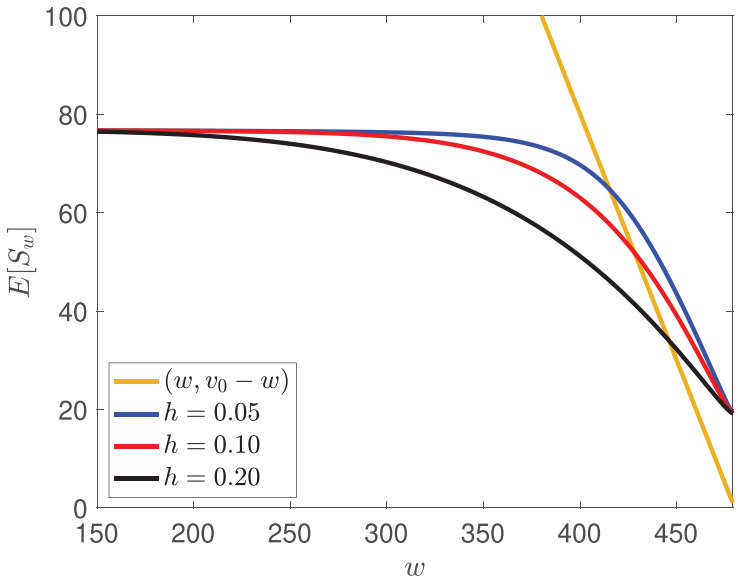

FIGURE 5 $E[S_w]$ as a function of the warning level when $v_0 = 480$ and $h \in \{0.05, 0.1, 0.2\}$

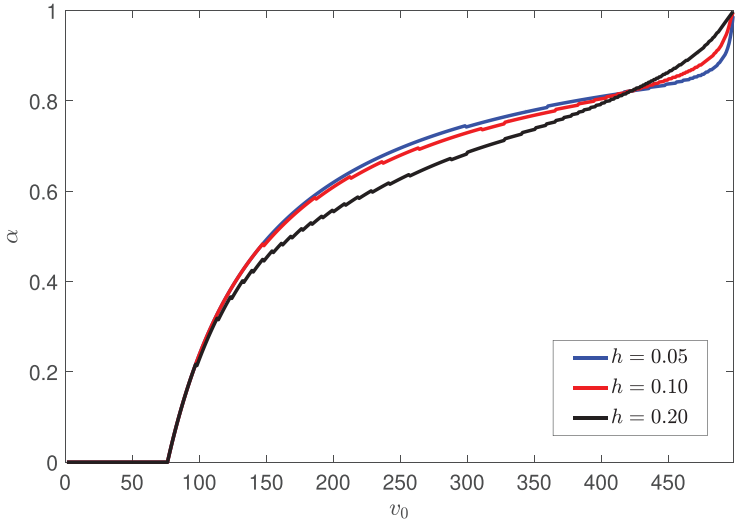

FIGURE 6 Lowest warning level, as a proportion of the initial coverage, satisfying $E[S_w] > v_0 - w$ for several vaccine failure probabilities

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 $\upsilon_0 = 480$ 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 υ_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 υ_0).

To illustrate this fact, we state the above criterion clearly. For a fixed initial vaccine coverage, υ_0, we choose the warning vaccination level as follows $w^* = min\{w \in [0, \upsilon_0) : E[S_w] \geq \upsilon_0 - w\}$.

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 $\{(v, i) : 0 \le v \le w, 0 \le i \le N - v_0 + w - v\}$. 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 $w + E[S_w] \geq \upsilon_0$ 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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Chapter 5

A Stochastic SVIR Model with Imperfect Vaccine and External Source of Infection

In this Chapter we analyze the stochastic SVIR model with external source of infection and imperfect vaccine described in Section 1.3.2.2.

The investigation is published in[120], as a conference paper during the 26^{th} International Conference on Analytical and Stochastic Modelling Techniques and Applications (ASMTA 2021). The publication was restricted to not exceed 15 pages, including figures, tables, and references. Consistent with standard practice, the submitted paper received rigorous peer reviewing.

At the end of the Chapter, a printed version of [120] is included, along with scientific information regarding the conference paper published.

5.1 Background

According to the epidemic model description appearing in Section 1.3.2.2, we study the propagation of infectious diseases that confer permanent immunity for a finite homogeneous population of constant size.
We describe the evolution of the epidemic process, at each time point t, in terms of a three-dimensional CTMC.
The state space of the Markov chain is finite and contains a unique absorbing state which corresponds to the situation when all individuals are recovered. An appropriate description of this state space will result in a bi-diagonal block structured infinitesimal generator that leads one to analyze its behaviour as a LD-QBD process.

Our interest is on the quantification of the speed of transmission analyzing the random variable $W(M)$ that denotes the time until a number M of infections are produced in the population. This random variable is not an improper one and the time to reach M infections in the population is finite with probability one, since the external source of infections ensures that all individuals will eventually infected.

5.2 Objectives

In this investigation we attain objectives (a), $(c.1)$, $(c.2)$, $(c.4)$, (d) and (e) described in Section 1.1.1. In more detail:
We construct the stochastic SVIR model with infection reintroduction and imperfect vaccine that is objective (a).
We study the impact of vaccination on the expansion of the infectious dis-

ease and measure the speed of transmission by analyzing the time until hit a threshold number of individuals to become infected in order to perform objectives $(c.1)$ and $(c.4)$.
Aims (d) and (e) are reached through several numerical examples where we analyze the random variable of interest by considering different selection in the model parameters.

5.3 Methodology

To analyze the behaviour of the epidemic process overtime, we apply the methodology detailed in Section 1.1.2.

Specifically, we describe the evolution of the epidemic process in terms of a three-dimensional CTMC and we organize the state space in levels and sub-levels that permits us to the study of a (LD-QBD) process.

To obtain moments of the random variable, $W(M)$, we derive a methodology based on Laplace–Stieltjes transforms and first-step arguments, adapting techniques in, [123, 124].

5.4 Conclusions

We analyse the speed of transmission describing the random variable, $W(M)$ and we obtain explicit expressions to compute its moments.

Computational times are very high when considering large size populations. In that sense, we only show numerical examples for small size populations.

Regarding the behaviour of the random variable, $W(M)$, we observe that the average time to reach a total M number of infections increases when we consider increasing values of M. When we vary the model parameters, we obtain that increasing transmission rates, β and ξ, produce lower average times, $E[W(M)]$. The vaccine failure probability has a big effect of the average, $E[W(M)]$. We observe that more effective vaccines produce longer periods to reach M infections. This effect is more relevant when we increase the value of M.

5.5 Publication

Title: A stochastic SVIR model with imperfect vaccine and external source of infection.

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A Stochastic SVIR Model with Imperfect Vaccine and External Source of Infection

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Abstract. A stochastic SIR (Susceptible - Infected - Recovered) type model, with external source of infection, is considered for the spread of a disease in a finite population of constant size. Our interest is in studying this process in the situation where some individuals have been vaccinated prior to the start of the epidemic, but where the efficacy of the vaccine to prevent infection is not perfect. The evolution of the epidemic is represented by an absorbing three-dimensional continuous-time Markov chain. We focus on analysing the time for a threshold number of individuals to become infected, and carry out a global sensitivity analysis for the impact of varying model parameters on the summary statistic of interest.

Keywords: Stochastic epidemic model · Markov chain · Time to absorption · Imperfect vaccine

1 Introduction

Infectious diseases have been a serious threat to society throughout history. Plague, cholera and smallpox are examples of epidemics in the past that killed many people. This is a problem that we still suffer today, with emerging diseases such as Ebola, SARS and COVID-19 that continue to claim lives every day.

Understanding epidemic processes is vitally important to forecast the incidence of a disease and to establish mitigation strategies, and mathematical modelling has proven to be a robust tool in this area. Deterministic models have been widely used due to their mathematical tractability [1,2], and are especially relevant when considering large populations or when stochastic effects can be neglected. On the other hand, when considering small populations or if extinction events play a relevant role, stochastic models need to be considered instead

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of classic ones due to the influence on the impact of the disease of random differences in infectiousness and susceptibility among individuals, while these random effects tend to cancel out each other as population size increases [3,4].

The Kermack and McKendrick model [5] has probably been the most influential in representing the spread of an epidemic in the last decades. It is a compartmental deterministic model that classifies individuals according to their "state" with respect to the disease over time: susceptible (S), infected (I) and recovered (R). This SIR model is appropriate for describing a disease for which individuals develop permanent immunity after infection. The SIR model, and a number of different variations, has been widely analysed both for homogeneous [6,7] and heterogeneous populations [8]. In these systems, of particular interest can be specific summary statistics that characterize an outbreak, such as the size of the outbreak [9], its length [10,11] or the reproduction number [12].

Vaccination is an effective preventive measure to limit or avoid an outbreak, where the presence of a high percentage of vaccinated individuals in a given population can prevent transmission, reducing the size and impact of epidemic outbreaks, or the probability of these outbreaks happening at all. A number of mathematical models have considered vaccinated individuals as an extra compartment in the model [13], and some studies have added vaccination strategies into these mathematical models [14–17]. In some cases, vaccines do not provide permanent immunity, and boosters are required [18]. In other occasions, a vaccine might not be fully effective in preventing disease [19], and a proportion of vaccinated individuals might still be partially susceptible against infection. In this situation of an *imperfect* vaccine, the population runs the risk of losing or not achieving herd immunity [20].

In the literature we can find examples of studies assuming either fully protective [21] or imperfect [22,23] vaccines. In [24,25], authors quantify disease transmission in a stochastic SIS model with external source of infection and imperfect vaccine and study preventive measures surrounding vaccination. Under the assumption of imperfect vaccine, authors in [26] study the stationary distribution of the system for a closed population in a stochastic SVIR-type model. On the other hand, in [27] the time to extinction is studied for a non-linear incidence rate model.

In this paper, we consider a SVIR model with imperfect vaccine and external source of infection for a finite homogeneous population of fixed size. Our interest is in analysing the time until a threshold number of individuals get infected, as a way of quantifying the timescales for disease spread. We do this by representing the epidemic process in terms of a multidimensional continuous-time Markov chain (CTMC), and studying a time to absorption in this process. We show how a particular organization of states in this CTMC leads to the study of a level-dependent quasi birth-and-death process (LD-QBD) [28], and propose an efficient scheme to analyse the summary statistic of interest. Our methodology is based on the analysis of Laplace-Stieltjes transforms and the implementation of first-step arguments, adapting techniques in [24,25].

This paper is organized as follows. In Sect. 2 we introduce the SVIR stochastic model with imperfect vaccine and external source of infection. In Sect. 3 we define the summary statistic of interest, and provide an efficient algorithm to compute any of its moments. In Sect. 4 we illustrate our methodology by carrying out a global sensitivity analysis on model parameters. Finally, we present our conclusions in Sect. 5, and discuss possible future lines of research.

2 Model Description

We model the spread of an infectious disease across a population of constant size N, where a percentage of individuals are vaccinated at time $t = 0$ as a prophylactic device to control disease spread. We assume that vaccine is not perfect so that vaccinated individuals can get the infection with probability $h \in (0, 1)$, which we refer to as the vaccine failure probability. Vaccine protection lasts for at least the length of an outbreak, hence further vaccination during the outbreak is not considered. We consider SIR-type dynamics, so that infected individuals become recovered after their infectious period, and denote the recovery rate by γ. Transmission can occur through direct contact, with rate β, or due to an external source of infection, with rate ξ.

We represent this epidemic process in terms of a three-dimensional continuous-time Markov chain (CTMC) $\mathcal{X} = \{(V(t), S(t), I(t)) : t \geq 0\}$, where $V(t)$, $S(t)$ and $I(t)$ represent the number of vaccinated, susceptible and infected individuals in the population at time $t \geq 0$. Given that the population size remains constant, it is clear that $R(t) = N - V(t) - S(t) - I(t)$ represents the number of recovered individual at time t. If one assumes that there are no recovered individuals at the beginning of the epidemic process, the initial state is given by $(V(0), S(0), I(0)) = (v_0, s_0, N - v_0 - s_0)$, for some $v_0, s_0 \geq 0$, with $v_0 + s_0 \leq N$. The state space of the Markov chain is then given by

$$\mathcal{S} = \{(v, s, i) : 0 \leq v \leq v_0, 0 \leq s \leq s_0, 0 \leq v + s + i \leq N\}, \tag{1}$$

which is finite and contains $(v_0 + 1)(s_0 + 1)(N + 1 - \frac{s_0 + v_0}{2})$ states, with a unique absorbing state $(0, 0, 0)$.

We assume that recoveries and contacts between individuals happen independently of each other, with exponentially distributed inter-event times. The evolution of the epidemic process over time is represented by transitions between states in $\mathcal{S}$, where the possible events/transitions are outlined in Table 1. In particular, given the current state $(v, s, i) \in \mathcal{S}$, possible events are:

(E_1) A susceptible individual gets infected, which occurs with rate

$$\lambda_{s,i} = s\left(\frac{\beta i}{N} + \xi\right).$$

(E_2) Considering imperfect vaccination with vaccine failure probability h, a vaccinated individual can still become infected at rate

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

(E_3) An infectious individual recovers with rate

$$\gamma_i = \gamma i.$$

Table 1. Possible events and their transition rates.

Effective outgoing event	Transition	Rate
Infection of susceptible individual	$(v, s, i) \to (v, s-1, i+1)$	$\lambda_{s,i}$
Infection of vaccinated individual	$(v, s, i) \to (v-1, s, i+1)$	$\eta_{v,i}$
Recovery	$(v, s, i) \to (v, s, i-1)$	γ_i

Times spent at each state $(v, s, i) \in \mathcal{S}$ are independent and exponentially distributed random variables, with rate $q_{v,s,i} = \lambda_{s,i} + \eta_{v,i} + \gamma_i$. The dynamics of $\mathcal{X}$ is determined by its infinitesimal generator, $\mathbf{Q}$, which one can efficiently construct by organising first the space of states $\mathcal{S}$ in terms of *levels* and *sub-levels*. In particular, for a particular initial state $(v_0, s_0, N - s_0 - v_0)$,

$$\begin{aligned} \mathcal{S} &= \cup_{v=0}^{v_0} l(v), \\ l(v) &= \cup_{s=0}^{s_0} l(v, s), \quad 0 \le v \le v_0, \\ l(v, s) &= \{(v, s, i) \in \mathcal{S} : \ 0 \le i \le N - v - s\}, \quad 0 \le s \le s_0, \ 0 \le v \le v_0. \end{aligned}$$

We note that the number of states in each sub-level is $\#l(v, s) = N - v - s + 1$, while the number of states in each level is $\#l(v) = (s_0+1)(N-v+1) - \frac{s_0(s_0+1)}{2}$.

By ordering states within each sub-level as

$$(v, s, 0) \prec (v, s, 1) \prec \cdots \prec (v, s, N - v - s),$$

and ordering then states by sub-levels and levels, the infinitesimal generator of $\mathcal{X}$, $\mathbf{Q}$, is given by

$$\mathbf{Q} = \begin{pmatrix} \mathbf{Q}_{0,0} & & & & \\ \mathbf{Q}_{1,0} & \mathbf{Q}_{1,1} & & & \\ & \mathbf{Q}_{2,1} & \mathbf{Q}_{2,2} & & \\ & & \ddots & \ddots & \\ & & & \mathbf{Q}_{v_0,v_0-1} & \mathbf{Q}_{v_0,v_0} \end{pmatrix},$$

with $v_0, s_0 \ge 0$ and $v_0 + s_0 \le N$.

We note that sub-matrices $\mathbf{Q}_{v,v^*}$ are of dimensions $\#l(v) \times \#l(v^*)$. Sub-matrices $\mathbf{Q}_{v,v}$, for $0 \le v \le v_0$, contain rates corresponding to transitions between states within the level $l(v)$. These events, according to the definition of levels and Table 1, correspond to susceptible individuals becoming infected, or infected individuals recovering. On the other hand, sub-matrices $\mathbf{Q}_{v,v-1}$, for $1 \le v \le v_0$, correspond to transitions from states in level $l(v)$ to states in level $l(v-1)$,

which occur due to vaccinated individuals becoming infected. More specifically, sub-matrices $\mathbf{Q}_{v,v^*}$ are described as follows:

$$\mathbf{Q}_{v,v-1} = \begin{pmatrix} \mathbf{A}_{v,v-1}(0,0) & & & \\ & \mathbf{A}_{v,v-1}(1,1) & & \\ & & \ddots & \\ & & & \mathbf{A}_{v,v-1}(s_0,s_0) \end{pmatrix}, \quad 1 \le v \le v_0,$$

$$\mathbf{Q}_{v,v} = \begin{pmatrix} \mathbf{A}_{v,v}(0,0) & & & & \\ \mathbf{A}_{v,v}(1,0) & \mathbf{A}_{v,v}(1,1) & & & \\ & \mathbf{A}_{v,v}(2,1) & \mathbf{A}_{v,v}(2,2) & & \\ & & \ddots & \ddots & \\ & & & \mathbf{A}_{v,v}(s_0,s_0-1) & \mathbf{A}_{v,v}(s_0,s_0) \end{pmatrix}, \quad 0 \le v \le v_0.$$

Sub-matrices $\mathbf{A}_{v,v-1}(s,s)$, for $1 \le v \le v_0$, $0 \le s \le s_0$, have dimensions $(N-v-s+1) \times (N-v-s+2)$, and contain the transition rates from states in sub-level $l(v,s)$ to states in sub-level $l(v-1,s)$. These transitions represent infections of vaccinated individuals. Sub-matrices $\mathbf{A}_{v,v}(s,s)$ contain the transition rates from states in sub-level $l(v,s)$ to states within the same sub-level, and correspond to recoveries of infected individuals. Sub-matrices $\mathbf{A}_{v,v}(s,s-1)$ contain transition rates from states in sub-level $l(v,s)$ to states in sub-level $l(v,s-1)$, corresponding to infections of susceptible individuals. In particular, these sub-matrices are defined as follows:

- For $0 \le v \le v_0$, $0 \le s \le s_0$, $\mathbf{A}_{v,v}(s,s)$ is a matrix of dimensions $(N-v-s+1) \times (N-v-s+1)$, with

$$\mathbf{A}_{v,v}(s,s) = \begin{pmatrix} -q_{v,s,0} & & & & \\ \gamma & -q_{v,s,1} & & & \\ & 2\gamma & -q_{v,s,2} & & \\ & & \ddots & \ddots & \\ & & & (N-v-s)\gamma & -q_{v,s,N-v-s} \end{pmatrix}.$$

- For $1 \le v \le v_0$, $0 \le s \le s_0$, $\mathbf{A}_{v,v-1}(s,s)$ is a matrix of dimensions $(N-v-s+1) \times (N-v-s+2)$, with

$$\mathbf{A}_{v,v-1}(s,s) = \begin{pmatrix} 0 & \eta_{v,0} & & \\ & 0 & \eta_{v,1} & \\ & & \ddots & \ddots \\ & & & 0 & \eta_{v,N-v-s} \end{pmatrix}.$$

- For $0 \leq v \leq v_0$, $1 \leq s \leq s_0$, $\mathbf{A}_{v,v}(s, s-1)$ is a matrix of dimensions $(N-v-s+1) \times (N-v-s+2)$, with

$$\mathbf{A}_{v,v}(s, s-1) = \begin{pmatrix} 0 & \lambda_{s,0} & & & \\ & 0 & \lambda_{s,1} & & \\ & & \ddots & \ddots & \\ & & & 0 & \lambda_{s,N-v-s} \end{pmatrix}.$$

3 Time Until M Individuals Get Infected

In this section, we analyse the speed of transmission by focusing on the time that it takes for a threshold number M of individuals to get infected, $W(M)$. $W(M)$ is a non-negative continuous random variable that denotes the time elapsed until a total of M individuals become infected. In order to analyse this summary statistic, we redefine the CTMC as $\mathcal{X}^* = \{(J(t), S(t), I(t)) : \ t \geq 0\}$ where $S(t)$ and $I(t)$ denote the number of susceptible and infected individuals respectively at time t, and $J(t) = S(t)+V(t)$ represents the sum of vaccinated and susceptible individuals at time t. For an initial state (j_0, s_0, i_0) and a threshold value M of interest, with $1 \leq M \leq N$, $W(M)$ can be defined as

$$W_{j_0,s_0,i_0}(M) = inf\{t \geq 0 : \ J(t) = N - M \mid (J(0), S(0), I(0)) = (j_0, s_0, i_0)\}.$$

To analyse this random variable, one can study the evolution of the Markov chain $\mathcal{X}^*$ in the set of states $\mathcal{S}^* = \{(j, s, i) : N-M \leq j \leq j_0, max(0, j+s_0-j_0) \leq s \leq s_0, max(0, N-M-j+1) \leq i \leq N-j\}$, and where trivially $W_{j_0,s_0,i_0}(M) \equiv 0$ if $M \leq N - j_0$. Then, the variable $W_{j_0,s_0,i_0}(M)$ can be studied as first-passage time to the set of absorbing states $S^*_M = \{(N-M, s, i) \in \mathcal{S}^*\}$ of the Markov chain $\mathcal{X}^*$.

For any initial state (j_0, s_0, i_0), and threshold value of interest $1 \leq M \leq N$, it is clear that $\mathbb{P}(W_{j_0,s_0,i_0}(M) < +\infty) = 1$, since the external source of infection ensures that all individuals will eventually become infected. On the other hand, the definition of $W_{j_0,s_0,i_0}(M)$ for the initial state of interest (j_0, s_0, i_0) can be extended to any other state $(j, s, i) \in \mathcal{S}^*$, and the random variable of interest $W_{j_0,s_0,i_0}(M)$ can be studied by analysing as well the auxiliary ones $W_{j,s,i}(M)$, $(j, s, i) \in \mathcal{S}^*$. In particular, we can introduce the Laplace-Stieltjes transforms for any $(j, s, i) \in \mathcal{S}^*$ as $\phi_{j,s,i}(z) = E\left[e^{-zW_{j,s,i}}\right]$, $z \in \mathbb{C}$, with $Re(z) \geq 0$, and where we omit M from notation from now on.

The Laplace-Stieltjes transforms $\phi_{j,s,i}(z)$ satisfy a set of linear equations, which is obtained via first-step arguments by conditioning on the possible transitions out of state $(j, s, i) \in \mathcal{S}^*$. In particular,

$$\begin{aligned}\phi_{j,s,i}(z) = (1-\delta_{i,0})\frac{\gamma_i}{z+q_{j-s,s,i}}\phi_{j,s,i-1}(z)\\ +(1-\delta_{s,0})\frac{\lambda_{s,i}}{z+q_{j-s,s,i}}\phi_{j-1,s-1,i+1}(z)\\ +\frac{\eta_{j-s,i}}{z+q_{j-s,s,i}}\phi_{j-1,s,i+1}(z),\end{aligned} \tag{2}$$

where $\delta_{i,j}$ represents the Kronecker's delta function, defined as 1 when $i = j$, and 0 otherwise. This system of equations has boundary conditions $\phi_{N-M,s,i}(z) = 1$ for those states at which the number M of infections is reached. We can also note that, by definition, $\phi_{j,s,i}(0) = 1$, for any $(j, s, i) \in \mathcal{S}^*$.

These Laplace-Stieltjes transforms could be computed, at any point $z \in \mathbb{C}$, by solving system (2). Furthermore, with the help of numerical methods for Laplace transforms inversion, it is possible to calculate the probability distribution function of $W(M)$ [29,30]. Although the numerical inversion is indeed possible, it is many times computationally not feasible. However, our interest instead here is in computing different order moments of these variables. In particular, moments can be computed from direct differentiation of the transform, as

$$m^k_{j,s,i} = E\left[W^k_{j,s,i}\right] = (-1)^k \frac{d^k \phi_{j,s,i}(z)}{dz^k}\bigg|_{z=0}, \quad k \geq 1. \tag{3}$$

Thus, by differentiating Eq. (2) with respect to z k times ($k \geq 1$) and evaluating at $z = 0$, we obtain the equations involving the moments as

$$q_{j,s,i} m^k_{j,s,i} = k m^{k-1}_{j,s,i} + \lambda_{s,i} m^k_{j-1,s-1,i+1} + \eta_{j-s,i} m^k_{j-1,s,i+1} + \gamma_i m^k_{j,s,i-1}, \tag{4}$$

with boundary conditions $m^0_{j,s,i} = 1$, $m^k_{N-M,s,i} = 0$ for any $k \geq 1$.

The loop-free structure of the transition rates of the CMTC $\mathcal{X}^*$ allows one to compute moments in a recursive way from the system above, for increasing values of $k \geq 1$ and taking into account that moments of order 0 are trivially equal to 1. Algorithm 1 outlines how to carry out this computation in an efficient and ordered way, which is based on Theorem 1 below. Proof of Theorem 1 is omitted here for the sake of brevity, since it consists of a recursive solution scheme directly based on Eq. (4).

Algorithm 1. Computation of the k^{th}-order moments of the random variable $W_{j_0,s_0,i_0}(M)$, for $1 \leq k \leq k_{max}$ for some maximum desired order k_{max}

Input: $j_0, s_0, i_0, N, M, \beta, \xi, \gamma$ and $kmax$.
Step 1: Set $j = N - M$
  Step 1a: Set $s = max(0, j + s_0 - j_0)$
  Step 1b: Set $k = 0$ and set $m^0_{N-M,s,i} = 1$ for $max(0, N-M-j+1) \leq i \leq N-j$.
  Step 1c: Set $k = k+1$, set $m^k_{N-M,s,i} = 0$ for $max(0, N-M-j+1) \leq i \leq N-j$.
  Step 1d: If $k < kmax$, go to Step 1c.
  Step 1e: Set $s = s + 1$. If $s \leq s_0$, go to Step 1b.
Step 2: Set $j = N - M + 1$.
  Step 2a: Set $s = max(0, j + s_0 - j_0)$.
  Step 2b: Set $k = 0$ and set $m^0_{j,s,i} = 1$ for $max(0, N - M - j + 1) \leq i \leq N - j$.
  Step 2c: Set $k = 1$ and set $m^k_{j,s,i}$ for $max(0, N - M - j + 1) \leq i \leq N - j$, from (6).
  Step 2d: Set $k = k+1$ and compute $m^k_{j,s,i}$ for $max(0, N-M-j+1) \leq i \leq N-j$, from (7)-(8).
  Step 2e: If $k < kmax$, go to Step 2d.
  Step 2f: If $s < s_0$, set $s = s + 1$ and go to Step 2b.
Step 3: If $j = j_0$, stop.
Step 4: Set $j = j + 1$.
  Step 4a: Set $s = max(0, j + s_0 - j_0)$.
  Step 4b: Set $k = 0$ and set $m^0_{j,s,i} = 1$ from $max(0, N-M-j+1) \leq i \leq N-j$.
  Step 4c: Set $k = k+1$ and compute $m^k_{j,s,i}$ for $max(0, N-M-j+1) \leq i \leq N-j$, from (7)-(8).
  Step 4d: If $k < kmax$, go to Step 4c.
  Step 4e: If $s < s_0$, set $s = s + 1$ and go to Step 4b.
Step 5: If $j < j_0$, go to Step 4. If $j = j_0$, stop.
Output: $m^k_{j_0,s_0,i_0}$, *for* $0 \leq k \leq kmax$.

Theorem 1. *Given a number of initial vaccinated and susceptible individuals* $v_0 \geq 0$ *and* $s_0 \geq 0$, *with* $0 \leq v_0 + s_0 \leq N$ *and an integer* k, $k \geq 0$, *and* $1 \leq M \leq N$, *the central moments of order* k *of the variable* $W_{j_0,s_0,i_0}(M)$, *are obtained from the following expressions for all* $(j, s, i) \in \mathcal{S}^*$*:*

$$m^0_{j,s,i} = 1, \quad m^k_{N-M,s,i} = 0, \text{ for } k \geq 1, \tag{5}$$

$$m^1_{N-M+1,s,i} = \sum_{r=0}^{i} \frac{i! \frac{\gamma^{i-r}}{r!}}{\prod_{l=r}^{i} q_{N-M-s+1,s,l}}, \tag{6}$$

$$m^k_{j,s,i} = \sum_{r=0}^{i} \frac{i! \frac{\gamma^{i-r}}{r!} T^k_{j,s,r}}{\prod_{l=r}^{i} q_{j-s,s,l}} \text{ for } k \geq 1 \tag{7}$$

with

$$T^k_{j,s,i} = k m^{k-1}_{j,s,i} + (1 - \delta_{s,0}) \lambda_{s,i} m^k_{j-1,s-1,i+1} + (1 - \delta_{j,s}) \eta_{j-s,i} m^k_{j-1,s,i+1}. \tag{8}$$

4 Results

In this section, we illustrate our analysis in Sect. 3 by carrying out a global sensitivity analysis on model parameters for the summary statistic of interest. We set the recovery rate $\gamma = 1.0$ in all the numerical experiments, so that the time unit is taken as the expected time that an infected individual takes to recover. We consider a population of $N = 100$ individuals here, and assume that 50% of them are partially protected against the infection through the vaccine, so that the initial state is $(v_0, s_0, i_0) = (50, 49, 1)$.

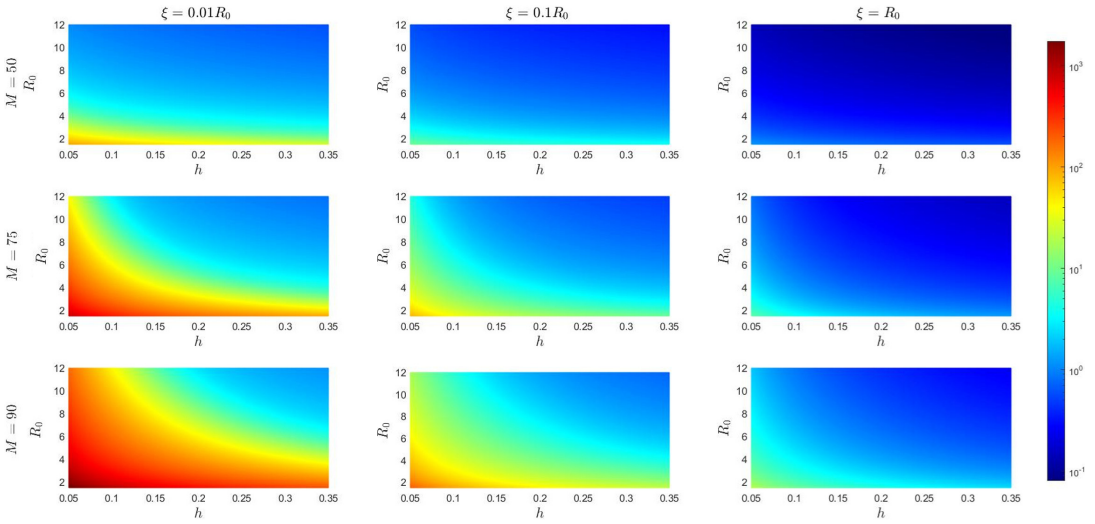

Fig. 1. Mean time $E[W(M)]$ until M individuals get infected, for different values of M, R_0, h and ξ. Initial state $(v_0, s_0, i_0) = (50, 49, 1)$.

In Fig. 1, we plot $\overline{W}_M = E[W(M)]$ for different values of the Basic Reproduction Number, $R_0 = \beta/\gamma$, ξ, h and M. The average time to reach a total of M infections increases with increasing values of M, as one would expect. On the other hand, $\overline{W}_M$ decreases with the external source of infection rate, ξ, since these external infections can contribute towards reaching the threshold M. An interplay can be observed between the value of the reproduction number R_0 and the vaccine failure probability h, so that large values of $\overline{W}_M$ can be due to small transmission rates (small R_0) or to small probability of vaccine failure, h. We note that the value of M, together with the proportion of individuals initially vaccinated, are directly relevant to understand the dynamics in Fig. 1. The relevance of h is observed to be smaller for $M = 50$, since in this situation the outbreak can reach 50 infections just by those infections suffered by susceptible individuals in this system. On the other hand, increasing values of M require infections to happen among the vaccinated sub-population, and thus small values of the vaccine failure probability lead to significantly increased times $\overline{W}_M$ to reach M infections. We also note that, for small values of ξ (e.g.; $\xi = 0.01R_0$), the mean time $\overline{W}_M$ to reach M infections can span several orders of magnitude

for different values of the parameters (M, R_0, h). This can be explained by the fact that, if the external source of infection is small and the outbreak was to finish without the level M of infections being reached, one would need to wait until a subsequent outbreak to occur in the remaining susceptible/vaccinated population, which would take long under small values of ξ. Larger values of ξ lead to "overlapping" outbreaks, where external infections can constantly occur, facilitating smaller values of the mean time $\overline{W}_M$.

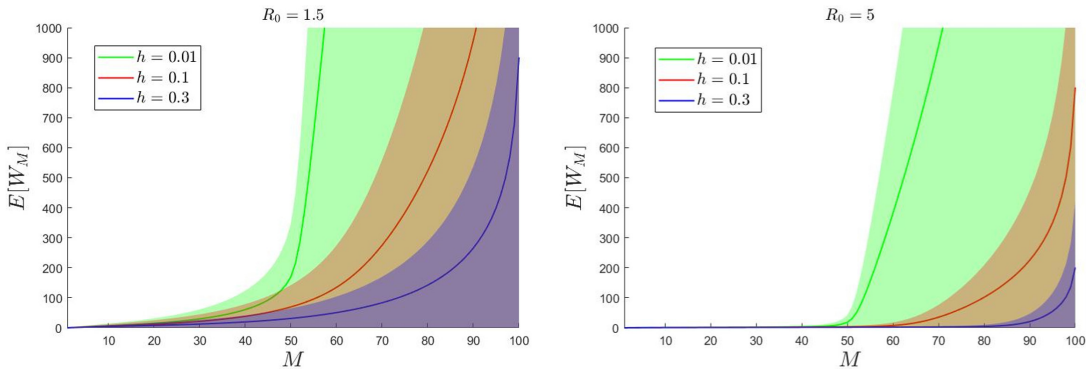

Fig. 2. Mean time $E[W(M)]$ (solid curves) plus and minus its standard deviation $\sigma[W(M)]$ (shaded area) versus M, for $\xi = 0.01R_0$, $N = 100$, $R_0 \in \{1.5, 5\}$ and $h \in \{0.01, 0.1, 0.3\}$. Initial state $(v_0, s_0, i_0) = (50, 49, 1)$.

Some of the dynamics described above can be better understood by exploring Fig. 2, that shows the expected time elapsed until M infections have been reached as a function of M, for a relatively small value of $\xi = 0.01R_0$ and for several values of h and two different values of R_0. Shaded areas are obtained by considering $E[W(M)] \pm \sigma[W(M)]$. As expected, increasing values of R_0 or decreasing values of h lead to increasing times to reach M infections. On the other hand, vaccines with higher probability of failure lead to situations where less time is needed in order to reach M infections, and in consequence the expansion of the disease is faster. This behaviour reveals the importance of the vaccine effectiveness. Particularly interesting is the asymptotic behaviour of the curves, where the time to reach M infections can significantly increase when approaching particular values of M in some situations. This is directly related to the vaccine failure probability h, and the initial number of susceptible and vaccinated individuals $(s_0, v_0) = (49, 50)$. In particular, and when focusing for example on $R_0 = 1.5$ and $h = 0.01$, the small vaccine failure probability means that infections in order to reach the threshold value M are likely to occur among susceptible individuals, and unlikely to happen among vaccinated ones. Since 50% of the population is vaccinated, and we start with 1 infected individual, up to $M = 50$ individuals can become infected in relatively short periods of time (given that $R_0 = 1.5$) by infections happening in the susceptible pool. However, as soon as M exceeds the value 50 infections among the vaccinated pool are required to happen for this threshold to be reached. These infections would be rare ($h = 0.01$), leading

to significant increases in the expected time $E[W(M)]$. These behaviours nicely illustrate the protection that a nearly perfect vaccination confers to the pool of vaccinated individuals, where a relatively fast outbreak (due to $R_0 = 1.5 > 1$) would decelerate when approaching $M = s_0 + i_0$. For significantly small values of h (e.g.; $h = 0.01$), the dynamics described above are relatively similar regardless of considering $R_0 = 5$ instead of $R_0 = 1.5$, although increasing values of R_0 facilitate an *overshoot* effect, as can be observed when comparing the two plots in Fig. 2. For relatively larger vaccine failure probabilities (e.g.; $h = 0.1$ or $h = 0.3$), these asymptotic behaviours can be partially compensated by increasing values of R_0, where some infections in the vaccinated pool can be achieved due to the large value of R_0, facilitating the attainment of the threshold number of infections M.

Numerical experiments show that the expected value of $W(M)$ presents an increasing behaviour, as a function of M. Moreover, when we increase the vaccination coverage v_0 and keep fixed the remaining model parameters, the mean time to achieve a number of M infections also increases. This is in accordance to intuition because when an outbreak starts with a big proportion of vaccine protected individuals, infections are becoming less likely and the time to infect M individuals is larger in comparison with outbreaks starting with a lesser number of vaccinated individuals.

Computational times are very high and complexity increases when considering populations larger than 1000 individuals. For instance, when $N = 1000$ individuals the state space $\mathcal{S}^*$ contains around 4.16×10^7 states, while for a population of 10000 individuals the number of states increases to 4.16×10^{10}. The elapsed time to compute $E[W(M)]$ takes around 4 min when $N = 1000$ and it lasts more than 5 h when $N = 10000$, in a personal computer with 8 GB of RAM, M1 memory Chip with GPU of 7 Kernels.

5 Conclusions

In this paper, we have considered a stochastic SVIR model with imperfect vaccine and external source of infection. We have represented this in terms of a multidimensional continuous-time Markov chain, and have showed that by appropriately ordering its space of states in terms of levels and sub-levels, this leads to the study of a LD-QBD. Our interest was in analysing the speed at which the epidemic occurs, by studying the time to reach a threshold number M of infections in the population. By means of first-step arguments, we have obtained a system of linear equations which can be solved efficiently and recursively, as outlined in Algorithm 1. In our results in Sect. 4, we have illustrated our methodology by carrying out a wide sensitivity analysis on model parameters, where an interplay can be observed between the reproduction number R_0, the threshold of interest M, the vaccine failure probability h, the external source of infection rate ξ, and the initial number of vaccinated individuals v_0. Our techniques can in principle be applied in order to study other summary statistics of potential interest in this system, such as the exact reproduction number [24,31] or the time until the end of the outbreak [8]. This remains the aim of future work.

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Chapter 6

On the Exact and Population Reproduction Numbers in a Stochastic SVIR Model with Imperfect Vaccine

In this research work we extend the investigation described in the previous Chapter for the SVIR epidemic model.

We focus on the quantification of the potential transmission of an infectious disease through reproduction numbers, as we made in Chapter 2, but with a novel approach that permits one to understand better the effect of vaccination on the potential transmission of the pathogen.

The article is being prepared for submission to a scientific journal.

6.1 Background

In this paper, we consider the stochastic SVIR model with external source of infection and imperfect vaccine that was analyzed in [120].

We quantify the potential transmission of the infectious disease analyzing the exact and population reproduction numbers, R_{e0} and R_p, but distinguishing infections produced to vaccinated from those of susceptible individuals. In this context, the reproduction numbers can be partitioned as follows:

$$R_{e0} = R_{e0}^V + R_{e0}^S,$$

$$R_p = R_p^V + R_p^S,$$

where superscripts V and S represent infections either to vaccinated or susceptible individuals, respectively.
Our analysis focus on the study of the bidimensional random variables (R_{e0}^V, R_{e0}^S) and (R_p^V, R_p^S).

6.2 Objectives

In this investigation we carry out objectives (b), $(c.1)$, $(c.2)$, (d) and (e) described in Section 1.1.1. In more detail:
We define the reproduction numbers, R_{e0}^V, R_{e0}^S, R_p^V and R_p^S to analyze the impact of vaccination in the propagation of the infectious disease and to measure its potential transmission in order to attain purposes $(c.1)$ and $(c.2)$.
We carry out a general sensitivity analysis by studying the effect of varying model parameters in the random variables of interest that are objectives (d) and (e).

6.3 Methodology

To derive joint probability mass functions and joint moments of the random variables (R_{e0}^V, R_{e0}^S) and (R_p^V, R_p^S), we apply a similar methodology to one in [121], but considering analogous bi-dimensional expressions for probability mass and generating functions and moments. We solve the linear system of equations involved applying recursive methods.

6.4 Conclusions

Numerical analysis shows that marginal probability mass functions for both random variables are right-skewed for all selection on the model parameters. In that sense, to avoid prolonged computations we use a stopping criterion that consists on iterate the algorithms provided, until the 95% of the marginal and the 99% of the joint mass points are accumulated.

In general, we obtain increasing expected values of the number of secondary cases produced by the index case, for increasing values of the internal contact rate, no mater if the infection is to a vaccinated or a susceptible individual. It means that, when we deal with long internal contact rates, β, the marked individual has more opportunities to infect individuals within the population no distinguishing if they are previously vaccinated or not. But, we appreciate that these averages are greater in the number of infections produced to susceptible individuals. Considering more effective vaccines we obtain, in the vaccinated pool of individuals, lower expected values of the exact reproduction number.

Regarding the vaccine coverage we observe that for lower v_0 values, we

obtain greater values of R_{e0}^S than R_{e0}^V and we notice that this effect is more accused for lower external contact rates, ξ.

The behavior of the random variables, R_p^V and R_p^S are very similar to their analogous exact reproductive numbers but we observe that in general we obtain larger expected values. This is a reasonable behavior since the exact reproduction number only record infections produced by the index case until the first case of recovery occurs and the population reproduction number counts infections produced by all entire population during this period of time.

On the exact and population reproduction numbers in a stochastic SVIR model with imperfect vaccine

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Abstract

We aim to quantify the spread of an infectious disease, that confers immunity, in a non-isolated finite and homogeneous population. A proportion of individuals is vaccinated prior the start of the infection with an imperfect vaccine. Vaccine failure implies that some vaccinated individuals can get the infection when being in touch with an infectious individual. We study the evolution of the epidemic process over time in terms of a continuous-time Markov chain, which represents a general SIR model with an additional compartment for vaccinated individuals. The basic reproduction number R_0 is probably the most used quantity in epidemiology to characterise the infectiousness of a pathogen within a population. In our stochastic model, we study two variables related to the basic reproduction number: the exact reproduction number, R_e, and the population reproduction number, R_p. We express both random variables in terms of a sum of two contributions, which corresponds to the number of infections caused by a single infected individual among the susceptible and vaccinated populations. Recursive algorithms are derived in order to compute joint probability mass functions and factorial moments for these random variables. We illustrate the applicability of our techniques by means of a set of numerical experiments.

Keywords: Stochastic epidemic model, Markov chain, Basic reproduction number, Imperfect vaccine
2000 MSC: 92D30, 60J28, 60J22

1. Introduction

Outbreaks have been nearly constant through history and they have killed millions of individuals around the world. For example, the Black Death, also

known as the Plague, was a bubonic plague pandemic that struck Europe and Asia in the mid-1300s. It is considered the most fatal pandemic recorded in human history and it caused around 200 million of deaths. In 1520, another devastating pandemic was caused by smallpox. Although the origin of this disease is unknown, there is evidence of its existence at a very early time, since remains have been found in Egyptian mummies dating from the third century BC [1]. Even in the modern era, epidemic outbreaks are a serious threat to public health. SARS, MERS, avian influenza, Ebola and COVID-19 among others have reminded the world of the risk associated with outbreaks of infectious diseases, and the importance of increase knowledge on disease spread dynamics with the goal to establish control policies to stop or reduce transmission.

Vaccination is one of the most powerful tools to prevent infectious diseases. Over the last two centuries, vaccination has enabled smallpox to be eradicated, it has reduced global child mortality rates preventing countless birth defects and lifelong disabilities [2, 3]. Vaccines can provide immunity against a disease, by helping the immune system to recognize the pathogens that cause the disease, without the need for the host to be exposed to it. However, lifelong immunity is not always provided by vaccines, and the duration of protection against a given pathogen depends on the type of infectious agent and the type of vaccine. In some occasions, several doses are necessary to guarantee immunity in the long-term, and even vaccine boosters or constant pulse vaccination programs in the population are required for some pathogens [4, 5, 6]. In other occasions, which is of interest for this work, vaccines are imperfect and do not provide full immunity to all individuals, so that some vaccinated individuals can eventually become infected if exposed to the corresponding pathogen [7].

As vaccination is an effective method to prevent the spread of infection, mathematical compartmental epidemic models, with a specific vaccination compartment, have been developed to study the efficacy of vaccination strategies to control relevant diseases and where the interest has sometimes been in studying the efficacy of different vaccination strategies for certain relevant diseases [8, 9, 10, 11, 12, 13, 14]. Some papers deal with compartmental epidemic models assuming that vaccine is 100% perfect [15, 16, 17, 18, 19, 20] but many others deal with vaccines that are imperfect, and where some vaccinated individuals in the population can still be infected by the infectious pathogen with certain probability [21, 22, 23].

The SIS and SIR models with imperfect vaccine have been analyzed by

a deterministic approach [24, 25]. On the other hand, the SIS model with imperfect vaccine is studied from a stochastic approach in [26, 27]. In [28, 4], authors study a stochastic SIS model with external source of infection and imperfect vaccine and quantify the efficacy of different preventive measures surrounding vaccination. Under the assumption of imperfect vaccine, authors in [29], study the stationary distribution in a closed population stochastic SVIR-type model. In [30], the time to extinction is studied for a non-linear incidence rate model and in [31], a latency period is included in the model.
In [32], we consider a constant size population, where individuals become infected due to either contacts with infectious individuals in the population or through an external source of infection. For community protection, a percentage of the population is vaccinated with an imperfect vaccine that fails with a certain probability. The underlying mathematical model involved is the stochastic SVIR model with external source of infection and imperfect vaccine and we represent the evolution of the epidemic process in terms of an absorbing three-dimensional CTMC. We show how a particular organization of the state space of the Markov chain leads us to the study of a QBD process. We analyze the time until reach total number M infections in order to quantify the timescales for disease spread.

In this paper we consider the same epidemic model as, in [32], and we focus on the potential transmission of an infectious disease by analyzing alternatives measures to the basic reproduction number, R_0 [39, 40, 41, 42, 43] and the control reproduction number, R_c.
When we are dealing with populations of small-to-moderate size, the basic reproduction and the control number quantities tend to overestimate the real number of infections caused by a single individual during each stochastic realisation of the process because they count infections to individuals that previously they have been infected. Instead of that, the exact and population reproduction numbers R_{e0} and R_p, respectively, do not count that repeated contacts that R_0 and R_c make and we provide exact measures to quantify the expansion of an epidemic process.
In this work, we reformulate the treatment of R_{e0} and R_p initiated in [28, 37], for a stochastic SVIR model. This refinement consists in analyzing both measures in terms of two different contributions each, by distinguishing between those infections caused across the susceptible or vaccinated pools of individuals in the population. In this way, one can better understand the contribution that susceptible and vaccinated individuals play in the overall transmission through the corresponding reproduction numbers.

This paper is organized as follows. Section 2 contains the description of the stochastic SVIR model with an external source of infection and imperfect vaccine. In Sections 3 and 4, we define and analyse the random variables R_{e0} and R_p regarding the compartment where the individuals were included immediately prior to get the infection. Section 5 contains a set of numerical experiments to illustrate our techniques, while concluding remarks are given in Section 6.

2. Model description

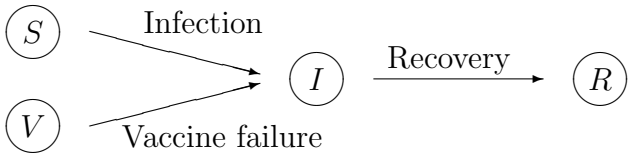
We consider a homogeneous and well-mixed population of constant size, N, where individuals are affected by a disease that confers permanent immunity. The pathogen is transmitted by direct contact with an infected individual. We assume that a proportion of the population is vaccinated with an available imperfect vaccine, meaning that some vaccinated individuals can get the disease with probability $h \in (0, 1)$ if exposed. Vaccination was implement at $t = 0$ and additional vaccination during the outbreak is not considered.

Population is not isolated and infections can be produced either trough direct contacts with infected individuals within the population following a time-homogeneous Poisson process with rate β/N or through an external source of infection (e.g.; external contacts with infected individuals) with rate ξ. Infected individuals recover after independent exponentially distributed times with rate γ.

We consider a general stochastic SIR-type model with an additional compartment of vaccinated individuals, where once an infected individual recovers from the disease they become immune. Thus, individuals within the population are classified into four groups, namely susceptible (S), vaccinated (V), infected (I) and recovered (R).

The epidemic dynamics are then represented by movement of individuals among these compartments over time, as it is shown in Figure 1.

Figure 1: Possible individual transitions between coompartments in the Susceptible-Vaccinated-Infected-Removed (SVIR) model.



At any time, $t > 0$, the state of the epidemic is described by random variables $V(t)$, $S(t)$ and $I(t)$. Since we consider a population of constant size, it is clear that the number of recovered individual is given by

$$R(t) = N - V(t) - S(t) - I(t).$$

We represent the evolution of the disease in terms of a three-dimensional continuous continuous-time Markov (CMTC),

$$\mathcal{X} = \{(V(t), S(t), I(t)) : t \geq 0\},$$

where $V(t)$, $S(t)$, and $I(t)$ record the number of vaccinated, susceptible and infected individuals, respectively, at time $t \geq 0$.
We assume that at $t = 0$ there are not recovered individuals so the initial state can be expressed as $(V(0), S(0), I(0)) = (v_0, s_0, N - v_0 - s_0)$ for some v_0, s_0, such that $0 \leq v_0 + s_0 \leq N$.
The state space of $\mathcal{X}$ is given by

$$\mathsf{S} = \{(v, s, i) : 0 \leq v \leq v_0, 0 \leq s \leq s_0, 0 \leq v + s + i \leq N\}. \tag{1}$$

and the cardinality of this set is given by $\#\mathsf{S} = (v_0+1)(s_0+1)\left(N + 1 - \frac{s_0+v_0}{2}\right)$, with an unique absorbing state in $(0, 0, 0)$.

The dynamics of the epidemic over time is represented by the transition of $\mathcal{X}$ across states in S. For a particular current state $(v, s, i) \in \mathsf{S}$, the following events can occur: (a) An infected individual contacts a susceptible individual, and they become infected; this occurs with rate $\lambda_{s,i} = \left(\frac{\beta i}{N} + \xi\right) s$. (b) A vaccinated individual contact an infected individual and, due to the imperfect vaccine, they become infected; this occurs with rate $\eta_{v,i} = h\left(\frac{\beta i}{N} + \xi\right) v$. (c) An infected individual recovers; this occurs with rate $\gamma_i = \gamma i$. Thus, the

infinitesimal transition rates of $\mathcal{X}$ are given by

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

where $q_{v,s,i} = (\frac{\beta i}{N}+\xi)s + h(\frac{\beta i}{N}+\xi)v + \gamma i$. We point out that $q_{v,s,i}^{-1}$ represents the average sojourn time spent at each state $(v,s,i) \in \mathsf{S}$.

To describe the infinitesimal generator of $\mathcal{X}$, $\mathbf{Q}$, we partition the space of states S in terms of levels and sub-levels, using the same ordering states as we considered in [32]. This organisation of states leads to a LD-QBD structure for $\mathbf{Q}$, as described in [32]. In particular, for a particular initial state $(v_0, s_0, N-s_0-v_0)$,

$$\begin{aligned} \mathsf{S} &= \cup_{v=0}^{v_0} l(v), \\ l(v) &= \cup_{s=0}^{s_0} l(v,s), \text{ for } \quad 0 \le v \le v_0, \\ l(v,s) &= \{(v,s,i) \in \mathsf{S} : \ 0 \le i \le N-v-s\}, \text{ for } \quad 0 \le s \le s_0, \ 0 \le v \le v_0. \end{aligned}$$

We notice that the number of states in each sub-level is $\#l(v,s) = N-v-s+1$, while the number of states in each level is $\#l(v) = (s_0+1)(N-v+1) - \frac{s_0(s_0+1)}{2}$.

As we are dealing with a finite state Markov chain and assuming $\xi > 0$, in long-term the process will become absorbed into the unique absorbing state in $(0,0,0)$, in a finite expected time.

3. The exact transmission variable R_{e0}

In this section we study the transmission potential of an infectious disease by studying the random variable R_{e0}, defined as the number of secondary infections caused directly by a marked infective individual during his/her infectious period.

During the infectious period of the marked individual, the underlying CTMC evolves in the following subset of S

$$\widehat{\mathsf{S}} = \{(v,s,i) \in \mathsf{S} : \ 1 \le i \le N-v-s\}.$$

We point out that although it is clear that R_{e0} depends on the initial state $(v_0, s_0, N - s_0 - v_0) \in \widehat{\mathsf{S}}$, with $s_0 + v_0 \leq N - 1$, we omit this from notation.

A particular novel approach in this work is to distinguish between transmission to susceptible and vaccinated individuals when analysing this measure. Thus, we define R_{e0}^V as the number of vaccinated individuals directly infected by the marked infective individual, and we denote by R_{e0}^S the number of susceptible individuals directly infected by the tracked infective individual. Hence,

$$R_{e0} = R_{e0}^V + R_{e0}^S. \tag{3}$$

As we are dealing with an infectious disease that confers permanent immunity and a finite state Markov chain, the maximum number of infections produced by the index case to vaccinated and susceptible individuals are v_0 and s_0, respectively. In consequence, R_{e0}^V and R_{e0}^S have finite supports.

Our aim is to characterize the joint distribution of the bidimensional random variable (R_{e0}^V, R_{e0}^S).

The homogeneous mixing assumption guarantees all-to-all interactions with no preferences in relationship among individuals. Therefore, individuals behave equally and we can then split contagions transition rates in (2), by distinguishing if the infection involves a susceptible or a vaccinated individual. That is, we partition contagion rates in the following way

$$\eta_{v,i} = h\left(\frac{\beta i}{N} + \xi\right) v \;=\; h\frac{\beta}{N} v + h\left(\frac{\beta(i-1)}{N} + \xi\right) v \;=\; \eta_v^* + \widetilde{\eta}_{v,i}, \tag{4}$$

$$\lambda_{s,i} = \left(\frac{\beta i}{N} + \xi\right) s \;=\; \frac{\beta}{N} s + \left(\frac{\beta(i-1)}{N} + \xi\right) s \;=\; \lambda_s^* + \widetilde{\lambda}_{s,i}, \tag{5}$$

where we denote

$$\eta_v^* = h\frac{\beta}{N} v, \tag{6}$$

$$\widetilde{\eta}_{v,i} = h\left(\frac{\beta(i-1)}{N} + \xi\right) v, \tag{7}$$

$$\lambda_s^* = \frac{\beta}{N} s, \tag{8}$$

$$\widetilde{\lambda}_{s,i} = \left(\frac{\beta(i-1)}{N} + \xi\right) s. \tag{9}$$

To study probability mass and generating functions, and factorial moments of the joint distribution (R_{e0}^V, R_{e0}^S) conditioned to the initial state $(v_0, s_0, N - v_0 - s_0)$, we rely on the following functions and moments conditioned to a specific state $(v, s, i) \in \widehat{\mathsf{S}}$:

$$\begin{aligned}
x_{v,s,i}^{l,k} &= P\left\{R_{e0}^V = l, R_{e0}^S = k \,|(V(0) = v, S(0) = s, I(0) = i)\right\}, \\
&\quad \text{for } 0 \leq l \leq v, 0 \leq k \leq s, \\
\varphi_{v,s,i}^{V,S}(z,w) &= E\left[z^{R_{e0}^V} w^{R_{e0}^S} \,|(V(0) = v, S(0) = s, I(0) = i)\right] \\
&= \sum_{r=0}^{v}\sum_{j=0}^{s} z^r w^j P\left\{R_{e0}^V = r, R_{e0}^S = j \,|(V(0) = v, S(0) = s, I(0) = i)\right\}, \\
&\quad \text{for } |z| \leq 1, |w| \leq 1, \\
m_{v,s,i}^{l,k} &= E\left[\Pi_{r=0}^{l-1}(R_{e0}^V - r)\Pi_{j=0}^{k-1}(R_{e0}^S - j) \,|(V(0) = v, S(0) = s, I(0) = i)\right] \\
&= \left.\frac{\partial^{l+k}\varphi_{v,s,i}^{V,S}(z,w)}{\partial z^l \partial w^k}\right|_{w=1,z=1} \text{for } l, k \geq 0,
\end{aligned}$$

where empty products are considered to be equal to 1 here and in what follows.

We point out that

$$P(\{R_{e0}^V < +\infty, R_{e0}^S < +\infty \,|V(0) = v, S(0) = s, I(0) = i\}) = 1,$$

for any $(v, s, i) \in \widehat{\mathsf{S}}$, due to both random variables have finite support. Consequently, $\sum_{l=0}^{v}\sum_{k=0}^{s} x_{v,s,i}^{l,k} = 1$, for any initial state $(v, s, i) \in \widehat{\mathsf{S}}$.

A first-step argument, conditioning on the possible transitions out of a fixed state $(v, s, i) \in \widehat{\mathsf{S}}$, shows that the joint mass function of the variable $\{(R_{e0}^V, R_{e0}^S) \,|(V(0) = v, S(0) = s, I(0) = i)\}$ satisfies the following relationship

$$\begin{aligned}
q_{v,s,i} x_{v,s,i}^{l,k} &= \delta_{l,0}\delta_{k,0}\gamma + ((1 - \delta_{v,0})((1 - \delta_{l,0})\eta_v^* x_{v-1,s,i+1}^{l-1,k} + \widetilde{\eta}_{v,i} x_{v-1,s,i+1}^{l,k}) \\
&\quad +(1 - \delta_{s,0})((1 - \delta_{k,0})\lambda_s^* x_{v,s-1,i+1}^{l,k-1} + \widetilde{\lambda}_{s,i} x_{v,s-1,i+1}^{l,k})) \\
&\quad +(i - 1)\gamma x_{v,s,i-1}^{l,k}, \qquad (10)
\end{aligned}$$

where $\delta_{a,b}$ represents the Kronecker's delta function, which takes the value 1 if $a = b$, and 0 otherwise.

Boundary conditions of this system of equations are given by $x^{0,0}_{0,0,i} = 1$, for $1 \leq i \leq N$, $x^{l,k}_{0,s,i} = 0$, for any $1 \leq l \leq v$ and $x^{l,k}_{v,0,i} = 0$, for any $1 \leq k \leq s$.

The *loop-free* structure of the transition events of the CMTC (see Figure 1) allows us to compute joint probability mass functions in a recursive way from Equation (10). In particular, Algorithm 1 outlines how to carry out this computation in an efficient and ordered way.

Algorithm 1 Computation of the joint mass function of the variable (R^S_{e0}, R^V_{e0}), for a given initial state of interest $(v_0, s_0, N - v_0 - s_0)$

Input: $N, v_0, s_0, i_0, \beta, \xi$ and γ.

Step 1: Set $k = 0$

Step 2: Set $l = 0$, $v = 0$ and $s = 0$

- Step 2b: set $x^{l,k}_{v,s,i} = 1$ for $1 \leq i \leq N - v - s$.
- Step 2c: Set $s = s + 1$, compute $x^{l,k}_{v,s,i}$ from (10) for $1 \leq i \leq N - v - s$.
- Step 2d: If $s < s_0$, go to Step 2c.
- Step 2e: Set $v = v + 1$. If $v \leq v_0$, set $s = -1$ and go to Step 2c.

Step 3: Set $l = l + 1$.

- Step 3a: Set $x^{l,k}_{v,s,i} = 0$ for $0 \leq v \leq l - 1$, $0 \leq s \leq s_0$ and $1 \leq i \leq N - v - s$.
- Step 3b: Set $v = l$ and $s = 0$
- Step 3c: Compute $x^{l,k}_{v,s,i}$ from (10) for $1 \leq i \leq N - v - s$.
- Step 3d: If $s < s_0$, set $s = s + 1$ and go to Step 3c.
- Step 3e: If $v < v_0$, set $v = v + 1$, $s = 0$ and go to Step 3c.
- Step 3f: If $l < v_0$, go to Step 3.

Step 4: Set $k = k + 1$ and $l = 0$ and $v = 0$.

- Step 4a: Set $x^{l,k}_{v,s,i} = 0$ for $0 \leq s \leq k - 1$, $1 \leq i \leq N - v - s$.
- Step 4b: Set $s = k$
- Step 4c: Compute $x^{l,k}_{v,s,i}$ from (10) for $1 \leq i \leq N - v - s$.
- Step 4d: Set $s = s + 1$, if $s < s_0$ go to step 4c
- Step 4e: If $v < v_0$, set $v = v + 1$ and go to Step 4a.

Step 5: Set $l = l + 1$

- Step 5a: Set $x^{l,k}_{v,s,i} = 0$ for $0 \leq v \leq l - 1$, $0 \leq s \leq s_0$ and $1 \leq i \leq N - v - s$.
- Step 5b: Set $v = l$ and $s = k$
- Step 5c: Compute $x^{l,k}_{v,s,i}$ from (10) for $1 \leq i \leq N - v - s$.
- Step 5d: If $v < v_0$, set $v = v + 1$ and go to step 5c.
- Step 5e: If $l < v_0$, set $l = l + 1$ go to step 5.
- Step 5f: If $k < s_0$ go to step 4.

Output: $x^{l,k}_{v_0,s_0,i_0}$, *for* $0 \leq k \leq v_0$ *and* $0 \leq l \leq s_0$.

Similarly, a first-step argument conditioning on the possible transitions out of a fixed state $(v, s, i) \in \widehat{\mathsf{S}}$, shows that the joint generating functions $\varphi^{V,S}_{v,s,i}(z, w)$ of (R^V_{e0}, R^S_{e0}) satisfy the following set of linear equations:

$$
\begin{aligned}
q_{v,s,i}\varphi^{V,S}_{v,s,i}(z,w) &= \gamma + ((1-\delta_{v,0})(\eta^*_v z\varphi^{V,S}_{v-1,s,i+1}(z,w) \\
&\quad +\widetilde{\eta}_{v,i}\varphi^{V,S}_{v-1,s,i+1}(z,w)) + (1-\delta_{s,0})(\lambda^*_s w\varphi^{V,S}_{v,s-1,i+1}(z,w) \\
&\quad +\widetilde{\lambda}_{s,i}\varphi^{V,S}_{v,s-1,i+1}(z,w)) + (1-\delta_{i,1})\gamma(i-1)\varphi^{V,S}_{v,s,i-1}(z,w).
\end{aligned} \tag{11}
$$

By differentiating Eq. (11) with respect to z repeatedly l times ($l \geq 1$) and w repeatedly k times ($k \geq 1$) and evaluating at $z = 1$ and $w = 1$, we obtain the following system of equations involving factorial moments conditioned to states $(v, s, i) \in \widehat{\mathsf{S}}$ of (R^V_{e0}, R^S_{e0})

$$
\begin{aligned}
q_{v,s,i}m^{l,k}_{v,s,i} &= ((1-\delta_{v,0})((1-\delta_{l,0})l\eta^*_v m^{l-1,k}_{v-1,s,i+1} \\
&\quad +\eta_{v,i}m^{l,k}_{v-1,s,i+1}) + (1-\delta_{s,0})((1-\delta_{k,0})k\lambda^*_s m^{l,k-1}_{v,s-1,i+1} \\
&\quad +\lambda_{s,i}m^{l,k}_{v,s-1,i+1})) + (1-\delta_{i,1})\gamma(i-1)m^{l,k}_{v,s,i-1},
\end{aligned} \tag{12}
$$

with boundary conditions $m^{l,0}_{0,s,i} = 0$, for $l > 0$, $m^{0,k}_{v,0,i} = 0$, for $k > 0$, $m^{l,k}_{0,0,i} = 0$, for $l, k > 0$ and $m^{0,0}_{v,s,i} = 1$.

Algorithm 2 Computation of the factorial moments $m_{v,s,i}^{l,k}$ of the joint variable (R_{e0}^V, R_{e0}^S)

Input: $v_0, s_0, i_0, \beta, \xi, \gamma, l_{max}$ and k_{max}.
Step 1: Set $k = 0$, $l = 0$ and $m_{v,s,i}^{l,k} = 1$, for $0 \leq v \leq v_0$, $0 \leq s \leq s_0$, $1 \leq i \leq N - v - s$.
Step 2: Set $l = l+1$, $v = 0$ and $m_{0,s,i}^{l,0} = 0$ for $0 \leq s \leq s_0$ and $1 \leq i \leq N-v-s$.
Step 3: set $v = v+1$, $s = 0$ and compute $m_{v,s,i}^{l,k}$ from (12) for $1 \leq i \leq N-v-s$.
  Step 3a: If $s < s_0$, set $s = s + 1$ and compute $m_{v,s,i}^{l,k}$ from (12) for $1 \leq i \leq N - v - s$ and go to Step 3a.
  Step 3b: If $v < v_0$ go to Step 3.
  Step 3c: If $l < l_{max}$, go to Step 2.
Step 4: Set $k = k + 1$ and $l = 0$,
  Step 4a: Set $v = 0$,
  Step 4b: Set $s = 0$, if $l = 0$ or $v = 0$ set $m_{v,0,i}^{0,k} = 0$ else compute $m_{v,s,i}^{l,k}$ from (12) for $1 \leq i \leq N - v - s$.
  Step 4c: If $s < s_0$, set $s = s + 1$ and compute $m_{v,s,i}^{l,k}$ from (12) for $1 \leq i \leq N - v - s$ and go to Step 4c.
  Step 4d: If $v < v_0$, set $v = v + 1$ and go to Step 4b.
Step 5: If $l < l_{max}$, set $l = l + 1$ and go to Step 4a.
Step 6: If $k < k_{max}$ go to Step 4.
Output: $m_{v_0,s_0,i_0}^{l,k}$, *for* $0 \leq k \leq k_{max}$ *and* $0 \leq l \leq l_{max}$.

4. The population transmission variable, R_p

A supplementary measure of the transmission potential of a contagious disease is R_p, which provides the global spread of the disease by counting all the infections that take place within the population (not just those directly caused by a marked individual) until the first recovery occurs. R_p is a random variable that can be analyzed either at the beginning of the outbreak or at any later time (i.e.; for any initial state $(v_0, s_0, N - v_0 - s_0) \in \widehat{\mathsf{S}}$).

Here, we also propose to characterize R_p while distinguishing between infections involving vaccinated and susceptible individuals, so that

$$R_p = R_p^V + R_p^S. \tag{13}$$

We point out that both random variables have finite support. In particular, $0 \leq Rp^V \leq v_0$ and $0 \leq Rp^S \leq s_0$.

Our aim is to characterize the joint distribution of (R_p^V, R_p^S) conditioned to an initial state $(v_0, s_0, N - v_0 - s_0)$.

To study this variable, we define the generating and probability mass functions of (R_p^V, R_p^S), and joint factorial moments of R_p^V and R_p^S, for any given initial state $(v, s, i) \in \widehat{\mathsf{S}}$, as

$$\begin{aligned}
X_{v,s,i}^{l,k} &= P\left\{R_p^V = l, R_p^S = k \,|(V(0) = v, S(0) = s, I(0) = i)\right\}, \\
&\quad \text{for } 0 \le l \le v, 0 \le k \le s, \\
\phi_{v,s,i}^{V,S}(z,w) &= E\left[z^{R_p^V} w^{R_p^S} \,|(V(0) = v, S(0) = s, I(0) = i)\right] \\
&= \sum_{r=0}^{v}\sum_{j=0}^{s} w^j z^r P\left\{R_p^V = r, R_p^S = j \,|(V(0) = v, S(0) = s, I(0) = i)\right\}, \\
&\quad \text{for } |z| \le 1 \text{ and } \ |w| \le 1, \\
M_{v,s,i}^{l,k} &= E[\Pi_{r=0}^{l-1}(R_p^V - r)\Pi_{j=0}^{k-1}(R_p^S - j) \,|(V(0) = v, S(0) = s, I(0) = i)]. \\
&\quad \text{for } l, k \ge 0.
\end{aligned}$$

For a given state $(v, s, i) \in \widehat{\mathsf{S}}$, the joint mass functions of the random vector $(R_p^V, R_p^S) \,|(V(0) = v, S(0) = s, I(0) = i)$ can be obtained through a direct recursive scheme based on the following relationship

$$\begin{aligned}
q_{v,s,i} X_{v,s,i}^{l,k} &= \delta_{l,0}\delta_{k,0}\gamma i + ((1-\delta_{l,0})(1-\delta_{v,0})\eta_{v,i} X_{v-1,s,i+1}^{l-1,k} \\
&\quad +(1-\delta_{k,0})(1-\delta_{s,0})\lambda_{s,i} X_{v,s-1,i+1}^{l,k-1}). \qquad (14)
\end{aligned}$$

A first-step argument, conditioning on the possible transitions out of a state $(v, s, i) \in \widehat{\mathsf{S}}$, shows that the joint generating functions $\phi_{v,s,i}^{V,S}(z,w)$ of (R_p^V, R_p^S) satisfy the following set of linear equations:

$$\begin{aligned}
q_{v,s,i}\phi_{v,s,i}^{V,S}(z,w) &= \gamma i + ((1-\delta_{v,0})\eta_{v,i} z \phi_{v-1,s,i+1}^{V,S}(z,w) \\
&\quad +(1-\delta_{s,0})\lambda_{s,i} w \phi_{v,s-1,i+1}^{V,S}(z,w)). \qquad (15)
\end{aligned}$$

Given l and k, positive integers, factorial moments of order $(l + k)$ are determined from Eq (15) by differentiating repeatedly l times regarding z and k times regarding w. Finally, evaluating the resulting expression at $z = w = 1$ we get the equations involving factorial moments conditioned to states $(v, s, i) \in \widehat{\mathsf{S}}$ of (R_p^V, R_p^S) as follows

$$
\begin{aligned}
q_{v,s,i}M^{l,k}_{v,s,i} \quad &= ((1-\delta_{l,0})l\eta_{v,i}M^{l-1,k}_{v-1,s,i+1} \\
&+(1-\delta_{v,0})\eta_{v,i}M^{l,k}_{v-1,s,i+1}) + (1-\delta_{s,0})((1-\delta_{k,0})k\lambda_{s,i}M^{l,k-1}_{v,s-1,i+1} \\
&+\lambda_{s,i}M^{l,k}_{v,s-1,i+1})),
\end{aligned} \tag{16}
$$

with boundary conditions $M^{l,0}_{0,s,i} = 0$ for $l \geq 1$, $M^{0,k}_{v,0,i} = 0$ for $k \geq 1$, $M^{l,k}_{0,0,i} = 0$ for $l, k > 0$ and $M^{0,0}_{v,s,i} = 1$.

Remark 1. *Mass functions and factorial moments of the bidimensional variable (R^V_p, R^S_p) can be computed from recursive schemes based on Eqs. (14) and (16), respectively. Their algorithmic computation are similar to Algorithm 1 and Algorithm 2 and are not explicitly reported here, but they are the basis for obtaining some of the numerical results in Section 5.*

5. Results

In this section, we illustrate theoretical results and algorithmic approaches described in previous sections.

We set the average infectious period length as $\gamma^{-1} = 1$, so that, it will represent the unit of time from now on. We consider a population of $N = 101$ individuals and assume $(V(0), S(0), I(0)) = (v_0, s_0, 1)$ as the initial situation.

In Figure 2, we represent probability mass distribution functions of R^V_{e0} and R^S_{e0}. We consider an initial coverage of $v_0 = 50$ vaccinated individuals and external contact rate $\xi = 0.01$. We vary the internal contact rate $\beta \in \{1.2, 5, 9\}$ and vaccine failure probability $h \in \{0.05, 0.3\}$. Although R^V_{e0} and R^S_{e0} have finite support, we only represent mass points that accumulate the 95% of cumulative probability to avoid confusion on visual elements.

Distributions are right-skewed for all scenarios. Mass probability functions of R^V_{e0}, present a decreasing shape. Increasing the internal contact rate gives more chance to larger number of infections on vaccinated individuals. Notice that, for $h = 0.05$, the probability that the marked individual does not transmit the disease among the protected group is at least 0.8, even for internal contact rates as large as $\beta = 9.0$.

R^S_{e0} distribution also presents a decreasing shape. Changes on the vaccine efficacy produce small effect on the number of susceptible individuals that get the infection through the index case. As could be expected, increasing the internal contact rate β gives distributions with longer right tails.

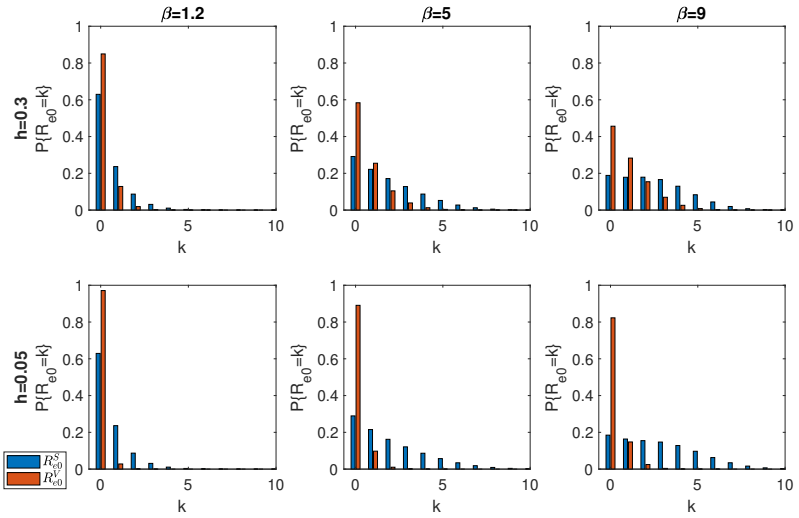


Figure 2: R_{e0}^S and R_{e0}^V probability mass functions. Scenarios correspond to a population of $N = 101$ individuals with a single infectious individual, initial vaccine coverage of 50%, $\gamma = 1$ and $\xi = 0.01$ when $\beta \in \{1.2, 5, 9\}$ and $h \in \{0.03, 0.3\}$

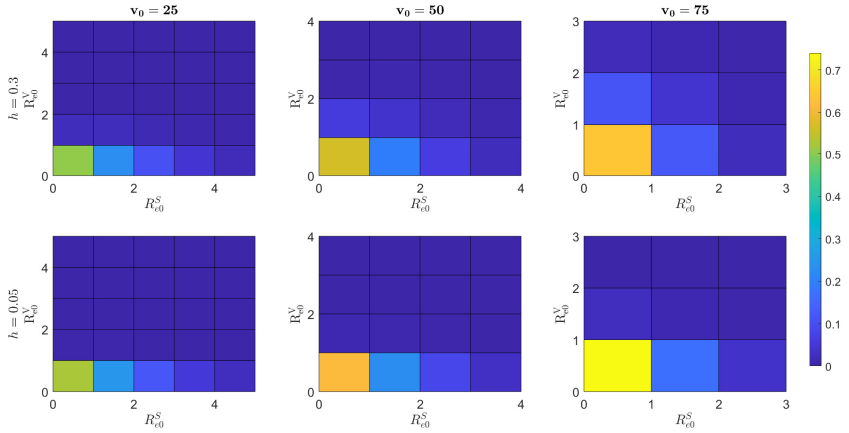


Figure 3: Joint mass distribution function of (R_{e0}^S, R_{e0}^V) for several values of h and v_0. Scenarios arise in a population of $N = 101$ individuals with an initial infected individual, $\gamma = 1$, $\beta = 1.2$ and $\xi = 0.01$ when $h \in \{0.03, 0.3\}$ and $v_0 \in \{25, 50, 75\}$

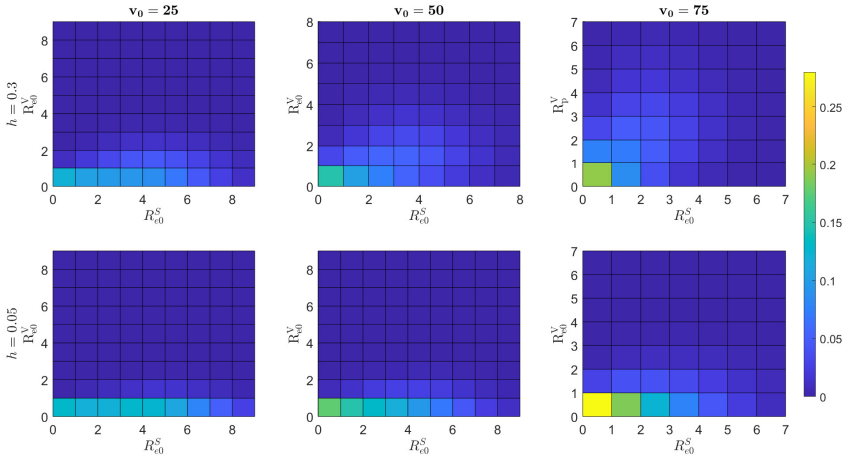


Figure 4: Joint mass distribution function of (R^S_{e0}, R^V_{e0}) for several values of h and v_0. Scenarios arise in a population of $N = 101$ individuals with an initial infectious individual, $\gamma = 1$, $\beta = 9$ and $\xi = 0.01$ when $h \in \{0.03, 0.3\}$ and $v_0 \in \{25, 50, 75\}$

In Figures 3 and 4, we represent the mass distribution function of the bidimensional variable (R^S_{e0}, R^V_{e0}) for two internal contact rates $\beta = 1.2$ and $\beta = 9$, assuming that vaccine failure is $h \in \{0.05, 0.3\}$ and initial vaccine coverage $v_0 \in \{25, 50, 75\}$. Graphs show bidimensional distributions on the set of mass points that accumulate the 99% of probability.
In general, when we increase vaccine coverage we obtain joint mass functions that accumulate the most part of the probability close to point $(0, 0)$. This behaviour is due to the fact that there are more people protected against the disease and less people susceptible to be infected. Increasing the internal contact rate β increases the dispersion of the epidemic transmission in relation to the mass point $(0, 0)$.

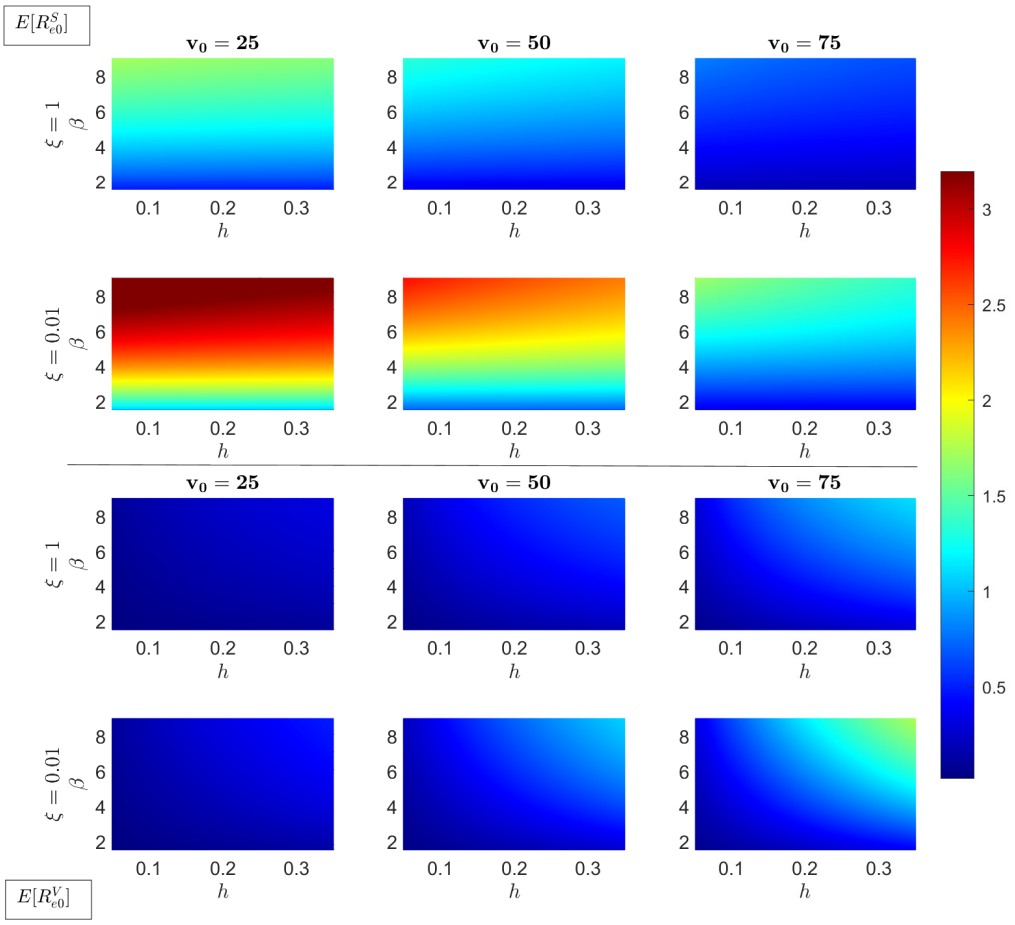


Figure 5: $E[R^S_{e0}]$ and $E[R^V_{e0}]$ as function of β and h. Different scenarios arise in a population of $N = 101$ individuals with an initial infected individual and $\gamma = 1$ when $v_0 \in \{25, 50, 75\}$ and $\xi \in \{0.01, 1\}$

In Figure 5, we plot the expected infections caused, by the index case before being recovered, within the susceptible group and within the vaccine protected individuals. The six top graphs correspond to $E[R^S_{e0}]$ and the six in the bottom correspond to $E[R^V_{e0}]$. Each graph represents the expected contagions as a function of internal contact rate β and vaccine failure h. We consider different scenarios by fixing an initial vaccination level $v_0 \in \{25, 50, 75\}$ and an external infection rate $\xi \in \{0.01, 1\}$.

One can observe that the expected number of infections involving susceptible individuals is always bigger than that involving vaccinated individuals, except for when considering situations with large vaccine coverage ($v_0 = 75$) and significant vaccine failure probability (e.g.; $h = 0.3$).
As to be expected, $E[R_{e0}^V]$ and $E[R_{e0}^S]$ increase with increasing transmission rates β. Large external infection rates ξ (e.g.; $\xi = 1$) lead to lower values of both random measures, since the marked individual has less opportunities to spread the disease. The average number of infections involving vaccinated individuals and caused by the index case, $E[R_{e0}^V]$, increases for increasing values of the vaccine coverage and for decreasing values of the external contact rate. On the other hand, for low vaccine coverages the effect of the vaccine efficacy parameter becomes less significant. On the other hand, increasing values of v_0 produce decreasing values of $E[R_{e0}^S]$.

Table 1: Summary statistics for R_{e0}^S and R_{e0}^V

β	h	$E[R_{e0}^S]$	$\sigma[R_{e0}^S]$	$CV[R_{e0}^S]$	$E[R_{e0}^V]$	$\sigma[R_{e0}^V]$	$CV[R_{e0}^V]$
1.2	0.05	0.5764	0.9323	1.6175	0.0297	0.1746	5.8788
5	0.05	2.0071	2.0218	1.0073	0.1219	0.3680	3.0189
9	0.05	2.7623	2.2155	0.8020	0.2120	0.4992	2.3547
1.2	0.30	0.5746	0.9285	1.6159	0.1764	0.4532	2.5692
5	0.30	1.8783	1.8461	0.9829	0.6592	0.9701	1.4716
9	0.30	2.4644	1.9495	0.7911	0.9624	1.1531	1.1982

In Table 1, we display summary statistics: expected value, standard deviation and coefficient of variation of R_{e0}^S and R_{e0}^V, for $\beta \in \{1.2, 5, 9\}$ and $h \in \{0.05, 0.3\}$, when $\xi = 0.01$, $v_0 = s_0 = 50$ and there is a single initial infected individual in the population.

For all scenarios, expected values and standard deviation for R_{e0}^S are greater than their counterpart measures for R_{e0}^V, due to the protection conferred by the vaccine. On the contrary, coefficient of variation is greater for the variable R_{e0}^V in every case. Hence, R_{e0}^S is more concentrated around its expected value $E[R_{e0}^S]$ than R_{e0}^V on its respective mean value. The expected transmission and deviation, on both vaccinated and susceptible individuals, increase when the internal contact rate increases. When fixing the internal contact rate, more effective vaccines make a decrease both on $E[R_{e0}^V]$ and

$\sigma[R_{e0}^V]$.

In Figure 6, we represent the ratio of means $E[R_{e0}^S]/E[R_{e0}^V]$ as a function of the transmission rate β and the vaccine failure probability h, for initial vaccine coverage $v_0 \in \{25, 50, 75\}$, and external rate of infection rate $\xi \in \{0.01, 1\}$. Ratios greater than 1 indicate that the expected number of infections involving susceptible individuals is bigger than the expected number of infections involving vaccinated individuals. The transmission rate β seems to affect both expected values in a similar way. Hence, changes on β have little effect on the ratio of these expected values. However, vaccine effectiveness presents a significant impact on the ratio of means, which presents a decreasing behavior when failure probability increases. Notice that, in scenarios with vaccine coverage $v_0 \leq 50$, the marked individual produces, in mean terms, more infections among susceptible individuals that among the vaccine protected ones.

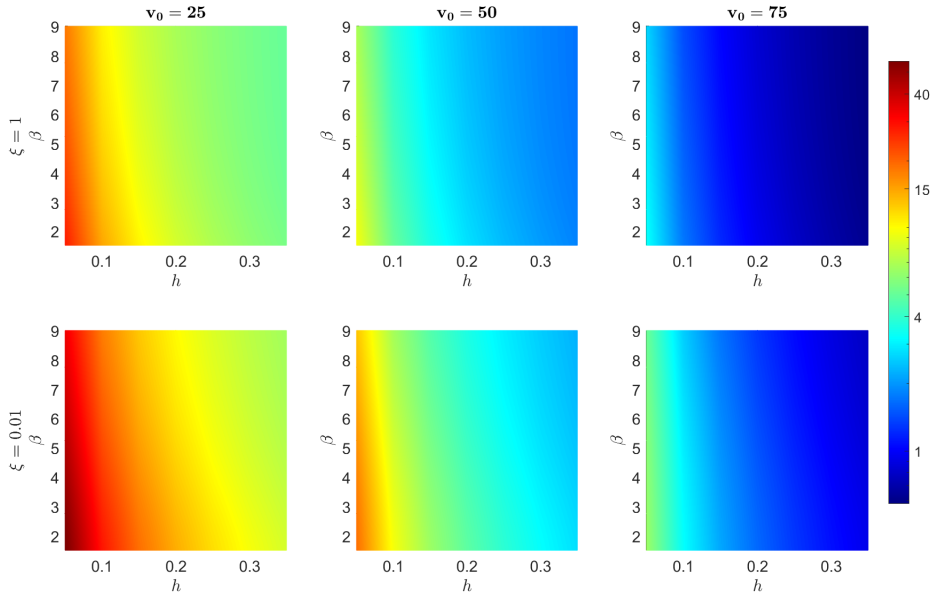


Figure 6: $E[R_{e0}^S]/E[R_{e0}^V]$ as a function of β and h. Different scenarios arise in a population of $N = 101$ individuals with an initial infectious individual and $\gamma = 1$ when $v_0 \in \{25, 50, 75\}$ and $\xi \in \{0.01, 1\}$

Next, we derive analogous numerical analysis for the random variables R_p^V and R_p^S.

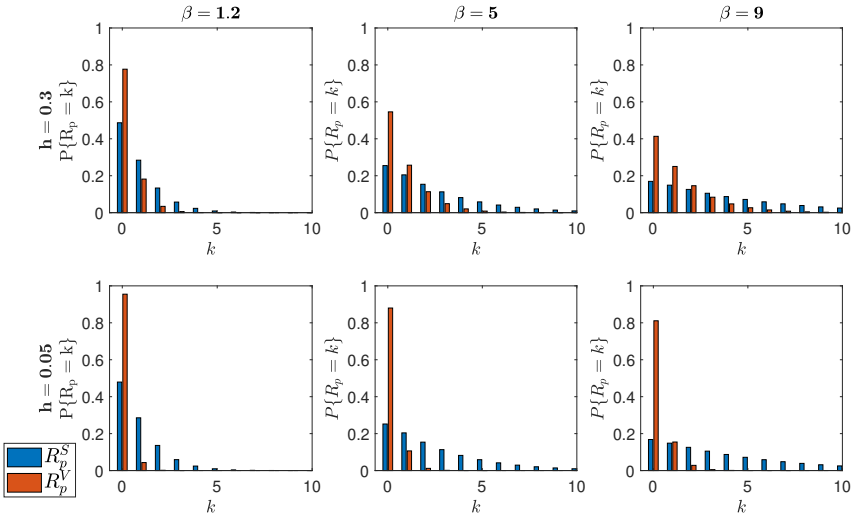


Figure 7: R_p^S and R_p^V mass functions for several values of β and h in a population of $N = 101$ with $S(0) = V(0) = 50$ and $i(0) = 1$ individuals, $\xi = 0.01$ and $\gamma = 1$.

In Figure 7, we represent marginal mass distribution functions of R_p^V and R_p^S for several values of the internal contact rate $\beta \in \{1.2, 5, 9\}$ and the vaccine failure probability $h \in \{0.05, 0.3\}$. As we made for the random variables, R_{e0}^V and R_{e0}^S, we only represent those points that accumulate a 95% of the probability.

All distributions are right-skewed and present a decreasing shape. For all scenarios the effect of the internal contact rate β and the vaccine failure probability is similar to Figure 2.

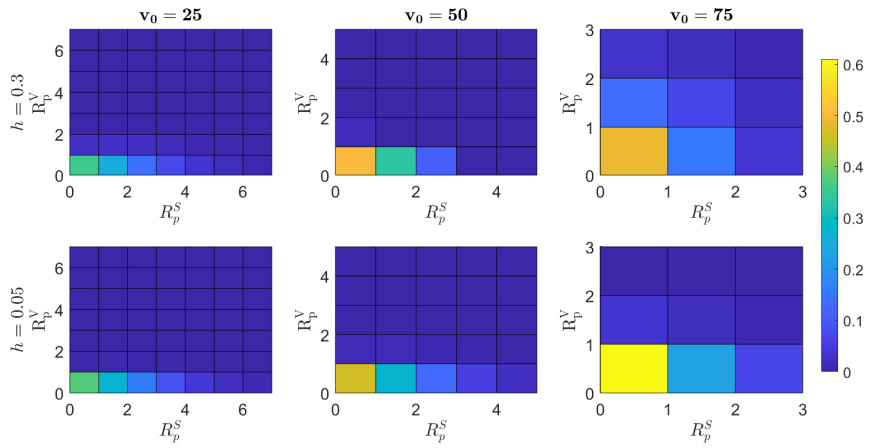


Figure 8: Joint mass distribution function of (R_p^V and R_p^S) for several values of h and vaccination levels in a population of $N = 101$ individuals with an initial infective individual, $\beta = 1.2$, $\gamma = 1$ and $\xi = 0.01$

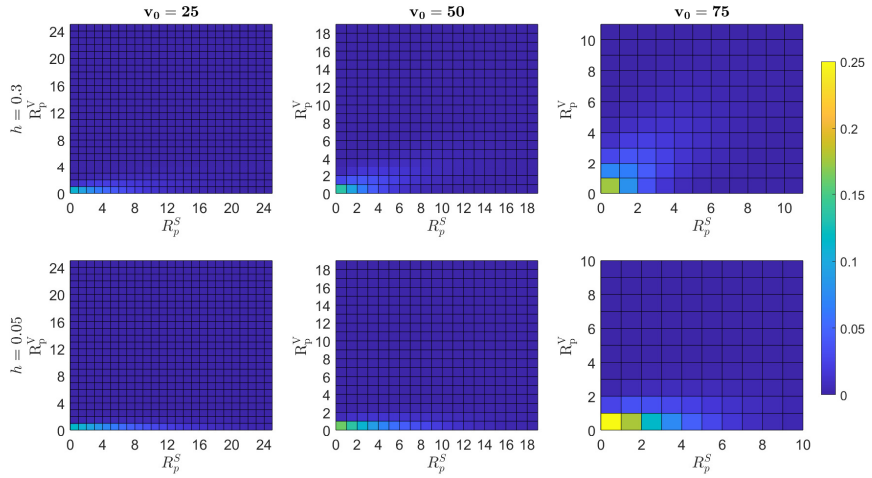


Figure 9: Joint mass distribution function of (R_p^V and R_p^S) for several values of h and vaccination levels in a population of $N = 101$ individuals with an initial infective individual and $\beta = 9$, $\gamma = 1$ and $\xi = 0.01$

Figure 8 and 9 represent joint mass distributions of (R_p^V, R_p^S) for $\beta = 1.2$ and $\beta = 9$, respectively, for $v_0 \in \{25, 50, 75\}$ and for $h \in \{0.05, 0.3\}$.

The behaviour of these distributions are similar to Figure 3 and 4. We point out that it is necessary more mass points to accumulate the 99% of the

probability distribution of (R_p^V, R_p^S) than in that of (R_{e0}^V, R_{e0}^S). Also probabilities in each point are smaller. This is accorded with the logic because this distribution counts the infections produced by the index cause and his/her successor and therefore is expected more infections and in consequence we need more mass points to cover the accumulate probability required.

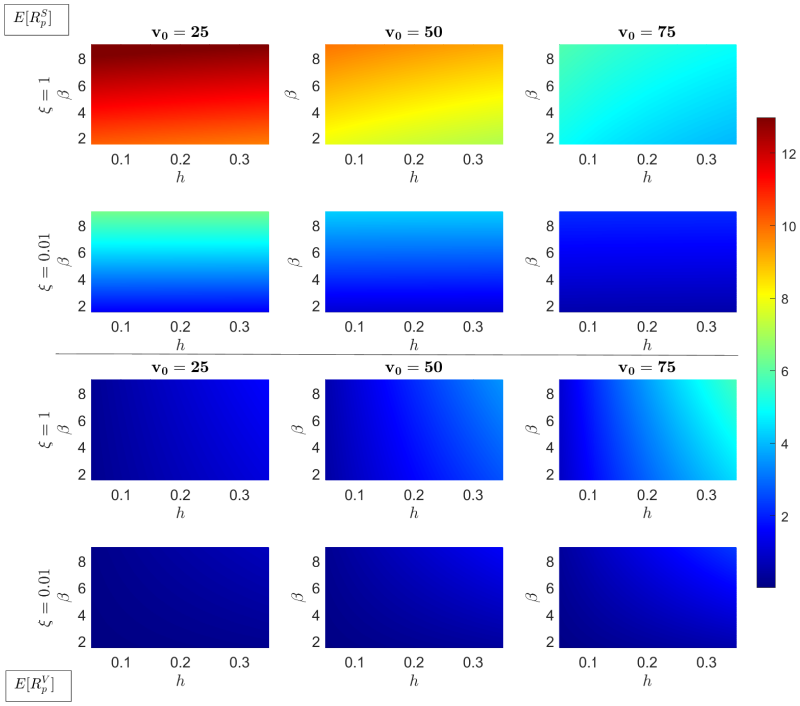


Figure 10: $E[R_p^S]$ and $E[R_p^V]$ as function of β and h. Different scenarios arise in a population of $N = 101$ individuals, with an initial infectious individual and $\gamma = 1$ when $v_0 \in \{25, 50, 75\}$ and $\xi \in \{0.01, 1\}$

In Figure 10, we represent the $E[R_p^S]$ (top of the figure) and $E[R_p^V]$ (botton of the figure) as a function of the internal transmission rate β and the vaccine failure probability h for vaccine coverage, $v_0 \in \{25, 50, 75\}$ and external contact rates, $\xi \in \{0.01, 1\}$.

The expected number of infections to susceptible individuals caused by all the infective individuals prior the firs recovery is greater than those to vaccinated individuals, for low vaccine failure, showing the importance of the vaccination procedures. Vaccine failure probabilities greater than 0.3 produce

an opposite behavior. Also when we are dealing with large external contact rates (e.g.; $\xi = 1$), $E[R_p^S] < E[R_p^V]$ when considering internal contact rates greater than 7.8 in combination with significant vaccine probability $h = 0.3$. The effect of the internal contact rate β and the vaccine failure probability h for $E[R_p^S]$ and $E[R_p^V]$ is similar to Figure 5.

In contrast to Figure 5 large external contact rates ξ (e.g.; $\xi = 1$) produce greater values of $E[R_p^V]$ and $E[R_p^S]$. This is a logic behaviour because with large external transmission rates there are more infections to susceptible and infected individuals and the average number of infections produced by the infected individuals in the population will be larger.

For increasing vaccine coverage produces greater values of $E[R_p^V]$ due to there are more vaccinated individuals in the population. For the same reason, when we increase the vaccine coverage we obtain smaller values of $E[R_p^S]$. The effect of the vaccine efficacy for large/small vaccines coverage is as stated in Figure 5.

Table 2: Summary statistics for R_p^V and R_p^S

β	h	$E[R_p^S]$	$\sigma[R_p^S]$	$CV[R_p^S]$	$E[R_p^V]$	$\sigma[R_p^V]$	$CV[R_p^V]$
1.2	0.05	0.9196	1.1860	1.2897	0.0466	0.2189	4.6974
5	0.05	2.5751	2.7818	1.0803	0.1350	0.3882	2.8756
9	0.05	4.2509	4.2596	1.0020	0.2307	0.5281	2.2891
1.2	0.30	0.8995	1.1725	1.3035	0.2727	0.5632	2.0653
5	0.30	2.5547	2.7710	1.0847	0.7935	1.1504	1.4498
9	0.30	4.2333	4.2520	1.0044	1.3482	1.7108	1.2690

In Table 2, we recompile some summary statistics of interest of the variables R_p^S and R_p^V. In particular we show the mean, standard deviation and coefficient of variation of these variables for $\beta \in \{1.2, 5, 9\}$ and $h \in \{0.05, 0.3\}$, when $\xi = 0.01$, $v_0 = s_0 = 50$ and there is a single initial infected individual in the population.

As we expected, average values and standard deviations are greater for R_p^S than for R_p^V due to the protection that confers the vaccine. In contrast, we obtain greater coefficient of variations for R_p^V than for R_p^S for the same reason explained in Table 1. The effect of the internal contact rate and the vaccine failure probability have the same behaviour as we stated in Table 1.

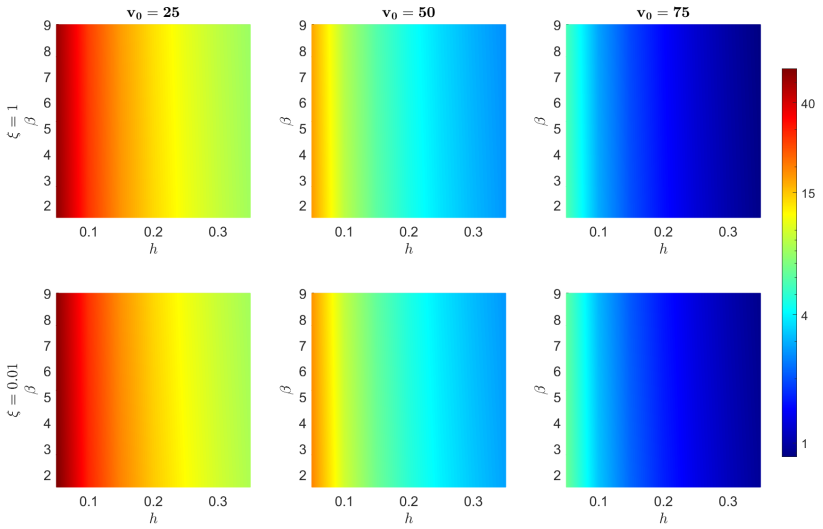


Figure 11: $E[R_p^S]/E[R_p^V]$ as function of β and h. Different scenarios arise in a population of $N = 101$ individuals with an initial infectious individual and $\gamma = 1$, when $v_0 \in \{25, 50, 75\}$ and $\xi \in \{0.01, 1\}$

In Figure 11, we represent the ratio $E[R_p^S]/E[R_p^V]$ as a function of β and h, for vaccine coverage varying in $\{25, 50, 75\}$ and external contact rate $\xi \in \{0.01, 1\}$.
When we increase vaccine failure, ratios decrease because vaccinated individuals are more vulnerable to get the infection and the expected number of infection to vaccinated individuals will be larger.

When at most the 50% is vaccinated, we obtain ratios greater than 1 and it means that population infect more susceptible individuals than vaccinated individuals.

6. Conclusions

This paper deals with a stochastic SIR-type model where an external source of infection has been considered and vaccination is implemented as a health control measure. The evolution of an infectious disease is modeled in term of a three-dimensional continuous-time Markov chain.

Our interest is to quantify the expansion of an epidemic process by analyzing the number of infections produced by a typical infective in the population prior his/her recovery (R_{e0}) and the number of infections produced by all

the individuals in the population before the first recovery occurs (R_p). These descriptors are more appropriated than the basic and control reproduction numbers, when we are dealing with small-to-moderate size populations.

The main contribution of the paper is that we have defined random variables that are able to quantify the potential transmission of an epidemic distinguishing in the susceptible or vaccinates pools of individuals in the population. In this context, one can understand better the effect of vaccination in the spread of a pathogen. Furthermore, we provide recursive methods for calculating the probabilistic behaviour of the random variables described. We have illustrated our methodology by carrying out a numerical analysis on model parameters. Numerical results are obtained through Algorithms 1, Algorithm 2 and Remark 1, and they will be completed by analyzing the dependency level of each marginal random variable of (R_{e0}^V, R_{e0}^S) and (R_p^V, R_p^S).

Another assumptions for the infectious disease dynamics is a latency period and temporal effectiveness of the vaccine can be considered and this is the aim of our future work.

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Appendices

Appendix A

Additional work on Chapter 2

Appendix A complements the research work described in [121].

For ease of reading, we recall that in that investigation we analyze the stochastic SVIS model with external source of infection and imperfect vaccine and we define the random variables, R_{e0} and R_p in a post-vaccination context. R_{e0}, is defined as the number of infective individuals that arise from contagions caused directly by the index case, and R_p counts all the infections that take place within the population, no matter who is the infectious spreader, before the first recovery occurs.

In the above cited work, specifically in Section 2.1, we point that the stationary distribution of the CTMC exists and assigns mass to every state with no vaccinated individuals. Thus in this Appendix we derive a complete stationary analysis of the Markov chain by providing the stationary distribution in terms of the model parameters and we demonstrate that the expression obtained agrees with the one provided in [270], for the stochastic SIS model with external source of infection.

In addition, in [121] (after Equation (16)) we point that numerical results appearing in Section 4, were obtained trough algorithms that were not stated in the cited work and we also provide them.

We extend the investigation in [121], by conducting a sensitivity analysis where elasticities for the mean and standard deviation of R_{e0} and R_p are derived.

Matrices and rates involved in this Chapter, have the same description and notation as in [121].

A.1 Stationary distribution of the SVIS model

In this section we analyze the stationary distribution of the CTMC, X, with state space S and infinitesimal generator $\mathbf{Q}$ described in [121].

We denote this stationary distribution by $p_{v,i}$, which is defined for any $(v,i) \in \mathsf{S}$ as follows

$$p_{v,i} = \lim_{t\to\infty} P\{V(t) = v, I(t) = i].$$

To obtain the stationary distribution, we start analyzing the CTMC, X, and classifying its states. As we made in [121], we organize the state space by levels as follows

$$\mathsf{S} = \cup_{v=0}^{v_0} L(v).$$

Each level $L(v)$ with $0 \leq v \leq v_0$ corresponds to a communicating class of states and in consequence, the CTMC X, is not an irreducible one. In addition, $L(0)$, is a single absorbing set of states and it is accessible from the rest of transient levels, $L(v)$, with $1 \leq v \leq v_0$. In that sense, the CTMC, X, will leave the transient levels and will visit the absorbing level, $L(0)$, in a finite time with probability one and remains there forever. In consequence, the stationary distribution is concentrated on the absorbing set $L(0)$,

$$\lim_{t\to\infty} P[V(t) = v, I(t) = i] = \begin{cases} 0, & \text{if } (v,i) \in \cup_{v=1}^{N} L(v), \\ p_{0,i}, & \text{if } (v,i) \in L(0). \end{cases}$$

$L(0)$ is a closed communicating class with a finite number of states and all its states are positive recurrent ones. Consequently, the stationary distribution is the unique solution of the following linear system of equations

$$\begin{aligned} \mathbf{P_0}^T \mathbf{Q_{0,0}} &= \mathbf{0}_{N+1}^T \\ \mathbf{P_0}^T \mathbf{1}_{N+1} &= 1, \end{aligned} \tag{A.1}$$

where $P_0 = (p_{0,0}, ..., p_{0,N})^T$. $\mathbf{0}_j$ and $\mathbf{1}_j$ are all-zeros and all-ones vectors, respectively, of dimension j and in what follows have the same description.

As we are dealing with a birth and death type process, the stationary distribution exists only if system (A.1) has unique and non-trivial solution and it happens when

$$\sum_{i=1}^{N} \frac{\alpha_{00}...\alpha_{0,i-1}}{\gamma_1...\gamma_i} < \infty,$$

where for $i = 0, ..., N$

$$\begin{aligned} \alpha_{0,i} &= \alpha^*_{0,i} + \widetilde{\alpha}_{0,i} = (N-i)(\beta i/N + \xi), \\ \gamma_i &= \gamma i, \end{aligned}$$

and the stationary distribution is given by

$$\left.\begin{aligned} p_{0i} = &\ \tfrac{\alpha_{00}...\alpha_{0,i-1}}{\gamma_1...\gamma_i} p_{00}, \text{ for } 1 \le i \le N \\ p_{00} = &\ \tfrac{1}{1+\sum_{i=1}^{N} \frac{\alpha_{00}...\alpha_{0,i-1}}{\gamma_1...\gamma_i}}, \text{ for } i = 0 \end{aligned}\right\}. \tag{A.2}$$

In terms of the model parameters Equations (A.2) can be expressed as follows

$$\left.\begin{aligned} p_{0i} = &\ p_{00}\tbinom{N}{i} \textstyle\prod_{m=0}^{k-1}(\xi + \beta m/N), \text{ for } 1 \le i \le N \\ p_{00} = &\ \tfrac{1}{1+\sum_{i=1}^{N} \binom{N}{i} \prod_{m=0}^{i-1}(\xi+\beta m/N)}, \text{ for } i = 0 \end{aligned}\right\}. \tag{A.3}$$

We demonstrate that the stationary distribution (A.3), agrees with the stationary distribution of an SIS-type model with an external source of infection provided by Stone et al. in Expressions (14) and (15), in [270].

A.2 Additional R_p-Algorithms

Next we provide efficient algorithms to compute factorial moments and probability mass functions of the population reproduction number, R_p, applying

inverse matrix methods.

A.2.1 R_p-Factorial moments algorithm

Algorithm 1. *Computation of R_p-Factorial moments. Let k be a non-negative integer. Given an initial number of vaccinated individuals, v_0, moments of order k of the random variable R_p, $\mathbf{M_v^k}$, can be determined numerically, according to the following scheme, for any $0 \leq v \leq v_0$:*

Step 1. Set $j = 0$.

Set 1a. For $0 \leq v \leq v_0$, set $\mathbf{M_v^0} = \mathbf{e_v}$.

Step 2. Set $j = 1$.

Step 2a. Set $v = 0$, and compute $\mathbf{W_0^j} = -j\widetilde{\mathbf{D}}_\mathbf{0}\widetilde{\mathbf{M}}_\mathbf{0}^{\mathbf{j-1}}$.

Step 2b. Compute $\mathbf{M_0^j} = \mathbf{H_0^{-1}W_0^j}$. Set $v = 1$. If $v_0 = 0$, go to Step 3.

Step 2c. Compute $\mathbf{W_v^j} = -\mathbf{D}_v\left(j\widehat{\mathbf{M}}_{v-1}^{j-1} + \widehat{\mathbf{M}}_{v-1}^{j}\right) - j\widetilde{\mathbf{D}}_\mathbf{v}\widetilde{\mathbf{M}}_\mathbf{v}^{\mathbf{j-1}}$.

Step 2d. Compute $\mathbf{M_v^j} = \mathbf{H_v^{-1}W_v^j}$. Set $v = v+1$. If $v \leq v_0$, go to Step 2c.

Step 3. Set $j = j + 1$. If $j \leq k$, go to Step 2a.

A.2.2 R_p-Probability mass functions algorithm

Algorithm 2. *Computation of R_p-Probability mass points, $\mathbf{z_v^k}$, given an initial number of vaccinated individuals, v_0 and for any integer $k \geq 0$ and $0 \leq v \leq v_0$:*

Step 1. Set $v = 0$.

Step 1a. Set $j = 0$ and compute $\mathbf{z_0^0} = \mathbf{d}_\gamma {\mathbf{D_Q}}^{-1}\mathbf{e_0}$.

Step 1b. Set $j = j + 1$. While $j \leq k$, compute $\mathbf{z_0^j} = {\mathbf{D_Q}}^{-1}\widetilde{\mathbf{D}}_\mathbf{v}\widetilde{\mathbf{z}}_\mathbf{v}^{\mathbf{k-1}}$.

Step 2. Set $v = 1$. If $v_0 = 0$, stop.

Step 2a. set $j = 0$ and compute $\mathbf{z_v^0} = \mathbf{d}_\gamma {\mathbf{D_Q}}^{-1}\mathbf{e_v}$.

Step 2b. Set $j = j + 1$. While $j \leq k$, compute

$$\mathbf{x_v^j} = -\mathbf{D_Q^{-1}}((1 - \delta_{v,0})\mathbf{D_v}\widehat{\mathbf{z}}_{\mathbf{v-1}}^{\mathbf{k-1}} + \widetilde{\mathbf{D}}_{\mathbf{v}}\widetilde{\mathbf{z}}_{\mathbf{v}}^{\mathbf{k-1}}).$$

Step 3. Set $v = v + 1$. If $v \leq v_0$, go to Step 2a.

A.3 Sensitivity analysis for R_{e0} and R_p

In this section we complement the analysis of the random variables R_{e0} and R_p in [121], by computing their elasticities for the mean and standard deviation.

A.3.1 Sensitivity analysis of the factorial moments of R_{e0}

To address this study, we start computing the first derivatives of the conditional R_{e0}-Factorial moments of order $k \geq 1$, $m_{v,i}^k$, for any $(v, i) \in \widehat{\mathcal{S}}$, with respect to the model parameters $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)^T = (\beta, \xi, \gamma, h)^T$.

The first derivative of the factorial moments of order k, respect to the parameter θ_r, with $r \in \{1, 2, 3, 4\}$ and denoted by $\frac{\partial m_{v,i}^k}{\partial \theta_r}$, gives the exchange rate of, $m_{v,i}^k$, for changing values of θ_r, when the rest of the parameters are constant. We compute them as follows.

We recall that Equation (7) in [121], involves factorial moments of order k, $m_{v,i}^k$, and has the following expression for any $(v, i) \in \widehat{\mathcal{S}}$

$$
\begin{aligned}
m_{v,i}^{k} &= (1-\delta_{v,0})\left(\frac{\beta_{v,i}}{q_{v,i}}m_{v-1,i+1}^{k}+k\frac{\beta_{v,i}^{*}}{q_{v,i}}m_{v-1,i+1}^{k-1}\right)+(1-\delta_{i,1})\frac{\gamma_{i-1}}{q_{v,i}}m_{v,i-1}^{k} \\
&\quad +(1-\delta_{i,N-v})\left(\frac{\alpha_{v,i}}{q_{v,i}}m_{v,i+1}^{k}+k\frac{\alpha_{v,i}^{*}}{q_{v,i}}m_{v,i+1}^{k-1}\right), \qquad \text{(A.4)}
\end{aligned}
$$

where $\alpha_{v,i}=\alpha_{v,i}^{*}+\widetilde{\alpha}_{v,i}$, $\beta_{v,i}=\beta_{v}^{*}+\widetilde{\beta}_{v,i}$ and boundary condition $m_{v,i}^{0}=1$. In what follows we omit the corresponding Dirac's Delta terms, $\delta_{a,b}$, to ease notation.

Taking derivatives on (A.4), respect to a single parameter of the model, keeping the others constant, we obtain the following expression that involves first derivatives of factorial moments and factorial moments, conditioned to an initial state, for any $k\geq 0$ and $(v,i)\in\widehat{\mathcal{S}}$

$$
\begin{aligned}
- &\quad \gamma_{i-1}\frac{\partial m_{v,i-1}^{k}}{\partial\theta_r}+q_{v,i}\frac{\partial m_{v,i}^{k}}{\partial\theta_r}-\alpha_{v,i}\frac{\partial m_{v,i+1}^{k}}{\partial\theta_r}=\beta_{v,i}\frac{\partial m_{v-1,i+1}^{k}}{\partial\theta_r} \qquad \text{(A.5)}\\
+ &\quad k\beta_{v}^{*}\frac{\partial m_{v-1,i+1}^{k-1}}{\partial\theta_r}+k\alpha_{v,i}^{*}\frac{\partial m_{v,i+1}^{k-1}}{\partial\theta_r}+\frac{\partial\beta_{v,i}}{\partial\theta_r}m_{v-1,i+1}^{k}+k\frac{\partial\beta_{v}^{*}}{\partial\theta_r}m_{v-1,i+1}^{k-1}\\
+ &\quad k\frac{\partial\alpha_{v,i}^{*}}{\partial\theta_r}m_{v,i+1}^{k-1}+\frac{\partial\gamma_{i-1}}{\partial\theta_r}m_{v,i-1}^{k}-\frac{\partial q_{v,i}}{\partial\theta_r}m_{v,i}^{k}+\frac{\partial\alpha_{v,i}}{\partial\theta_r}m_{v,i+1}^{k}.
\end{aligned}
$$

We observe that first derivatives of moments of order k are obtained from first derivatives of factorial moments of one order less and factorial moments of order k and one order less.

We continue introducing the following notation for the derivatives of conditional moments respect to each parameter θ_j, with $r\in\{1,2,3,4\}$

$$
\frac{\partial m_{v,i}^{k}}{\partial\theta_r}=A_{v,i}^{k}(\theta_r),
$$

and we define $\rho^k_{v,i}(\theta_r)$ as

$$\begin{aligned}\rho^k_{v,i}(\theta_r) &= \frac{\partial\beta_{v,i}}{\partial\theta_r}m^k_{v-1,i+1} + k\frac{\partial\beta^*_v}{\partial\theta_r}m^{k-1}_{v-1,i+1} + k\frac{\partial\alpha^*_{v,i}}{\partial\theta_r}m^{k-1}_{v,i+1} \\ &\quad + \frac{\partial\gamma_{i-1}}{\partial\theta_r}m^k_{v,i-1} - \frac{\partial q_{v,i}}{\partial\theta_r}m^k_{v,i} + \frac{\partial\alpha_{v,i}}{\partial\theta_r}m^k_{v,i+1}.\end{aligned}$$

According the above notation Equation (A.5) can be expressed for any θ_r and $k \geq 0$ with $(v,i) \in \widehat{\mathcal{S}}$ as follows

$$\begin{aligned}&-\gamma_{i-1}A^k_{v,i-1}(\theta_r) + q_{v,i}A^k_{v,i}(\theta_r) - \alpha_{v,i}A^k_{v,i+1}(\theta_r) = \\ &\beta_{v,i}A^k_{v-1,i+1}(\theta_r) + k\beta^*_v A^{k-1}_{v-1,i+1}(\theta_r) + k\alpha^*_{v,i}A^{k-1}_{v,i+1}(\theta_r) + \rho^k_{v,i}(\theta_r),\end{aligned} \tag{A.6}$$

and boundary conditions, $A^0_{v,i}(\theta_r) = 0$ for any $(v,i) \in \widehat{\mathcal{S}}$.

Computing derivatives of the rates $\alpha^*_{v,i}$, $\alpha_{v,i}$, β^*_v, $\beta_{v,i}$, γ_{i-1} and $q_{v,i}$ respect to each model parameter, θ_r, we obtain the following expressions for each $\rho^k_{v,i}(\theta_r)$, with $\theta_r \in \{\beta, \xi, \gamma, h\}$

$$\rho^k_{v,i}(\theta_j) = \begin{cases} \frac{hvi}{N}m^k_{v-1,i+1} + k\frac{hv}{N}m^{k-1}_{v-1,i+1} + k\frac{N-v-i}{N}m^{k-1}_{v,i+1} & \\ -(\frac{(N-v-i)i}{N} + \frac{hvi}{N})m^k_{v,i} + \frac{(N-v-i)i}{N}m^k_{v,i+1}, & \text{if } \theta_j = \beta, \\ hvm^k_{v-1,i+1} - ((N-v-i) + hv)m^k_{v,i} & \\ +(N-v-i)m^k_{v,i+1}, & \text{if } \theta_j = \xi, \\ (i-1)(m^k_{v,i-1} - m^k_{v,i}), & \text{if } \theta_j = \gamma, \\ v(\frac{\beta i}{N} + \xi)m^k_{v-1,i+1} + k\frac{\beta v}{N}m^{k-1}_{v-1,i+1} - v(\frac{\beta i}{N} + \xi)m^k_{v,i}, & \text{if } \theta_j = h. \end{cases}$$

Given a fixed initial number of vaccinated individuals, v_0 and for each model parameter, θ_r, and any $k > 0$, we obtain from Equation (A.6) a system of linear equations for any $0 \leq v \leq v_0$ and $1 \leq i \leq N - v$. This linear system

of equations can be expressed in matrix form for any level $0 \leq v \leq v_0$ and θ_r with $r \in \{1, 2, 3, 4\}$ as follows

$$\begin{aligned}
\mathbf{A_v^0}(\theta_\mathbf{r}) &= \mathbf{0}_{N-v}, \text{ for } 0 \leq v \leq v_0, && \text{(A.7)} \\
\mathbf{R_v}\mathbf{A_v^k}(\theta_\mathbf{r}) &= (1-\delta_{v,0})(\mathbf{D}_{\beta,v}\widehat{\mathbf{A}}^k_{\mathbf{v-1}}(\theta_r) + k\mathbf{D}^*_{\beta,v}\widehat{\mathbf{A}}^{k-1}_{\mathbf{v-1}}(\theta_r)) + k\mathbf{D}^*_{\alpha,v}\widetilde{\mathbf{A}}^{k-1}_{\mathbf{v}}(\theta_r) \\
&+ (1-\delta_{v,0})(\mathbf{D}'_{\beta,v}\widehat{\mathbf{m}}^k_{\mathbf{v-1}} + k(\mathbf{D}^*_{\beta,v})'\widehat{\mathbf{m}}^{k-1}_{\mathbf{v-1}}) \\
&+ k(\mathbf{D}^*_{\alpha,v})'\widetilde{\mathbf{m}}^{k-1}_{\mathbf{v}} - \mathbf{R_v}'m^k_{v,i}. && \text{(A.8)}
\end{aligned}$$

Matrices appearing in Equations (A.7) and (A.8) are described as follows: $\mathbf{R_v}$ and its gradient matrix $\mathbf{R_v}'$ are tri-diagonal square matrices of dimension $N - v$ with non-null entries given by

$$\mathbf{R_v}(i,j) = \begin{cases} -\gamma_{i-1}, & \text{if } j = i-1 \text{ and } 2 \leq i \leq N-v, \\ q_{v,i}, & \text{if } j = i \text{ and } 1 \leq i \leq N-v, \\ -\alpha_{v,i}, & \text{if } j = i+1 \text{ and } 1 \leq i \leq N-v-1, \end{cases}$$

$$\mathbf{R_v}'(i,j) = \begin{cases} -\frac{\partial \gamma_{i-1}}{\partial \theta_r}, & \text{if } j = i-1 \text{ y } 2 \leq i \leq N-v, \\ \frac{\partial q_{v,i}}{\partial \theta_r}, & \text{if } j = i \text{ and } 1 \leq i \leq N-v, \\ -\frac{\partial \alpha_{v,i}}{\partial \theta_r}, & \text{if } j = i+1 \text{ and } 1 \leq i \leq N-v-1. \end{cases}$$

$\mathbf{D}_{\beta,\mathbf{v}}$,$\mathbf{D}^*_{\beta,\mathbf{v}}$ $\mathbf{D}^*_{\alpha,\mathbf{v}}$ and their respective gradient matrices $\mathbf{D}'_{\beta,\mathbf{v}}$,$(\mathbf{D}^*_{\beta,\mathbf{v}})'$ and $(\mathbf{D}^*_{\alpha,\mathbf{v}})'$ are diagonal matrices of dimension $(N-v)$, with non-null diagonal elements given by $\mathbf{D}_{\beta,v}(i,i) = \beta_{v,i}$, $\mathbf{D}^*_{\beta,v}(i,i) = \beta^*_{v,i}$, $\mathbf{D}^*_{\alpha,v}(i,i) = \alpha^*_{v,i}$, $\mathbf{D}'_{\beta,\mathbf{v}}(i,i) = \frac{\partial \beta_{v,i}}{\partial \theta_r}$, $\mathbf{D}^*_{\beta,\mathbf{v}}{}'(i,i) = \frac{\partial \beta^*_{v,i}}{\partial \theta_r}$, $\mathbf{D}^*_{\alpha,\mathbf{v}}{}'(i,i) = \frac{\partial \alpha^*_{v,i}}{\partial \theta_r}$, for $1 \leq i \leq N-v$.
The rest of vectors are defined as follows

$$
\begin{aligned}
\mathbf{A_v^k} &= (A_{v,1}^k, ..., A_{v,N-v}^k)^T, \\
\widetilde{\mathbf{A}}_\mathbf{v}^\mathbf{k} &= (A_{v,2}^k, ..., A_{v,N-v}^k, 0)^T, \\
\widehat{\mathbf{A}}_\mathbf{v}^\mathbf{k} &= (A_{v,2}^k, ..., A_{v,N-v}^k)^T, \\
\mathbf{m_v^k} &= (m_{v,1}^k, ..., m_{v,N-v}^k)^T, \\
\widetilde{\mathbf{m}}_\mathbf{v}^\mathbf{k} &= (m_{v,2}^k, ..., m_{v,N-v}^k, 0)^T, \\
\widehat{\mathbf{m}}_\mathbf{v}^\mathbf{k} &= (m_{v,2}^k, ..., m_{v,N-v}^k)^T.
\end{aligned}
$$

We obtain the first derivatives of the factorial moments of order $k \geq 1$ of the random variable R_{e0}, solving the system of linear equations (A.8) applying an inverse matrix method for each parameter, θ_r and taking into account the boundary condition (A.7), in a recursive way starting from $k = 1$ in natural order and for $0 \leq v \leq v_0$.

For a given state $(v, i) \in \widehat{\mathsf{S}}$, derivatives of conditioned expected values and standard deviations respect to any model parameter, θ_r, denoted by $\frac{\partial E[R_{e0}]}{\partial \theta_r}$ and $\frac{\partial Sd[R_{e0}]}{\partial \theta_r}$ respectively, can be computed as follows

$$
\begin{aligned}
\frac{\partial E[R_{e0}]}{\partial \theta_r} &= \frac{\partial m_{v,i}^1}{\partial \theta_r} = A_{v,i}^1(\theta_r), && \text{(A.9)} \\
\frac{\partial Sd[R_{e0}]}{\partial \theta_r} &= \frac{\partial (m_{v,i}^2 + m_{v,i}^1 - (m_{v,i}^1)^2)^{\frac{1}{2}}}{\partial \theta_r} \\
&= \frac{A_{v,i}^2(\theta_r) + A_{v,i}^1(\theta_j) - 2m_{v,i}^1 A_{v,i}^1(\theta_r)}{2Sd[R_{e0}]}. && \text{(A.10)}
\end{aligned}
$$

Applying elasticity definition (1.5) appearing in Section 1.1.2 and Expressions (A.9) and (A.10), the elasticities for the mean and standard deviation of R_{e0},

conditioned to any state $(v,i) \in \widehat{\mathcal{S}}$, respect to each model parameter θ_r are given by

$$\varepsilon_{E[R_{e0}]} = \frac{\partial E[R_{e0}]/\partial \theta_r}{E[R_{e0}]/\theta_r} = \frac{A^1_{v,i}(\theta_r)}{m^1_{v,i}/\theta_r},$$

$$\varepsilon_{Sd[R_{e0}]} = \frac{\partial Sd[R_{e0}]/\partial \theta_r}{Sd[R_{e0}]/\theta_r} = \frac{\theta_r(A^2_{v,i}(\theta_r) + A^1_{v,i}(\theta_r) - 2m^1_{v,i}A^1_{v,i}(\theta_r))}{2Sd^2[R_{e0}]}.$$

A.3.2 Sensitivity analysis of the factorial moments of R_p

In this section we derive a sensitivity analysis for the random variable, R_p. We apply the same methodology as we made for R_{e0}, so we omit the procedure and only we give the general results obtained.

We recall that factorial moments of order $k \geq 1$, satisfy the following equation for any $(v,i) \in \widehat{\mathcal{S}}$

$$q_{v,i}M^k_{v,i} \;=\; \alpha_{v,i}\left(kM^{k-1}_{v,i+1} + M^k_{v,i+1}\right) + \beta_{v,i}\left(kM^{k-1}_{v-1,i+1} + M^k_{v-1,i+1}\right),$$

with boundary conditions

$$M^0_{v,i} = 1.$$

We introduce the following notation for the first derivatives of the R_p-Factorial moments order k, respect to each parameter θ_r, $\frac{\partial M^k_{v,i}}{\partial \theta_r}$, and $\alpha^k_{v,i}(\theta_r)$:

$$\begin{aligned}\frac{\partial M^k_{v,i}}{\partial \theta_r} &= \mathbb{A}^k_{v,i}(\theta_r),\\ \alpha^k_{v,i}(\theta_r) &= -\frac{\partial q_{v,i}}{\theta_r} M^k_{v,i} + \frac{\partial \alpha_{v,i}}{\theta_r}[kM^{k-1}_{v,i+1} + M^k_{v,i+1}]\\ &\quad + \frac{\partial \beta_{v,i}}{\partial \theta_r}[kM^{k-1}_{v-1,i+1} + M^k_{v-1,i+1}].\end{aligned}$$

Taking derivatives on Equation (A.11), respect to each parameter θ_r, and applying the above notation, we obtain the following Equation for any $k \geq 0$ and any $(v,i) \in \widehat{\mathcal{S}}$,

$$\begin{aligned}q_{v,i}\mathbb{A}^k_{v,i}(\theta_r) - \alpha_{v,i}\mathbb{A}^k_{v,i+1}(\theta_r) &= \alpha_{v,i}k\mathbb{A}^{k-1}_{v,i+1}(\theta_r) + \beta_{v,i}[k\mathbb{A}^{k-1}_{v-1,i+1}(\theta_r)\\ &+ \mathbb{A}^k_{v-1,i+1}(\theta_r)] + \alpha^k_{v,i}(\theta_r), \qquad (A.11)\end{aligned}$$

and boundary conditions

$$\mathbb{A}^0_{v,i}(\theta_r) = 0, \qquad (A.12)$$

with

$$\rho^k_{v,i}(\theta_r) = \begin{cases} -(\frac{(N-v-i)i}{N} + \frac{hvi}{N})M^k_{v,i} + \frac{(N-v-i)i}{N}[kM^{k-1}_{v,i+1} + M^k_{v,i+1}] & \\ +\frac{hvi}{N}[kM^{k-1}_{v-1,i+1} + M^k_{v-1,i+1}], & \text{if } \theta_r = \beta,\\ -[(N-v-i)+hv]M^k_{v,i} + (N-v-i)[kM^{k-1}_{v,i+1} + M^k_{v,i+1}] & \\ +hv[kM^{k-1}_{v-1,i+1} + M^k_{v-1,i+1}], & \text{if } \theta_r = \xi,\\ -iM^k_{v,i}, & \text{if } \theta_r = \gamma,\\ (\frac{\beta i}{N} + \xi)v[kM^{k-1}_{v-1,i+1} + M^k_{v-1,i+1} - M^k_{v,i}], & \text{if } \theta_r = h.\end{cases}$$

At any level $0 \leq v \leq v_0$, Equations (A.11), can be expressed in matrix form

for $k \geq 0$ and $1 \leq i \leq N - v$, as follows

$$\begin{aligned} \mathbf{A_v^0}(\theta_\mathbf{r}) &= \mathbf{0}_{N-v}, & \text{(A.13)} \\ \mathbf{H_v A_v^k}(\theta_\mathbf{r}) &= k\mathbf{L_v}\widehat{\mathbf{A}}_\mathbf{v}^{\mathbf{k-1}}(\theta_\mathbf{r}) + \mathbf{D_v}[k\widetilde{\mathbf{A}}_{v-1}^{k-1}(\theta_r) + \widetilde{\mathbf{A}}_{v-1}^{k}(\theta)] - \mathbf{H'}_v(\theta_r)M_v^k \\ &+ \mathbf{D'_v}(\theta_r)[\widetilde{M}_{v-1}^{k-1} + \widetilde{M}_{v-1}^{k}] + k\mathbf{L'_v}(\theta_r)\widehat{\mathbf{M}}_\mathbf{v}^{\mathbf{k-1}}, & \text{(A.14)} \end{aligned}$$

where

$$\begin{aligned} A_v^k &= (\mathbb{A}_{v,1}^k, ..., \mathbb{A}_{v,N-v}^k)^T, \\ \widetilde{A}_{v-1}^k &= (\mathbb{A}_{v-1,2}^k, ..., \mathbb{A}_{v-1,N-v}^k)^T, \\ \widehat{A}_v^{k-1} &= (\mathbb{A}_{v,2}^{k-1}, ..., \mathbb{A}_{v,N-v}^{k-1}, 0)^T, \\ \widetilde{M}_{v-1}^k &= (M_{v-1,2}^k, ..., M_{v-1,N-v+1}^k)^T, \\ \widehat{M}_v^{k-1} &= (M_{v,2}^{k-1}, ..., M_{v,N-v}^{k-1}, 0)^T. \end{aligned}$$

$\mathbf{H_v}$ and its gradient matrix $\mathbf{H'_v}$ are squared bi-diagonal matrices of dimension $(N - v)$, with non-null entries given by

$$\mathbf{H_v}(i,j) = \begin{cases} q_{v,i}, & \text{if } j = i \text{ and } 1 \leq i \leq N - v, \\ -\alpha_{v,i}, & \text{if } j = i + 1 \text{ and } 1 \leq i \leq N - v - 1, \end{cases}$$

$$\mathbf{H'_v}(i,j) = \begin{cases} \frac{\partial q_{v,i}}{\partial \theta_r}, & \text{if } j = i \text{ and } 1 \leq i \leq N - v, \\ \frac{-\partial \alpha_{v,i}}{\partial \theta_r}, & \text{if } j = i + 1 \text{ and } 1 \leq i \leq N - v - 1. \end{cases}$$

$\mathbf{D_v}$, $\mathbf{L_v}$ and their respective gradient matrices, $\mathbf{D'_v}$ and $\mathbf{L'_v}$ are diagonal matrices of dimension $(N - v)$, with non-null diagonal elements given by $\mathbf{D_v}(i,i) = \beta_{v,i}$, $\mathbf{D'_v}(i,i) = \frac{\partial \beta_{v,i}}{\partial \theta_r}$, $\mathbf{L_v}(i,i) = \alpha_{v,i}$, $\mathbf{L'_v}(i,i) = \frac{\partial \alpha_{v,i}}{\partial \theta_r}$.

For a given state $(v,i) \in \widehat{\mathcal{S}}$, first derivatives of conditioned expected values and standard deviations of R_p, respect to any parameter, θ_r, can be calculated as follows

$$\begin{aligned}
\frac{\partial E[R_p]}{\partial \theta_r} &= \frac{\partial M^1_{v,i}}{\partial \theta_r} = A^1_{v,i}(\theta_r), \\
\frac{\partial Sd[R_p]}{\partial \theta_r} &= \frac{\partial (M^2_{v,i} + M^1_{v,i} - (M^1_{v,i})^2)^{\frac{1}{2}}}{\partial \theta_r} = \frac{A^2_{v,i}(\theta_r) + A^1_{v,i}(\theta_r) - 2M^1_{v,i}A^1_{v,i}(\theta_r)}{2Sd[R_p]}.
\end{aligned}$$

For any $0 \leq v \leq v_0$ and $1 \leq i \leq N - v$, elasticities for the conditioned mean and standard deviation, for each parameter θ_r, are given by

$$\varepsilon_{E[R_p]} = \frac{\partial E[R_p]/\partial \theta_r}{E[R_p]/\theta_r} = \frac{A^1_{v,i}(\theta_r)}{M^1_{v,i}/\theta_r},$$

$$\varepsilon_{Sd[R_p]} = \frac{\partial Sd[R_p]/\partial \theta_r}{Sd[R_p]/\theta_r} = \frac{\theta_r(A^2_{v,i}(\theta_r) + A^1_{v,i}(\theta_r) - 2M^1_{v,i}A^1_{v,i}(\theta_r))}{2Sd^2[R_p]}.$$

Appendix B

Additional work on Chapter 3

Appendix B complements the research work described in [123].

We recall that in the mentioned article we introduce a threshold for the number of vaccinated individuals in the population denoted by, w, and define the random variables, T_w and N_w.

T_w analyzes the period of time that the infectious process needs to hit the warning level and N_w quantify the epidemic transmission in the vaccinated compartment during that period of time.

In [123], in Remark 1 we point that Equation (7) can be solved recursively starting from the boundary condition appearing in Expression (6). In that sense, we obtained explicit expressions for the T_w-Laplace transforms and also for T_w-Moments and generating and probability mass functions and factorial moments of the random variable, N_w, that they were not included in the published work. In this Appendix we present them to complement the investigation.

The reason for not including explicit expressions in [123], is that since we do

not have closed form expressions for the moments of the random variables analyzed, we prefer to take advantage of the matrix-form results to derive recursive equations in the local sensitivity analysis, involving first derivatives and elasticities of both random variables respect to any parameter.

We use the same notation for matrices and rates as in [123].

B.1 T_w-Laplace transforms theorem

Next we supply with an additional theorem to obtain the Laplace transforms of the random variable, T_w, described in [120]. In this case, we obtain explicit expressions and this result is summarized as follows.

Theorem 1. *For a fixed warning vaccination level w, with $0 \leq w \leq v_0$, and $s \in \mathbb{C}$, with $Re(s) \geq 0$,the set of Laplace transforms $\{\psi_{v,i}(s) : (v,i) \in \widehat{W}\}$ are obtained in a recursive way from the following expressions*

$$\begin{aligned}
\psi_{w,i}(s) &= 1, \text{ for } 0 \leq i \leq N-w, && \text{(B.1)}\\
\psi_{v,N-v}(s) &= \frac{T_{v,N-v}(s)}{C_{v,N-v}(s)}, \text{ for } w+1 \leq v \leq v_0, && \text{(B.2)}\\
\psi_{v,i}(s) &= \left(\prod_{j=i}^{N-v-1} \frac{\lambda_{v,j} C_{v,j-1}(s)}{C_{v,j}(s)}\right) \psi_{v,N-v}(s)\\
&+ \sum_{j=i}^{N-v-1} \frac{T_{v,j}(s)}{C_{v,j}(s)} \left(\prod_{m=i}^{j-1} \frac{\lambda_{v,m} C_{v,m-1}(s)}{C_{v,m}(s)}\right) && \text{(B.3)}
\end{aligned}$$

for $w+1 \leq v \leq v_0$ and $0 \leq i \leq N-v$, where

$$C_{v,j}(s) = \begin{cases} 1, & \text{if } j < 0,\\ (s+q_{v,0}), & \text{si } j = 0,\\ (s+q_{v,j})C_{v,j-1}(s) - \gamma_j \lambda_{v,j-1} C_{v,j-2}(s), & \text{if } 1 \leq j \leq N-v, \end{cases}$$

$$T_{v,j}(s) = \begin{cases} \eta_{v,0}\psi_{v-1,1}(s), & \text{if } j = 0,\\ \gamma_j T_{v,j-1}(s) + \eta_{v,j} C_{v,j-1}(s)\psi_{v-1,j+1}(s), & \text{if } 1 \leq j \leq N-v. \end{cases}$$

Proof. Since the random variable, T_w, is defined as the time until the number of vaccinated individuals reaches the warning level, w, Result (B.1) is trivially true from its definition.

For a fixed warning vaccination level w, and for a fixed $s \in \mathbb{C}$ with $Re(s) \geq 0$, the Laplace transforms appearing in Expression (7) in [123], satisfy the following Equation for $w+1 \leq v \leq v_0$ and $0 \leq i \leq N-v$

$$-\gamma_i \psi_{v,i-1}(s) + (s + q_{v,i})\psi_{v,i}(s) - \lambda_{v,i}\psi_{v,i+1}(s) = \eta_{v,i}\psi_{v-1,i+1}(s). \quad \text{(B.4)}$$

Given a $w+1 \leq v \leq v_0$, the above Equation can be expressed for $0 \leq i \leq N-v-1$, as follows

$$-\gamma_i \psi_{v,i-1}(s) + A_{v,i}(s)\psi_{v,i}(s) - \lambda_{v,i}\psi_{v,i+1}(s) = B_{v,i}(s), 0 \leq i \leq N-v, \text{(B.5)}$$

where $A_{v,i}(s) = s + q_{v,i}$ and $B_{v,i}(s) = \eta_{v,i}\psi_{v-1,i+1}(s)$.
Equations (B.5) can be solved in a recursive way, in the natural order for v, starting from the boundary condition (B.1).
Applying a Forward Elimination Backward Substitution (FEBS) procedure, Equation (B.5) can be expressed in triangular form as

$$C_{v,i}(s)\psi_{v,i}(s) - \lambda_{v,i}C_{v,i-1}(s)\psi_{v,i+1}(s) = T_{v,i}(s), \text{for } 0 \leq i \leq N-v-1, \text{(B.6)}$$

where constants $C_{v,i}(s) = 1$, $C_{v,0}(s) = A_{v,0}(s)$, $T_{v,0}(s) = B_{v,0}$ and, for $1 \leq i \leq N-v$, $C_{v,i}(s) = C_{v,i-1}(s)A_{v,i}(s) - \gamma_i\lambda_{v,i-1}C_{v,i-2}(s)$, $T_{v,i}(s) = \gamma_i T_{v,i-1}(s)$ $+C_{v,i-1}(s)B_{v,i}(s)$.
Working on Equation (B.6), for $i = N-v-1$, and on Equation (B.4) we obtain for $i = N-v$

$$\psi_{v,N-v}(s) = \frac{T_{v,N-v}(s)}{C_{v,N-v}(s)},$$

that matches with the explicit solution appearing in Equation (B.2).

In addition, $\psi_{v,i}(s)$ can be expressed in terms of $\psi_{v,i+1}(s)$ for $w+1 \leq v \leq v_0$ as follows

$$\psi_{v,i}(s) = \frac{T_{v,i}(s) + \lambda_{v,i} C_{v,i-1}(s) \psi_{v,i+1}(s)}{C_{v,i}(s)}, \text{ for } 0 \leq i \leq N-v-1. \quad \text{(B.7)}$$

Iterating Equations (B.7), we obtain Expression (B.3). □

B.2 T_w-Moments theorem

The following theorem help us to obtain the T_w-Moments of order $k \geq 0$, in a recursive way.

Theorem 2. *For a given $k \geq 0$, the central moments of order k, $\{M^k_{v,i}, (v,i) \in \widehat{W}\}$, are obtained in a recursive way from the following expressions*

$$M^0_{v,i} = 1, \textit{ for } (v,i) \in \widehat{W}, \quad \text{(B.8)}$$

$$M^k_{w,i} = 0, \textit{ for } k \geq 1 \textit{ and } 0 \leq i \leq N-w, \quad \text{(B.9)}$$

and for $w+1 \leq w \leq v_0$ moments can be obtained as

$$M^k_{v,N-v} = \frac{T^k_{v,N-v}}{C_{v,N-v}}, \quad \text{(B.10)}$$

$$M^k_{v,i} = \left(\prod_{j=i}^{N-v-1} \frac{\lambda_{v,j} C_{v,j-1}}{C_{v,j}} \right) M^k_{v,N-v} + \sum_{j=i}^{N-v-1} \frac{T^k_{v,j}}{C_{v,j}} \left(\prod_{m=i}^{j-1} \frac{\lambda_{v,m} C_{v,m-1}}{C_{v,m}} \right), \textit{ for } 0 \leq i \leq N-v-1, \quad \text{(B.11)}$$

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

$$C_{v,j} = \begin{cases} 1, & \text{if } j < 0, \\ q_{v,0}, & \text{if } j = 0, \\ q_{v,j}C_{v,j-1} - \gamma_j \lambda_{v,j-1} C_{v,j-2}, & \text{if } 1 \leq j \leq N - v, \end{cases} \tag{B.12}$$

$$T^k_{v,j} = \begin{cases} kM^{k-1}_{v,0} + \eta_{v,0} M^k_{v-1,1}, & \text{if } j = 0, \\ \gamma_j T^k_{v,j-1} + C_{v,j-1}\left(kM^{k-1}_{v,j} + \eta_{v,j} M^k_{v-1,j+1}\right), & \text{if } 1 \leq j \leq N - v. \end{cases} \tag{B.13}$$

Proof. Equations (B.8) and (B.9) are the scalar version of the trivial results and boundary conditions stated in Expressions (8) and (9), respectively, in [123]. The rest of the proof is equivalent to the one of Theorem 1. Equation (B.10) has a similar structure to Equation (B.2) in Theorem 1. In particular, Equations (B.10)-(B.11) come from substitute $\psi_{v,i}(s)$ for $M^k_{v,i}$, $A_{v,i}(s)$ for $A_{v,i} = q_{v,i}$ and $B_{v,i}(s)$ for $B^k_{v,i} = kM^k_{v,i} + \eta_{v,i} M^k_{v-1,i+1}$, in the Forward Elimination Backward Substitution (FEBS) procedure. □

B.3 N_w-Generating functions theorem

Next, we derive a complementary theorem to obtain the N_w-Generating functions described in [120]. In this case, we obtain explicit recursive expressions.

Theorem 3. *For a fixed warning level, w, with $0 \leq w \leq v_0$, and any point z, with $|z| \leq 1$, the generating functions $\{\phi_{v,i} : (v,i) \in \widehat{W}\}$ are obtained as*

follows:

$$\begin{aligned}
\phi_{w,i}(z) &= 1, \textit{ for } 0 \leq i \leq N-w, && \text{(B.14)}\\
\phi_{v,N-v}(z) &= \frac{T_{v,N-v}(z)}{C_{v,N-v}(z)}, \textit{ for } w+1 \leq v \leq v_0, && \text{(B.15)}\\
\phi_{v,i}(z) &= \left(\prod_{j=i}^{N-v-1} \frac{\lambda_{v,j} C_{v,j-1}(z)}{C_{v,j}(z)}\right) \phi_{v,N-v}(z)\\
&+ \sum_{j=i}^{N-v-1} \frac{T_{v,j}(z)}{C_{v,j}(z)} \left(\prod_{m=i}^{j-1} \frac{\lambda_{v,m} C_{v,m-1}(z)}{C_{v,m}(z)}\right), && \text{(B.16)}
\end{aligned}$$

for $w+1 \leq v \leq v_0$ *and* $0 \leq i \leq N-v$*, where empty products in (B.16) and in what follows, are defined as* 1*,*

$$C_{v,j}(z) = \begin{cases} 1, & \textit{if } j < 0,\\ q_{v,0}, & \textit{if } j = 0,\\ q_{v,j} C_{v,j-1}(z) - z\gamma_j \lambda_{v,j-1} C_{v,j-2}(z), & \textit{if } 1 \leq j \leq N-v, \end{cases}$$

$$T_{v,j}(z) = \begin{cases} \eta_{v,0} \phi_{v-1,1}(z), & \textit{if } j = 0,\\ \gamma_j T_{v,j-1}(z) + \eta_{v,j} C_{v,j-1}(z) \phi_{v-1,j+1}(s), & \textit{if } 1 \leq j \leq N-v. \end{cases}$$

Proof. For any $(v,i) \in \widehat{W}$ and given a point z, with $|z| \leq 1$, the generating functions are the solution of the following equations system

$$\phi_{v,i}(s) = \frac{\gamma_i}{q_{v,i}} \phi_{v,i-1}(z) + \frac{\lambda_{v,i}}{q_{v,i}} z \phi_{v,i+1}(z) + \frac{\eta_{v,i}}{q_{v,i}} \phi_{v-1,i+1}(z). \qquad \text{(B.17)}$$

For $v = w$ and $0 \leq i \leq N-w$, generating functions satisfy the boundary conditions $\phi_{w,i}(z) = 1$.

Applying a *Forward Elimination Backward Substitution* (FEBS) procedure, Equation (19) in [123], can be expressed for $w+1 \leq v \leq v_0$, as follows

$$-\gamma_i \phi_{v,i-1} + q_{v,i}\phi_{v,i}(z) - z\lambda_{v,i}\phi_{v,i+1}(z) = \eta_{v,i}\phi_{v-1,i+1}(z). \tag{B.18}$$

For $w+1 \leq v \leq v_0$ and $0 \leq i \leq N-v-1$, Equation (B.18) can be expressed as

$$C_{v,i}\phi_{v,i}(z) - zC_{v,i-1}\lambda_{v,i}\phi_{v,i+1}(z) = T_{v,i}(z).$$

The above Expression is similar to (B.5) in the proof of Theorem 1 so working on Equation (B.19), we obtain the explicit expression for $i = N-v$ presented in (B.15) and $\phi_{v,i}(z)$ can be expressed in terms of $\phi_{v,i+1}(z)$ for $0 \leq i \leq N-v-1$ as follows

$$\phi_{v,i}(z) = \frac{T_{v,i}(z) + zC_{v,i-1}\lambda_{v,i}\phi_{v,i+1}(z)}{C_{v,i}}, \tag{B.19}$$

where the constants $C_{v,i}$ and $T_{v,i}$ match the definition in he statement of the Theorem 3 and iterating it we obtain Expression (B.16).

□

B.4 N_w-Distribution moments theorem

Following we derive explicit expressions for the factorial moments of order $k \geq 1$ of the random variable, N_w and the result is summarized in the following theorem

Theorem 4. *For a fixed warning level, w, with $0 \leq w \leq v_0$, the factorial moments of order $k \geq 0$, $\{m_{v,i}^k : (v,i) \in \widehat{W}\}$, are obtained as follows:*

$$
\begin{aligned}
m_{v,i}^0 &= 1, \text{ for any } (v,i) \in \widehat{W}, && \text{(B.20)}\\
m_{w,i}^k &= 0, \text{ for } 0 \leq i \leq N-w, \text{ and } k \geq 1, && \text{(B.21)}\\
m_{v,N-v}^k &= \frac{\mathcal{T}_{v,N-v}^k}{\mathcal{C}_{v,N-v}}, \text{ for } w+1 \leq v \leq v_0, && \text{(B.22)}\\
m_{v,i}^k &= \left(\prod_{j=i}^{N-v-1} \frac{\lambda_{v,j}\mathcal{C}_{v,j-1}}{\mathcal{C}_{v,j}} \right) m_{v,N-v}^k \\
&\quad + \sum_{j=i}^{N-v-1} \frac{\mathcal{T}_{v,j}^k}{\mathcal{C}_{v,j}} \left(\prod_{m=i}^{j-1} \frac{\lambda_{v,m}\mathcal{C}_{v,m-1}}{\mathcal{C}_{v,m}} \right), && \text{(B.23)}
\end{aligned}
$$

for $w+1 \leq v \leq v_0$ and $0 \leq i \leq N-v$, where

$$
\mathcal{C}_{v,j} = \begin{cases} 1, & \text{if } j < 0, \\ q_{v,0}, & \text{if } j = 0, \\ q_{v,j}\mathcal{C}_{v,j-1} - \gamma_j \lambda_{v,j-1}\mathcal{C}_{v,j-2}, & \text{if } 1 \leq j \leq N-v, \end{cases} \qquad \text{(B.24)}
$$

$$
\mathcal{T}_{v,j}^k = \begin{cases} k\lambda_{v,0} m_{v,1}^{k-1} + \eta_{v,0} m_{v-1,1}^k, & \text{if } j = 0, \\ k\lambda_{v,j} m_{v,j+1}^{k-1} + \eta_{v,j} m_{v-1,j+1}^k + \gamma_j \mathcal{T}_{v,j-1}^k, & \text{if } 1 \leq j \leq N-v. \end{cases}
$$

Proof. Expressions (B.20) and (B.20) are the scalar versions of Equations (20) and (21), in Theorem 2 in [123]. Applying the same methodology as in the Proof of Theorem 3 on this section, factorial moments satisfy the following equation

$$
\mathcal{C}_{v,i} m_{v,i}^k - \mathcal{C}_{v,i-1}\lambda_{v,i} m_{v,i+1}^k = \mathcal{T}_{v,i}^k, \text{ for } 0 \leq i \leq N-v-1. \qquad \text{(B.25)}
$$

In consequence for $i = N-v$, factorial moments are computed from expression (B.22). To obtain the rest of factorial moments, appearing in expression

(B.23), we work on Equation (B.25), from $i = N - v - 1$ to $i = 0$, applying Expression (B.22), as we made in the proof of Theorem 3.

□

B.5 N_w-Probability mass functions theorem

Theorem 5 summarizes additional explicit expressions to compute the auxiliary probabilities, $\{x^k_{v,i} : (v,i) \in \widehat{W}\}$ of N_w.

Theorem 5. *Given a warning vaccination level, v_0, an integer $k \geq 0$ and a fixed warning level w, the set of auxiliary probabilities $\{x^k_{v,i} : (v,i) \in \widehat{W}\}$ are computed by the equations*

$$x^0_{w,i} = 1; \text{ for } 0 \leq i \leq N - w, \tag{B.26}$$

$$x^k_{w,i} = 0; \text{ for } k \geq 1 \text{ and } 0 \leq i \leq N - w, \tag{B.27}$$

$$x^k_{v,0} = \frac{\mathcal{B}^k_{v,0}}{q_{v,0}}, \text{ for } w + 1 \leq v \leq v_0, \tag{B.28}$$

$$x^k_{v,i} = \left(\prod_{j=1}^{i} \frac{\gamma_j}{q_{v,j}}\right) x^k_{v,0} + \sum_{j=1}^{i} \mathcal{B}^k_{v,j} \frac{\prod_{m=j+1}^{i} \gamma_m}{\prod_{l=j}^{i} q_{v,l}}, \tag{B.29}$$

where coefficients $\mathcal{B}^k_{v,j}$ are determined recursively as follows:

$$\mathcal{B}^k_{v,j} = \begin{cases} \eta_{v,j} x^k_{v-1,j+1} & \text{if } j = N - v, \\ \eta_{v,j} x^k_{v-1,j+1} + \lambda_{v,j} x^{k-1}_{v,j+1}, & \text{if } 0 \leq j \leq N - v - 1. \end{cases} \tag{B.30}$$

Proof. we recall that wake-up time, 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

$$x^0_{w,i} = 1; \text{ for } 0 \leq i \leq N - w, \tag{B.31}$$

and

$$x^k_{w,i} = 0; \text{ for } k \geq 1, 0 \leq i \leq N - w. \tag{B.32}$$

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 $k \geq 1$ and $w+1 \leq v \leq v_0$, we have that

$$x^k_{v,i} = \frac{\gamma_i}{q_{v,i}} x^k_{v,i-1} + \frac{\lambda_{v,i}}{q_{v,i}} x^{k-1}_{v,i+1} + \frac{\eta_{v,i}}{q_{v,i}} x^k_{v-1,i+1}, \text{ for } 0 \leq i \leq N - v,$$

or equivalently

$$-\gamma_i x^k_{v,i-1} + q_{v,i} x^k_{v,i} = \lambda_{v,i} x^{k-1}_{v,i+1} + \eta_{v,i} x^k_{v-1,i+1}, \text{ for } 0 \leq i \leq N - v. \tag{B.33}$$

that the expression in the left-hand side of equation (B.33) depends on model parameters and auxiliary probabilities of one order less, $k-1$, and one level of vaccination less, $v-1$.

Starting from the boundary results (B.31) and (B.32), for every mass point $k \geq 0$, it is possible to solve the equations in (B.33) in a recursive way, in the natural order starting for $k = 0$ and from $v = w + 1$ to $v = v_0$. By using a *Forward Elimination Backward Substitution* (FEBS) procedure, the equation (B.33) can be written in triangular form as follows:

$$-\gamma_i x^k_{v,i-1} + q_{v,i} x^k_{v,i} = \mathcal{B}^k_{v,i}, \text{ for } 0 \leq i \leq N - v. \tag{B.34}$$

where the constant $\mathcal{B}^k_{v,i}$ match the definition in Expression (C.1).

Working on equation (B.34), for $0 \leq i \leq N - v$, we get that

$$x_{v,i}^k = \frac{T_{v,i}^k}{\prod_{j=0}^{N-v-1} q_{v,j}}, \tag{B.35}$$

where $T_{v,i}^k$ is defined as

$$T_{v,j}^k \quad = \quad \begin{cases} \mathcal{B}_{v,j}^k, & \text{for } j = 0, \\ \prod_{j=0}^{i-1} q_{v,j} B_{v,j}^k + \gamma_j T_{v,j-1}^k, & \text{for } 1 \leq j \leq N - v, \end{cases} \tag{B.36}$$

and for $k \geq 0$ and $w + 1 \leq v \leq v_0$, Equation (B.34) gives auxiliary probabilities $x_{v,i+1}^k$ in terms of probabilities $x_{v,i}^k$.

Finally iterating (B.35) we obtain the relationship appearing in expression (B.29). □

Appendix C

Additional work on Chapter 4

In appendix D we complement the work described in [124].

In order to facilitate the reading we recall that in this article we use the warning level, w, to define the random variables, S_w and R_w, that give information about the distribution of susceptible individuals, when the number of vaccinated individuals first reaches that level and 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, respectively.

In the mentioned article, in the Conclusions and Future work Section we pointed that the results presented were obtained exploiting the special structure of the system of equations involved to derive explicit recursive expressions but, they can be derived by the matrix-analytics methodology. Therefore, in this Appendix we provide additional S_w-Probability mass functions and R_w-Laplace transforms theorems to compute them applying matrix methods.

Matrix and rates appearing in this Appendix have the same description and notation as in [124].

C.1 S_w-Probability mass functions theorem

Equations (14) appearing in [124], can be expressed in matrix form and this result is set out in the Theorem 6.

Theorem 6. *Given an integer* $1 \leq k \leq N - w$ *and a fixed warning level* w*, the set of auxiliary probabilities* $\{x_{v,i}^k : w \leq v \leq v_0, 0 \leq i \leq N - v\}$*, are computed by the matrix equations:*

$$-\mathbf{Q_v}\mathbf{x}_v^k = \mathbf{D}_v\widetilde{\mathbf{x}}_{v-1}^k,$$

and initial conditions, $\mathbf{x}_w^k = (\delta_{k,0}, \delta_{k,1}, ..., \delta_{k,N-w})^T$*, where* $\mathbf{Q_v} = [Q_v(i,j)]$ *and* $\mathbf{D}_v$ *are (N-v+1) square matrices whose non-null entries are given by*

$$Q_v(i,j) = \begin{cases} \gamma_i & \text{if } 1 \leq i \leq N - v, j = i - 1, \\ -q_{v,i} & \text{if } 0 \leq i = j \leq N - v, \\ \lambda_{v,i} & \text{if } 0 \leq i \leq N - v - 1, j = i + 1, \end{cases}$$

$\mathbf{x}_v^k$ *and* $\widetilde{\mathbf{x}}_{v-1}^k$ *are vectors of dimension* $(N - v + 1)$ *determined as follows:*

$$\begin{aligned} \mathbf{x}_v^k &= (x_{v,0}^k, x_{v,1}^k, ..., x_{v,N-v}^k)^T, \\ \widetilde{\mathbf{x}}_{v-1}^k &= (x_{v-1,1}^k, x_{v-1,2}^k, ..., x_{v-1,N-v+1}^k)^T. \end{aligned}$$

C.2 R_w-Laplace transforms theorem

Equations (55) in [124], can be expressed in matrix form and this result is set out in Theorem 7.

Theorem 7. *The Laplace transforms of the random variables* $R_{v,i}$*,* $\{\psi_{v,i}(z) : (v,i) \in \widehat{W}\}$*, are computed in matrix form as follows*

$$\mathbf{Q}_v(z)\widetilde{\psi}_v(z) = \mathbf{T}_v(z), \tag{C.1}$$

where $\mathbf{Q}_v(z) = [a^v_{i,j}(z)]$ *is a squared matrix of dimension* $(v_0 - v)$ *where non-null entries are given by*

$$a^v_{i,j}(z) \;=\; \begin{cases} -\gamma_{N-v_0+i}, & \text{if } j = i-1 \text{ and } 2 \le i \le v_0 - v, \\ (z + q_{v,N-v_0+i}), & \text{if } j = i \text{ and } 1 \le i \le v_0 - v, \\ -\lambda_{v,N-v_0+i}, & \text{if } j = i+1 \text{ and } 1 \le i \le v_0 - v - 1, \end{cases}$$

$\widetilde{\psi}_v(z)$ *is vector of dimension* $(v_0 - v)$ *defined for* $0 \le v \le w$ *as follows*

$$\widetilde{\psi}_v(z) = [\psi_{v,N-v_0+1}(z), ..., \psi_{v,N-v}(z)]^T,$$

$T_v(z) = [B^{v,z}_{(i)}]$ *with* $1 \le i \le v_0 - v$*, is a vector of dimension* $(v_0 - v)$ *whose elements are defined as*

$$B^{v,z}_{(i)} = \delta_{i,1}\gamma_{N-v_0+i} + \mu_{v,N-v_0+i}\psi_{v-1,N-v_0+i+1}(z),$$

and $T_0(z)$ *is a vector of dimension* v_0 *defined as follows*

$$T_0(z) = (\gamma, 0, ..., 0)^T,$$

and boundary conditions

$$\psi_{v,i}(z) = 1, \text{ for } 0 \le v \le w, 0 \le i \le N - v_0. \tag{C.2}$$

Appendix D

Additional work on Chapter 5

In Appendix D, we extend the research work described in [120].

We recall that the underlying mathematical model is the stochastic SVIR model with external source of infection and imperfect vaccine and we described the random variable, $W(M)$, that measure the time until a total M of infections are produced in the population.

In the mentioned work, in the Conclusions section we point out that our technique can be applied in order to study the time until the end of the outbreak. In that sense, in this Appendix we define the random variable, $\mathcal{T}_0$, that measure the time until the Markov chain reaches the absorbing sate, $(0, 0, 0)$, to carry out that purpose. We provide Laplace transforms and distribution moments theorems of the mentioned measure and for the analysis we use the same notation appearing in [120].

This random variable could not be included in [120] due to the space restrictions of the scientific journal where it was published.

D.1 Time until absorption, $\mathcal{T}_0$

We recall that $\mathcal{X} = \{(V(t), S(t), I(t)); t \geq 0\}$ is a CTMC, with state space $(0,0,0) \in \mathcal{S}$ where

$$\mathcal{S} = \{(v,s,i) : 0 \leq v \leq v_0, 0 \leq s \leq s_0, 0 \leq v+s+i \leq N\},$$

that contains a single absorbing state: $(0,0,0)$ representing the state of a population where everybody has been recovered from the disease of interest.

We introduce the random variable, $\mathcal{T}_0$, representing the time until the CTMC $\mathcal{X}$ reaches the absorbing state $(0,0,0)$. More properly, we define

$$\mathcal{T}_0 = inf\{t \geq 0 : (V(t), S(t), I(t)) = (0,0,0)\}.$$

We assume that at the beginning of the outbreak the population dwells v_0 vaccinated individuals, s_0 susceptible and a single infectious individual, satisfying $v_0 + s_0 = N - 1$.

To study the probabilistic behaviour of the time until absorption we analyze the following set of conditioned random variables for any $(v,s,i) \in \mathcal{S}$

$$\{\mathcal{T}_0 \,|(V(0) = v, S(0) = s, I(0) = i)\}.$$

These random variables can be seen as first passage times to the state $(0,0,0)$ conditioned to the current state.

When conditioning to the initial state of the epidemic process we obtain the following results

$$P(\mathcal{T}_0 = 0 \,|V(0) = 0, S(0) = 0, I(0) = 0) = 1, \tag{D.1}$$

$$P(\mathcal{T}_0 < \infty \,|V(0) = v, S(0) = s, I(0) = i) = 1, \text{for } (v,s,i) \in \mathcal{S}. \tag{D.2}$$

Result appearing in Expression (D.1) is trivially true due to the own definition of the variable $\mathcal{T}_0$.
Expression (D.2) is consequence of the well-known theory of absorbing CTMC with finite space state.

D.1.1 $\mathcal{T}_0$-Laplace transform

We introduce appropriate notation for the Laplace transforms of the conditioned random variables $\{(\mathcal{T}_0\,|V(0)=v, S(0)=s, I(0)=i)\}$, for any $(v,s,i)\in\mathcal{S}$. Given $z\in\mathbb{C}$, with $Re(z)\geq 0$, we define

$$\psi_{v,s,i}(z)=E[e^{-z\mathcal{T}_0}\,|V(0)=v, S(0)=s, I(0)=i]. \tag{D.3}$$

Notice that, from Expressions (D.1-D.2), we obtain the following boundary condition

$$\psi_{v,s,i}(0)=1,\ \text{for } (v,s,i)\in\mathcal{S}, \tag{D.4}$$

and from Equation (D.3), we obtain for a given $z\in\mathbb{C}$, with $Re(z)\geq 0$, the following initial condition

$$\psi_{0,0,0}(z)=1. \tag{D.5}$$

Assuming that the current state of the Markov chain is $(v,s,i)\in\mathcal{S}$ and applying a first-step methodology, we obtain the following relationship

$$\psi_{v,s,i}(z)=\frac{\gamma_i}{z+q_{v,s,i}}\psi_{v,s,i-1}(z)+\frac{\lambda_{s,i}}{z+q_{v,s,i}}\psi_{v,s-1,s,i+1}(z)+\frac{\eta_{v,i}}{z+q_{v,s,i}}\psi_{v-1,s,i+1}(z),$$

where $\lambda_{s,i}=s\left(\frac{\beta i}{N}+\xi\right)$, $\eta_{v,i}=vh\left(\frac{\beta i}{N}+\xi\right)$, $\gamma_i=\gamma i$ and $q_{v,s,i}=\lambda_{s,i}+\eta_{v,i}+\gamma_i$.

The above expression is equivalent to

$$-\gamma_i \psi_{v,s,i-1}(z) + (z + q_{v,s,i})\psi_{v,s,i}(z) - \lambda_{s,i}\psi_{v,s-1,i+1}(z) = \eta_{v,i}\psi_{v-1,s,i+1}(z) \quad \text{(D.6)}$$

D.1.2 $\mathcal{T}_0$-Distribution moments

We introduce appropriate notation for k^{th}-order moments of $\mathcal{T}_0$ conditioned to $(v, s, i) \in \mathcal{S}$ and $k \geq 0$

$$M^k_{v,s,i} = E[\mathcal{T}_0^k \,|V(0) = v, S(0) = s, I(0) = i]. \quad \text{(D.7)}$$

Notice that, from Expressions (D.4-D.5), we obtain the following boundary conditions

$$M^0_{v,s,i} = 1, \text{ for } (v, s, i) \in \mathcal{S}, \quad \text{(D.8)}$$

and in consequence,

$$M^k_{0,0,0} = 0, \text{ for } k > 0. \quad \text{(D.9)}$$

The loop-free structure of the transition rates of the CTMC $\mathcal{X}$ allows us to obtain explicit expressions and avoid matrix structures.

This result is summarized in the following theorem

Theorem 8. *Given integers k, v_0 and s_0, satisfying $k \geq 0$ and $0 \leq v_0 + s_0 \leq N$, moments of order k, conditioned to states $(v, s, i) \in \mathcal{S}$, are recursively determined from the following equations:*

$$\begin{aligned} M^0_{v,s,i} &= 1, \\ M^k_{0,0,0} &= 0, \ \textit{for } k > 0, \\ M^k_{v,s,i} &= \sum_{r=0}^{i} \frac{i! \frac{\gamma^{i-r}}{r!} \widehat{T}^k_{v,s,r}}{\prod_{l=r}^{i} q_{v,s,l}}, \end{aligned}$$

where

$$\widehat{T}^k_{v,s,i} = kM^{k-1}_{v,s,i} + (1-\delta_{v,0})\eta_{v,i}M^k_{v-1,s,i+1} + (1-\delta_{s,0})\lambda_{s,i}M^k_{v,s-1,i+1}. \quad \text{(D.10)}$$

Proof. For any initial state $(v, s, i) \in \mathcal{S}$, moments of order $k \geq 1$ are obtained by differentiating k times Expression (D.6) respect to z, and by evaluating the resulting equation at $z = 0$.

After that, we obtain equations involving the moments of order k, which look as follows

$$-\gamma_i M^k_{v,s,i-1} + q_{v,s,i}M^k_{v,s,i} - \lambda_{s,i}M^k_{v,s-1,i+1} = \eta_{v,i}M^k_{v-1,s,i+1} + kM^{k-1}_{v,s,i}. \quad \text{(D.11)}$$

The right-hand side of Equation (D.11) depends on model parameters and moments of lower levels in v and on moments of one order less. For a given order k, we can solve Equation (D.11) in a recursive way (from $v = 0$ to $v = v_0$ and $s = 0$ to $s = s_0$), for every $0 \leq i \leq N - v - s$, starting from the boundary condition (D.9).

Applying a Forward Elimination Backward Substitution (FEBS) procedure, Equation (D.11) can be expressed in triangular form as

$$q_{v,s,i}M^k_{v,s,i} = \widehat{T}^k_{v,s,i} + \gamma_i M^k_{v,s,i-1}, \ \text{for } 0 \leq i \leq N - v - s, \quad \text{(D.12)}$$

where the constant $\widehat{T}^k_{v,s,i}$ is described in (D.10).

We notice that Equation (D.12) is similar to Equation (B.19) in Appendix B and in consequence, the proof of Theorem 8 is similar to Theorem 1 appearing in Appendix B. Hence, we omit it. □

Chapter 7

Research contents: Discussion

A significant part of the results obtained through this thesis have been published in JCR indexed scientific journals. Hence, that part of the research work is shown on Chapters 2-5 including the printed version of the articles along with a description of the main aspects referring to each paper.

Chapter 6 includes a research article which is in final stages of proofreading before submission to a scientific journal. It has the same structure as the previous Chapters.

Additional results that have not been published are shown in Appendices A-D and complement the investigation showed on Chapters 2-5, respectively.

The objective of this thesis is to study the effect of vaccination in epidemic models with stochastic transmission.

We focus on the study of infectious diseases that are transmitted by direct contact with infected individuals in constant and moderate size populations under a stochastic approach.

This approach takes into account the inherent random nature of an infectious process and it is preferable to the analogous deterministic one for describing the expansion of a disease in small communities. In this sense, results obtained can be applied to the study of infectious processes in hospitals, nursery schools and refugee camps, among others.

We have described the compartmental SVIS and SVIR mathematical models. We have represented the evolution of the epidemic processes in terms of Markov chains. Comparing with the existing literature the main feature of this investigation is to consider non-isolated populations and that prior the onset of the epidemic, individuals have been vaccinated to prevent disease with an imperfect vaccine.

The consequence of assuming that population is not isolated is that individuals can be infected by direct contact with non-community members. This hypothesis seems to be more realist than considering isolated populations where individuals only contact each others.

Currently, the most of vaccines that are administered to the population are not perfect. In that sense, considering that individuals have been vaccinated to prevent disease with an imperfect vaccine presents a more realistic scenario that considering a perfect one.

Results of this study indicate that the epidemic behaviour, considering the SVIS and SVIR models with external source of infection and imperfect vaccine, differs from the observed in the traditional analogous models.
In particular, to consider the external source of infection and imperfect vaccine hypothesis plays a fundamental role in the evolution of an epidemic.

For the SVIS model described on Chapters 2-5 and their related Appendices, results indicate that according to the non-isolated population hypothesis, it is possible a reintroduction of the disease when there are not infected individuals in the community. Furthermore, to administer an imperfect vaccine to the population to prevent disease can produce that the number of vaccinated individuals could be descend and in consequence, the population protection conferred by herd immunity could be lost. In that sense, in long-term the number of vaccinated individuals will be zero and the disease could remain in the population forever.

These findings suggested us to quantify the potential transmission of an infectious disease and to provide a tool to alert health authorities about the possibility of losing the community protection to the pathogen.

The quantification of the potential transmission of the disease was carried out by analyzing alternative measures to the basic reproduction number, R_0. In particular, we defined exact and population reproduction numbers, R_{e0} and R_p analogous to those in [41]. With this analysis, we obtained an exact quantification of the spread of a pathogen in a post-vaccination context.

To alert health authorities about a decline in the number of vaccinated individuals in the population, which could lead to a loss of herd immunity, we introduce a threshold for the number of vaccinated individuals in the community, w. When the number of protected individuals decreases below this threshold, we propose triggering an alarm to warn about that risk. In addition, we analyze the time from the beginning of the outbreak until the alarm is activated and the incidence of the disease during that period by defining the random variables, T_w and N_w, respectively.

We point out that the threshold, w, can be fixed in advance by health authorities by applying well-established scientific criteria or using the exact and population reproduction numbers described in this research, which demonstrates the great applicability of the measures analyzed.

In addition, we offer appropriate tools to select the threshold in the number of vaccinated individuals in order to evaluate and organize an immediate re-vaccination of the population. This aim is achieved by analyzing the random variable S_w, that denotes the number of susceptible individuals in the population at the time in which the number of individuals reaches the threshold, w. If a re-vaccination can not be launched immediately, we analyze the time until it can be executed through the random variable, R_w.

Regarding the study of the SVIR model with an external source of in-

fection and imperfect vaccine, described on Chapters 5-6 and their related Appendices, we observe that the hypotheses considered lead to the fact that the disease could be reintroduced into the population even if there are not infected individuals in the community and the number of vaccinated individuals in the population could dissipate as occurs with the analyzed SVIS model but, presenting some differences in the long-term behavior. Due to the permanent immunity acquired after recovery from the disease, results show that in long-term all individuals will be recovered from the disease. This behavior is different from that observed in the traditional SIS and SVIR models. These results suggested us to analyze the speed and potential transmission of the disease.

The speed of transmission was studied by describing the random variables $W(M)$ and $\mathcal{T}_0$, that denote the time until reach a total of M infections and the time until all individuals have been recovered in the population, respectively.

The main difference that we observe between these random variables and their analogous for the traditional SIR and SVIR models is that the external source of infection and imperfect vaccine hypothesis lead to have both random variables with finite support and therefore the expected times obtained are also finite.

The study of the potential transmission of the disease was carried out through the analysis of exact and population reproduction numbers but with a different approach to the original one in [41] and Chapter 2.

In this case, we separate the contagions produced to vaccinated individuals from those caused to susceptible individuals. This new approach has allowed us to study the effect of vaccination on the potential transmission of the

disease by comparing the infections produced between these two groups of individuals.

Overall, results of this study have permit us to quantify the expansion of an epidemic, including vaccination as a control measure to control an epidemic process, through the analysis of reproduction numbers, incidence and time measures. In addition, tools have been proposed, involving the random variables studied, to help health authorities to stop the spread of the infectious process.

The methodology applied to derive theoretical results, that it has been detailed in Section 1.1.2 and throughout this thesis, can be extended to the study of these and other measures and for other mathematical models therefore, it is not limited to the described models.

One of the limitations or weaknesses that we have found during this investigation is that considering homogeneous populations where all individuals can contact each other with equal probability may not be in line with the reality. In this sense, we are considering future lines of investigation considering populations with heterogeneous contacts or assuming some type of structure in the population.

Likewise, we plan to continue developing future research work considering vaccines that confer protection that wanes over time.

Chapter 8

Contenido de la investigación: Discusión

Una gran parte de los resultados obtenidos en esta investigación han podido publicarse en revistas científicas indexadas JCR. Por lo tanto, esa parte del trabajo ha sido mostrado en los Capítulos 2-5, incluyendo las versiones impresas de las publicaciones junto con una descripción de los aspectos más importantes referentes a cada uno de los artículos.

El Capítulo 6 incluye un artículo de investigación que está en preparación para poder ser enviado a una revista científica y tiene la misma estructura que los anteriores capítulos.

Resultados adicionales que no han sido publicados se muestran en los Apendices A-D, complementando la investigación desarrollada en los Capítulos 2-5, respectivamente.

Esta tesis tiene como propósito investigar el efecto de la vacunación en la expansión de epidemias con un enfoque estocástico.

Nos hemos centrado en estudiar la propagación de enfermedades cuya transmisión se produce mediante contacto directo con individuos que están infectados, considerando poblaciones de tamaño constante y moderado con un enfoque estocástico.

Este enfoque tiene en cuenta la naturaleza aleatoria intrínseca de un proceso epidémico y es más adecuado que su análogo determinista para describir la evolución de una epidemia en poblaciones pequeñas. De esta forma, los resultados obtenidos podrían ser bien aplicados al estudio de procesos infecciosos en hospitales, guarderías o campos de refugiados, entre otros.

Hemos descrito dos modelos matemáticos compartimentales de tipo SVIS y SVIR y hemos representado la evolución de los procesos epidémicos mediante cadenas de Markov, donde a diferencia de la literatura existente, hemos

considerado que la población no está aislada y que los individuos han sido vacunados preventivamente contra la enfermedad con una vacuna imperfecta.

Asumir que la población no está aislada tiene como consecuencia que los individuos también podrían infectarse por contacto directo con otros individuos infectados que no pertenezcan a la población. Esta hipótesis parece ajustarse mejor a la realidad que considerar poblaciones aisladas donde los individuos que la conforman solamente contactan entre ellos.

Actualmente nos encontramos que la mayoría de las vacunas administradas a la población no son perfectas. Por lo tanto, asumir que la población ha sido inmunizada preventivamente contra la enfermedad con una vacuna imperfecta refleja la realidad mejor que considerar vacunas perfectas.

Observamos que el comportamiento de la epidemia en los modelos estudiados difiere bastante respecto a si consideramos los modelos tradicionales SVIS y SVIR.

En particular, asumir que existe una fuente externa de infección y que la vacuna admisnistrada es imperfecta juega un papel fundamental en el transcurso de la epidemia.

Así, en el modelo SVIS mostrado en los Capítulos 2-5 y sus correspondientes anexos, los resultados muestran que aunque el número de individuos infectados sea cero en un determinado instante, la enfermedad podría reintroducirse en la población a causa de la fuente externa de infección. Además considerar que la vacuna administrada es imperfecta provoca que el número de individuos vacunados en la población pueda descender y como consequencia la proteccion de la población frente a la enfermedad podría perderse. En este sentido, a largo plazo nos encontramos que no habrá individuos vacuna-

dos en la población y que la enfermedad podría establecerse en la población para siempre.

A partir de este comportamiento creímos que era importante cuantificar la transmisión potencial de la enfermedad y ofrecer una herramienta que alertara a las autoridades sanitarias de la posible perdida de inmunidad colectiva.

La cuantificación potencial de la enfermedad se llevó a cabo mediante la aplicación de medidas alternativas al tradicional número reproductivo básico, R_0. En concreto definimos números reproductivos exacto, R_{e0} y poblacional, R_p, análogos a los descritos en [41]. De esta forma, hemos podido obtener una cuantificación exacta de la propagación de la enfermedad en un contexto post-vacunación.

Para alertar a las autoridades sanitarias del descenso en el número de individuos vacunados en la población, lo que podría ocasionar una perdida de inmunidad colectiva, introducimos un umbral en la cantidad de individuos vacunados, w. Cuando el número de individuos protegidos decrece por debajo de dicho umbral proponemos que se establezca una alarma para alertar sobre este riesgo. Además, analizamos el tiempo desde el comienzo del brote hasta que se activa la alarma y la incidencia de la enfermedad durante ese período definiendo las variables aleatorias, T_w y N_w, respectivamente.

Cabe destacar, que este umbral puede ser establecido de antemano por las autoridades sanitarias aplicando criterios científicos bien establecidos o bien emplear los números reproductivos exactos y poblacionales descritos en esta investigación, lo que demuestra la gran aplicabilidad de estas medidas estudiadas.

Además ofrecemos herramientas para seleccionar adecuadamente este um-

bral de número de individuos vacunados para poder evaluar y organizar una re-vacunación inmediata de la población. Esto se consigue mediante el análisis de las variable aleatoria S_w que denota al número de individuos susceptibles en la población en el intante en el que el número de individuos alcanza el umbral, w. En el caso de que la re-vacunación no pueda ejecutarse de forma inmediata analizamos el tiempo hasta que puede llevarse a cabo mediante la variable, R_w.

Respecto al estudio del modelo SVIR con fuente de infeccion externa y vacuna imperfecta, mostrado en los Capítulos 5-6 y sus correspondientes anexos, podemos decir que las hipótesis consideradas conducen a que la enfermedad podría reintroducirse en la población aunque no hubiera individuos infectados en la población y que el número de individuos vacunados en la población puede disiparse, al igual que ocurre con el modelo SVIS analizado, pero con un comportamiento a largo plazo diferente. Debido a la permanente inmunidad adquirida tras la recuperación de la enfermedad, los resultados muestran que a largo plazo todos los individuos estarán recuperados de la enfermedad siendo este comportamiento bien distinto al observado en los modelos tradicionales SIS y SVIR. Tras observar estos resultados creímos conveniente analizar la velocidad y potencial transmisión de la enfermedad.

La velocidad de transmisión se estudió definiendo las variables aleatorias $W(M)$ y $\mathcal{T}_0$, que denotan al tiempo hasta que se han infectado un total de M individuos y tiempo hasta que todos los individuos de la población se han recuperado, respectivamente.

La principal diferencia que observamos en estas variables respecto a los modelos tradicionales SIR y SVIR existentes en la literatura publicada, es

que las hipótesis de la fuente externa de infección y vacuna imperfecta, hacen que estas variables tenga soporte finito y por lo tanto los tiempos medios obtenidos sean también finitos.

El estudio de la transmisión potencial de la enfermedad se llevó a cabo mediante el análisis de números reproductivos exactos y poblacionales pero con un enfoque diferente al propuesto en el estudio original [41] y el Capítulo 2.

En este caso, creimos que era interesante separar los contagios producidos a individuos vacunados de los provocados a individuos susceptibles. Este nuevo planteamiento nos ha permitido poder estudiar el efecto de la vacunación en la transmisión potencial de la enfermedad comparando los contagios producidos en estos dos grupos de individuos.

En general podemos decir que esta investigación ha permitido cuantificar la expansión de una epidemia, incluyendo la vacunación como medida de contención de la enfermedad, mediante el análisis de números reproductivos, medidas de incidencia y de tiempo. Además se han proporcionado herramientas en las que intervienen las variables aleatorias estudiadas, para ayudar a que las autoridades pertinentes puedan frenar la expansión del proceso infeccioso.

La metodología utilizada para la obtención de los resultados y que ha sido detallada en la Sección 1.1.2 y a lo largo de toda la tesis, puede extenderse al estudio de estas u otras medidas y otros modelos matemáticos y por lo tanto no está limitada a los modelos considerados.

Nos gustaría mencionar que una de las limitaciones o debilidades que hemos encontrado durante esta investigación es considerar poblaciones ho-

mogéneas donde todos los individuos puedan contactar entre sí con igual probabilidad. Esta asunción parece no ajustarse muy bien a la realidad y en este sentido, se nos plantean futuras líneas de trabajo considerando poblaciones con contactos heterogéneos o asumir algun tipo de estructura en la población.

De igual forma nos planteamos seguir avanzando en futuras investigaciones considerando que la eficacia de la vacuna se pierde a largo plazo.

Chapter 9

Conclusions

Next we resume the general conclusions of this thesis.

For the SVIS and SVIR models with external source of infection and imperfect vaccine, vaccination has a big effect on the spread of an infectious disease. This effect has been analyzed by studying the evolution of the epidemic in the short and long-term and describing several measures that have led us to quantify its expansion. We obtain the following results.

For both models, the consequence of assuming an external source of infection and an imperfect vaccine hypothesis is that in long-term there will not be vaccinated individuals in the population.

Overall, we observe that large vaccination coverage control the spread of the disease obtaining larger propagation times and lower disease incidence.

Likewise, the vaccine failure probability plays a fundamental role in the transmission of the disease. More effective vaccines produce lower number of contagions and lower transmission speeds than those with large vaccine failure probability values.

The internal transmission rate has a big effect on the spread of the pathogen. Diseases with large rates of transmission can produce severe epidemics. We detected for these cases, that it is necessary to administer very effective vaccines and to achieve vaccination coverage close to 100% of the population to control its expansion.

Regarding the methodology and algorithmic implementation of the theoretical results, the main conclusions are the following:

The organization by levels and sub-levels of the state space of the CTMC's analyzed has allowed us to simplify the study and analyze the Markov chains involved as birth and death processes allowing their subsequent analysis using

matrix methods.

The block bi-diagonal structure of the infinitesimal generators involved permit us to obtain theoretical results applying iterative methods.

Numerical algorithms provide results depending strongly on the population size . Computation times are very high when considering populations larger than 1000 individuals. For instance, when $N = 1000$ and over, we obtain elapsed times greater than 5 hours. In contrast for small communities, around $N = 100$ individuals, we obtain elapsed times lower than one minute.

Chapter 10

Conclusiones

A continuación se muestran la conclusiones generales que se han obtenido tras el estudio de investigación realizado a lo largo de esta tesis.

En los modelos SVIS y SVIR con fuente externa de infección y vacuna imperfecta, la vacunación tiene un gran efecto en la propagación de enfermedades infecciosas. Este efecto se ha analizado estudiando a corto y largo plazo la evolución del brote epidémico y estudiando diferentes medidas que han permitido cuantificar su expansión obteniedose los siguientes resultados.

Para ambos modelos las hipótesis de que exista una fuente externa de infección y que la vacuna administrada sea imperfecta tienen como consecuencia que a largo plazo no haya individuos vacunados en la población.

En general observamos que grandes coberturas vacunales frenan la expansión de la enfermedad obteniéndose tiempos de propagación más largos e incidencias de la enfermedad más bajas.

De igual forma, la eficacia de la vacuna juega un papel fundamental en la transmisión de la enfermedad. A mayor efectividad de la vacuna obtenemos un número menor de contagios y velocidades de transmisión mucho más lentas.

La tasa de contagio interna influye de manera considerable en la propagación del patógeno. Enfermedades con elevadas tasas de contagio pueden producir epidemias muy severas. Incluso hemos detectado que en estos casos es necesario disponer de vacunas muy efectivas y lograr coberturas vacunales cercanas al 100% de la población para poder controlar su expansión.

Referente a la metodología e implementación algorítmica de los resultados teóricos, las principales conclusiones que obtenemos son las siguientes:

La organización por niveles y sub-niveles del espacio de estados, de las

CTMC de ambos modelos, nos ha permitido simplificar el estudio y analizar estas cadenas de Markov como procesos de nacimiento y muerte permitiendo su posterior análisis mediante métodos matriciales.

La estructura bi-didiagonal por bloques de los generadores infinitesimales de estas cadenas han hecho posible obtener los resultados teóricos aplicando además métodos recursivos.

Respecto a la implementación algorítmica de los resultados teóricos, hemos obtenido que los tiempos de computación dependen mucho de los tamaños poblacionales. En concreto, cuando consideramos poblaciones de tamaño pequeño en torno a N=100 individuos, obtenemos tiempos de ejecución inferiores al minuto. En cambio, cuando trabajamos con poblaciones grandes, N=1000 o superiores, estos tiempos son bastante más elevados incluso llegando a necesitar más de 5 horas de ejecución.

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