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► **To cite this version:**

Quentin Richard, Samuel Alizon, Marc Choisy, Mircea T Sofonea, Ramsès Djidjou-Demasse. Age-structured non-pharmaceutical interventions for optimal control of COVID-19 epidemic. PLoS Computational Biology, 2021, 10.1371/journal.pcbi.1008776 . hal-02879512v2

HAL Id: hal-02879512

<https://hal.science/hal-02879512v2>

Submitted on 26 Feb 2021 (v2), last revised 28 Sep 2021 (v3)

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Age-structured non-pharmaceutical interventions for optimal control of COVID-19 epidemic

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Abstract

In an epidemic, individuals can differ widely in how they spread the infection depending on their age or on the number of days they have been infected for. In the absence of pharmaceutical interventions such as a vaccine or treatment, non-pharmaceutical interventions (*e.g.* physical distancing) are essential to mitigate the pandemic. We develop an original approach to identify the optimal age-stratified control strategy to implement as a function of the time since the onset of the epidemic. This is based on a model with a double continuous structure in terms of host age and time since infection. By applying optimal control theory to this model, we identify a solution that minimizes deaths and costs associated with the implementation of the control strategy itself. We also implement this strategy to three countries with contrasted age distributions (Burkina-Faso, France, and Vietnam). Overall, the optimal strategy varies over the course of the epidemic, with a more intense control early on. It also depends on host age, with a stronger control over the older population, except in the scenario where the cost associated with the control is low. In the latter scenario, we find strong differences across countries because the control extends to younger population in France and Vietnam 2 to 3 months after the onset of the epidemic, but not in Burkina Faso. Finally, we show that the optimal control strategy strongly outperforms a constant uniform control over the whole population or over its younger fraction only. This improved understanding of the effect of age-based control interventions opens new perspectives for the field, especially for age-based contact tracing.

Key words. COVID-19; Optimal control; Age-structured model; Age of infection; Outbreak ; Epidemiology

1 Introduction

Following its emergence in December 2019, COVID-19 has become an international public health emergency [1]. The infection has many similarities with that caused by influenza virus regarding clinical manifestations and transmission mechanism [1]. Contrary to seasonal influenza, COVID-19 has become pandemic by spreading rapidly among completely naive host populations, *i.e.* with no pre-existing immunity [2–5]. At the start of the pandemic, no pharmaceutical interventions such as vaccines or treatments were available and, based on earlier epidemics, it will take several months before their deployment. For this reason, non-pharmaceutical intervention strategies, such as physical distancing, are key to controlling the pandemic [6].

When an intervention is summarized by one or few parameter values, identifying an optimal strategy according to some criterion variable can readily be done, *e.g.* using a gradient approach [7]. Things become much more challenging when the intervention parameter value is a function of time. Optimal control theory [8], also known as Pontryagin’s maximum principle, specifically addresses this issue by identifying a function of time such that, over a finite time interval, some criterion is optimized. This has allowed studies to identify optimal non-pharmaceutical interventions to control infectious diseases such as influenza and COVID-19 [9–12]. However, a strong limitation of these studies is that they all ignore at least one aspect of the host population structure. First, infection parameters vary with infection age, *i.e.* depending on the number of days since infection. Second, hosts vary in age. The latter point is particularly important because in addition to being a function of time since the onset of the outbreak, optimal strategies involving physical distancing can also vary depending on host age [13–17]. Accounting for two dimensions, time and host age, make the optimization procedure more challenging because Pontryagin’s maximum principle is applied to ordinary differential equations (ODEs) –something very common– while here we are working on partial differential equations (PDEs) –which is less common, and more challenging. Here, we address this challenge and identify interventions varying in intensity with time and host age, that significantly reduce morbidity associated with COVID-19 at a minimal cost. Furthermore, we compare the situation in countries with contrasted age-structure, namely Burkina-Faso, France, and Vietnam, to show how this affects optimal strategies.

The age structure of the population is a known key determinant of acute respiratory diseases, especially when it comes to infection severity. For example, children are considered to be responsible for most of the transmission of influenza virus [18], but the related hospitalization and mortality burden is largely carried by people of ages over 65 years [19, 20]. While much remains unknown about the COVID-19 epidemics, evidence to date suggests that mortality among people who have been tested positive for the coronavirus is substantially higher at older ages and near zero for young children [3, 21]. Moreover, the infectiousness of an individual has been reported to vary as a function of time since infection [22], which is known to affect epidemic spread [23–26].

Our epidemiological model for the disease stage-progression [24] is structured both by a (con-

67 tinuous) age of the host and a (continuous) age of infection. A variety of epidemiological models
 68 allow for one or the other type of structure [27–30], starting with a seminal article from the 1920s
 69 [23]. However, models allowing for a double continuous structure are rare [30–37]. Such a double
 70 structure is particularly suited to investigate an infection such as COVID-19, with strong host and in-
 71 fection age effects. Indeed, in addition to taking into account the age-structure of the host population,
 72 as well as the gradient of disease severity from mild to critical symptoms, the model readily captures
 73 the variation in infectiousness as a function of the time since infection. From a theoretical point of
 74 view, age-structured models have been proposed to investigate the spread of acute respiratory diseases
 75 [38–42], and some rare models of acute respiratory diseases consider both structures as continuous
 76 variables [30, 32], although not in the context of optimal control theory.

77 In Section 2, we first introduce the mathematical model. The model parameters and outputs are
 78 then defined in Section 3. In Section 4, we characterize the optimal control strategy that minimizes the
 79 number of deaths as well as the cost due to the implementation of the control strategy itself. Section 5
 80 contains the main body of the results. We first analyze the epidemic spread without any intervention
 81 for three countries with contrasted age distributions (Burkina-Faso, France, and Vietnam). Next, the
 82 performance of optimal control in terms of deaths and hospitalizations is compared for different costs
 83 of the control measure. Finally, the optimal control is compared to two other strategies using the same
 84 amount of resources to control the outbreak. The article ends by a discussion in Section 6.

85 2 An age-structured epidemiological model

86 2.1 Model overview

87 We denote the density of individuals of age $a \in [0, a_{max}]$ that are susceptible to the infection at time
 88 $t \in [0, T]$ by $S(t, a)$. These individuals can become infected with a rate called the force of infection
 89 and denoted $\lambda(t, a)$. We assume that a fraction p of these individuals are paucisymptomatic, which
 90 means that they will develop very mild to no symptoms, and enter group I_p . Note that this class
 91 can also be interpreted as the fraction of the population that will not isolate themselves during their
 92 infection. Other individuals are assumed to develop more symptomatic infections, either severe I_s with
 93 proportion $q(a)$ depending on the age a , or mild I_m with proportion $1 - q(a)$.

94 Each of the three infected host populations are structured in time since infection, so that $I_v(t, a, i)$,
 95 $v \in \{p, s, m\}$, denotes the density at time t of individuals of age a that have been infected for a duration
 96 $i \in \mathbb{R}_+$. Upon infection, all exposed individuals are assumed to remain non-infectious during an
 97 average period i_{lat} . Next, they enter an asymptomatic period during which they are infectious. Only
 98 I_m and I_s develop significant symptoms after an average time since infection i_{sympt} , which can allow
 99 them to self-isolate to limit transmission. During their infection, individuals can recover at a rate
 100 $h_v(a, i)$ ($v \in \{p, m, s\}$) that depends on the severity of the infection and the time since infection i .
 101 Severely infected individuals of age a may also die from the infection at rate $\gamma(a, i)$.

102 The infection life cycle is shown in Figure 1. The total size of the host population of age a at time

$$N(t, a) = S(t, a) + R(t, a) + \int_0^\infty (I_p(t, a, i) + I_m(t, a, i) + I_s(t, a, i)) di. \quad (1)$$

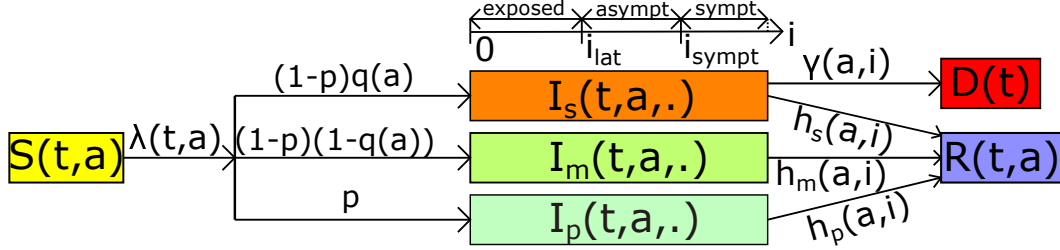


Figure 1: **The model flow diagram.** Susceptible hosts of age a at time t ($S(t, a)$) are exposed to the virus with a force of infection $\lambda(t, a)$. A fraction p of exposed individuals, which are infected since time i , will never develop symptoms and enter the group of paucisymptomatic infections ($I_p(t, a, i)$). The rest will develop symptomatic infections, either severe ($I_s(t, a, i)$) with proportion $q(a)$ depending on age a of individuals, or mild ($I_m(t, a, i)$). Exposed individuals remain non-infectious for a duration i_{lat} after infection. Next, they become asymptomatic infectious and only symptomatic infected will develop symptoms at time i_{sympt} after infection. Infected individuals recover at rate $h_v(a, i)$. Only severely infected of age a die from the infection at rate $\gamma(a, i)$. Notations are shown in Table 1.

104 **Remark 2.1** *Contrarily to classical SEAIR models, disease-stage progression in our model is not cap-*
 105 *tured by discrete compartments (exposed, asymptomatic, and infected) with exponentially distributed*
 106 *waiting times to switch between compartments. The advantage of our formalism is that disease pro-*
 107 *gression can be modelled using a continuous variable, called the time since infection (in days) denoted*
 108 *here by i . Every infected person then remains in the “infection compartment” from exposure until re-*
 109 *covery (or death). The time since infection grows linearly with time, according to the derivative with*
 110 *respect to i . Latency from exposed to asymptomatic and time of symptoms onset are not needed for*
 111 *this modelling approach because these are captured through the functions describing the transmission*
 112 *rate, the mortality rate, and the recovery rate at time i post infection. More precisely, the average*
 113 *latency from exposed to asymptomatic (i_{lat}) is simply mentioned to define the average time to infection*
 114 *onset (i_{sympt}), and also to help the readers to understand the model flow diagram (Figure 1). On the*
 115 *other hand, the time to infection onset (i_{sympt}) is used to define infectiousness reduction factors (ξ_s, ξ_m)*
 116 *and the mortality rate due to the infection (γ).*

117 2.2 Age-structured transmission and severity

We use two components to model the infection process. First, we define the transmission probability $\beta_v(a, i)$ ($v \in \{p, m, s\}$) for each contact between an infected of age a and a susceptible person, which depends on the time since infection i . Second, we introduce the kernel $K(a, a')$ that represents the average number of contacts by unit of time between an individual of age a' and an individual of age a .

Here, this contact matrix is informed by data from earlier study [43]. The force of infection underwent by susceptible individuals of age a at time t is then given by

$$\lambda(t, a, c) = (1 - c(t, a)) \int_0^{a_{\max}} K(a, a') \int_0^{\infty} (\beta_s(a', i) I_s(t, a', i) + \beta_m(a', i) I_m(t, a', i) + \beta_p(a', i) I_p(t, a', i)) di da' \quad (2)$$

118 Here, $c = c(t, a)$ is the percentage of contacts reduction towards people with age a , due to public
 119 measures, at time t . The total force of infection at time t in the whole population is computed as
 120 $\int_0^{a_{\max}} \lambda(t, a, c) da$. The dynamics of newly infected individuals (*i.e.* $i = 0$) in each group is thus defined
 121 by

$$\begin{cases} I_s(t, a, 0) &= (1 - p)q(a)\lambda(t, a, c)S(t, a), \\ I_m(t, a, 0) &= (1 - p)(1 - q(a))\lambda(t, a, c)S(t, a), \\ I_p(t, a, 0) &= p\lambda(t, a, c)S(t, a). \end{cases} \quad (3)$$

122 Note that p likely depends on age, but because is it totally unknown, we assume it is a constant.
 123 Further, we assume that only severe infections I_s lead to hospitalization and we denote by

$$H(t) = \int_0^{a_{\max}} \int_{i_{\text{sympt}}}^{\infty} I_s(t, a, i) di da \quad (4)$$

the total population hospitalized at time t , where i_{sympt} is the average time to symptoms onset. Each individual of age a dies at a rate $\mu(a, H(t))$ at time t , defined by

$$\mu(a, H(t)) = \mu_{\text{nat}}(a) + \mu_{\text{add}}(a, H(t)).$$

124 In the latter equation, μ_{nat} denotes the natural mortality rate when hospitals are not saturated. Further,
 125 we assume that this rate increases significantly as soon as the number of severe cases exceeds the
 126 healthcare capacity H_{sat} and μ_{add} is such additional death rate due to hospital saturation (see Section
 127 3.2).

We apply the same reasoning by assuming that the disease-related mortality can increase because of hospital saturation. Therefore, severely infected individuals of age a infected since time i die at time t at rate $\gamma(a, i, H(t))$ defined by

$$\gamma(a, i, H(t)) = (\gamma_{\text{dir}}(a) + \gamma_{\text{indir}}(a, H(t))) \mathbf{1}_{[i_{\text{sympt}}, i_{\text{max}}^s]}(i).$$

128 Here, γ_{dir} and γ_{indir} are mortality rates directly and indirectly due to the COVID-19 respectively (see
 129 Section 3.2). The disease-related mortality occurs after the emergence of symptoms and before the
 130 mean final time of infection for severe cases, *i.e.* for $i \in [i_{\text{sympt}}, i_{\text{max}}^s]$.

131 Finally, infected individuals of age a infected since time i recover at rates $h_s(a, i)$, $h_m(a, i)$ and
 132 $h_p(a, i)$ for severe, mild and paucisymptomatic infections respectively.

The boundary conditions (3) are coupled with the following equations:

$$\left\{ \begin{array}{l} \frac{\partial S}{\partial t}(t, a) = -\mu(a, H(t))S(t, a) - \lambda(t, a, c)S(t, a), \\ \left(\frac{\partial I_s}{\partial t} + \frac{\partial I_s}{\partial i}\right)(t, a, i) = -[\mu(a, H(t)) + \gamma(a, i, H(t)) + h_s(a, i)]I_s(t, a, i), \\ \left(\frac{\partial I_m}{\partial t} + \frac{\partial I_m}{\partial i}\right)(t, a, i) = -[\mu(a, H(t)) + h_m(a, i)]I_m(t, a, i), \\ \left(\frac{\partial I_p}{\partial t} + \frac{\partial I_p}{\partial i}\right)(t, a, i) = -[\mu(a, H(t)) + h_p(a, i)]I_p(t, a, i), \\ \frac{\partial R}{\partial t}(t, a) = \sum_{v \in \{s, m, p\}} \int_0^\infty h_v(a, i)I_v(t, a, i)di - \mu(a, H(t))R(t, a), \end{array} \right. \quad (5)$$

for any $(t, a, i) \in (0, T) \times [0, a_{\max}] \times \mathbb{R}_+$, with initial conditions (at $t = 0$):

$$S(0, a) = S_0(a), \quad R(0, a) = 0, \quad I_s(0, a, i) = I_{s,0}(a, i), \quad I_m(0, a, i) = I_{m,0}(a, i), \quad I_p(0, a, i) = I_{A,0}(a, i)$$

for each $(a, i) \in [0, a_{\max}] \times \mathbb{R}_+$. The initial conditions of infected populations are detailed in Section 3.3. Using (3) and an integration over i of (5), one may observe that the total population N defined by (1) is strictly decreasing since it satisfies the following inequality:

$$\frac{\partial N}{\partial t}(t, a) \leq -\mu_{nat}(a)N(t, a), \quad \forall a \in [0, a_{\max}], \quad \forall t \geq 0.$$

This is due to the fact that population aging and births are neglected in this model since we consider a time horizon of only one year. Further, basic properties of the model such as existence and positiveness of solutions is out of the primary scope of our study. However, these can be specifically addressed using an integrated semigroup approach and Volterra integral formulation (see *e.g.* [44–47] and references therein). More specifically, one may follow [31] where the well-posedness of an epidemiological model with a double continuous structure is handled.

3 Epidemiological outputs, model parameters and initial conditions

In this section we briefly describe some useful epidemiological outputs, the shape of age-dependent parameters considered for the simulations of model (3)-(5), and the initial conditions. All state variables and other parameters are summarized in Table 1.

3.1 Epidemiological outputs

In addition to the total number of hospitalized cases $H(t)$ at time t defined by (4), we define additional epidemiological outputs such as the number of non-hospitalized cases ($N_H(t)$)

$$N_H(t) = \int_0^{a_{\max}} \left[\int_0^{i_{sympt}} I_s(t, a, i)di + \int_0^\infty (I_m(t, a, i) + I_p(t, a, i)) di \right] da. \quad (6)$$

147 Note that the latter encompasses paucisymptomatic, mildly infected, and severely infected but not yet
 148 hospitalized hosts.

149 For the cumulative number of deaths, we distinguish between those directly due to COVID-19
 150 infections ($D_{dir}^{cum}(t)$), and those indirectly due to the epidemic ($D_{indir}^{cum}(t)$), which originate from the
 151 saturation of the health system:

$$D_{dir}^{cum}(t) = \int_0^t D_{dir}(s)ds, \quad D_{indir}^{cum}(t) = \int_0^t D_{indir}(s)ds, \quad (7)$$

152 where $D_{dir}(t)$ and $D_{indir}(t)$ are the number of deaths at time t respectively defined by

$$D_{dir}(t) = \int_0^{a_{max}} \int_{i_{symp}}^{i_{max}^s} \gamma_{dir}(a) I_s(t, a, i) di da,$$

$$D_{indir}(t) = \int_0^{a_{max}} \mu_{add}(a, H(t)) N(t, a) da + \int_0^{a_{max}} \gamma_{indir}(a, H(t)) \int_{i_{symp}}^{i_{max}^s} I_s(t, a, i) di da.$$

Every aforementioned output implicitly depends on parameter $c = c(t, a)$, which we will omit in the notations when no confusion is possible. However, for clarity, we do explicitly write this dependence to compare public health measures. The relative performance between two strategies c_1 and c_2 , denoted by $\Delta(c_1, c_2)$, is estimated by assessing the cumulative number of deaths in the whole population during the T days of control period with the strategy c_1 relatively to deaths with the strategy c_2 . Formally we have

$$\Delta(c_1, c_2) = 1 - \frac{D_{dir}^{cum}(c_1, T) + D_{indir}^{cum}(c_1, T)}{D_{dir}^{cum}(c_2, T) + D_{indir}^{cum}(c_2, T)}.$$

153 Hence, a relative performance $\Delta(c_1, c_2) = 0.1$ implies that the strategy c_1 reduces the number of deaths
 154 by 10% relatively to c_2 .

155 3.2 Model parameters

156 Mortality rates

157 We assume that indirect mortality, *i.e.* not directly due to COVID-19, increases when the number of
 158 hospitalisations $H(t)$, at time t , exceeds a healthcare capacity threshold H_{sat} (which is approximated
 159 with the maximal intensive care capacity). The natural mortality rate then increases by $\mu_{add}(a, H)$ for
 160 the whole population, and by $\gamma_{indir}(a, H)$ for severely infected individuals of age a . These rates are
 161 modelled by logistic functions that are arbitrarily chosen as:

$$\mu_{add}(a, H(t)) = \frac{10^{-2} \mu_{nat}(a)}{1 + 99 \exp\left(-10 \left(\frac{H(t)}{H_{sat}} - 1\right)\right)}, \quad \gamma_{indir}(a, H(t)) = \frac{\gamma_{dir}(a)}{1 + 99 \exp\left(-10 \left(\frac{H(t)}{H_{sat}} - 1\right)\right)}. \quad (8)$$

This choice of functional parameters implies that

$$\mu_{add}(a, 0) \approx 0, \quad \gamma_{indir}(a, 0) \approx 0, \quad \mu_{add}(a, H_{sat}) = 10^{-4} \mu_{nat}(a), \quad \gamma_{indir}(a, H_{sat}) = 10^{-2} \gamma_{dir}(a)$$

which means these additional mortalities are negligible when hospitals are not saturated (Figure 2 b). In case of full saturation, we have

$$\lim_{H \rightarrow \infty} \mu_{add}(a, H) = 10^{-2} \mu_{nat}(a), \quad \lim_{H \rightarrow \infty} \gamma_{indir}(a, H) = \gamma_{dir}(a)$$

162 for each $a \in [0, a_{\max}]$, meaning that the natural mortality rate is only increased by 1%, while the
 163 disease-induced mortality rate γ is doubled. Indeed, according to [48], less than 50% of patients in
 164 critical care will die in case of no saturation of hospitals.

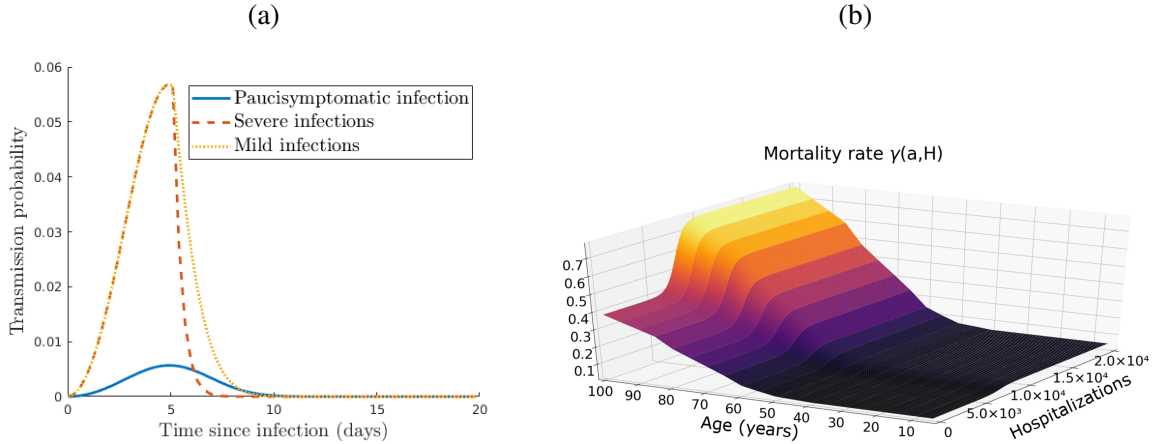


Figure 2: (a) Transmission probabilities of paucisymptomatic infections β_p , symptomatic severe β_s and mild infections β_m . (b) Disease induced mortality rate with a maximal healthcare capacity $H_{sat} = 5 \times 10^3$.

165 Transmission rates

166 The infectiousness of an individual aged a , which is infected since time i , is given by $\beta_v(a, i)$ ($v \in$
 167 $\{s, m, p\}$). Based on estimates described in [22], we assume that β_v does not depend on host age a ,
 168 *i.e.*, $\beta_v(a, i) = \beta_v(i)$. This assumption is only made for parameterization purpose and does not impact
 169 the general formulation of the model proposed here (this is discussed later in Section 6).

170 The transmission rate at a given day i post infection of a given type of infectious host is defined
 171 such that $\beta_v(i) = \alpha \times \xi_v(i) \times \bar{\beta}(i)$, for $v \in \{s, m, p\}$. As detailed below, α is a scaling parameter ob-
 172 tained from the value of the basic reproduction number R_0 , which is the mean number of secondary
 173 infections caused by an infected host [24]. As [22], we assume that parameter $\bar{\beta}$, which strongly de-
 174 pends on the generation interval, follows a Weibull distribution $\bar{\beta} \sim W(3, 5.65)$. Finally, parameters
 175 $\xi_v(i)$ are factors that capture variations in infectiousness based on the type of host. For paucisymp-
 176 tomatic individuals, for instance, these are assumed to be constant ($\xi_p(i) = \xi_p$), while the reduction
 177 factor in more symptomatic infections (severe and mild) is assumed to vary after symptom onset to

178 capture admission in a healthcare facility or self-isolation at home. More precisely, we assume that

$$\xi_s(i) = \begin{cases} 1 & \text{if } i \in [0, i_{sympt}], \\ e^{-\ln(10)(i-i_{sympt})} & \text{if } i > i_{sympt} \end{cases}, \quad \text{and } \xi_m(i) = \begin{cases} 1 & \text{if } i \in [0, i_{sympt}], \\ e^{-\ln(2)(i-i_{sympt})} & \text{if } i > i_{sympt}. \end{cases} \quad (9)$$

179 These two functions are chosen arbitrarily by assuming that individuals do not isolate before symp-
180 toms onset ($i \leq i_{sympt}$), and that isolation is stronger when symptoms are more severe (Figure 2 a). We
181 therefore assume that the transmission probability $\bar{\beta}$ is divided by 10 (respectively 2) every day after
182 the average time of symptoms onset for individuals severely (resp. mildly) infected.

183 Recovery rates

184 We assume that recovery rates $h_v(a, i)$, $v \in \{s, m, p\}$, of infected individuals of age a infected since
185 time i are independent of the age a and take the following form:

$$h_s(\cdot, i) = \mathbf{1}_{[i_{max}^s, \infty)}(i), \quad h_m(\cdot, i) = h_p(\cdot, i) = \mathbf{1}_{[i_{max}^m, \infty)}(i), \quad \forall i \in \mathbb{R}_+. \quad (10)$$

186 That is, one can recover from severe (resp. mild and paucisymptomatic) infections only after a time
187 since infection i_{max}^s (resp. i_{max}^m) corresponding to the mean duration of infection.

188 3.3 Initial conditions

The initial susceptible population S_0 and epidemic size I_0 are given in Table 1. Since, initially, screen-
ing is usually restricted to individuals with severe symptoms, we assume that all initial cases are severe
infections. Thus, we set $\int_{i_{sympt}}^{i_{max}^s} \int_0^{a_{max}} I_{s,0}(a, i) da di = I_0$ as the initial severely infected individuals, which
we assume to be uniformly distributed with respect to the time since infection i on the interval $[0, i_{max}^s]$.
Using estimates from [55, 60] on the age distribution of hospitalised people, we derive an estimation
of $I_{s,0}(a, i)$ for each $(a, i) \in [0, a_{max}] \times \mathbb{R}_+$. Next, following the life cycle (Figure 1), we obtain an
estimation of the total initial infected population by $\frac{I_{s,0}(a, i)}{(1-p)q(a)}$. From there, we deduce the initial mildly
and paucisymptomatic infected populations, which can be denoted respectively by

$$I_{m,0}(a, i) = \frac{1-q(a)}{q(a)} I_{s,0}(a, i) \quad \text{and} \quad I_{A,0}(a, i) = \frac{p}{q(a)(1-p)} I_{s,0}(a, i).$$

189 4 Optimal intervention

As explained above, our goal is to find an optimal control strategy that is allowed to vary depending on
the number of days since the onset of the epidemic (t) and on host age (a). In this section, following
well established methodology in optimal control theory [13–16, 61], we search for the optimal control
effort function c^* that minimizes the objective functional $J : L^\infty(\mathbb{R}_+ \times [0, a_{max}]) \ni c \mapsto J(c) \in \mathbb{R}$,
where

$$J(c) = D_{dir}^{cum}(c, T) + D_{indir}^{cum}(c, T) + \int_0^T \int_0^{a_{max}} B(a) c^2(t, a) da dt,$$

Param.	Description (unit)	Values [source]		
State variables				
S	Susceptible individuals			
I_s	Severely infected individuals			
I_m	Mildly infected individuals			
I_p	Paucisymptomatic infected individuals			
R	Recovered individuals			
General parameters				
t, T	time and final time of simulations (days)	$t \in [0, T]$ (ad hoc)		
a, a_{\max}	age and maximal age of individuals (years)	$a \in [0, a_{\max}]$, $a_{\max} = 100$ (ad hoc)		
i	time since infection (days)	\mathbb{R}_+ (ad hoc)		
i_{lat}	average latency from exposed to asympt. (days)	4.2 [49]		
i_{sympt}	average time of symptoms onset (days)	$i_{lat} + 1 = 5.2$ [48]		
i_{\max}^s	mean final time of infection for severe cases (days)	$i_{sympt} + 20 = 25.2$ [50]		
i_{\max}^m	mean final time of infection for mild cases (days)	$i_{sympt} + 17 = 22.2$ [50]		
μ_{add}	additional death rate (days^{-1})	defined by (8)		
$\beta_s, \beta_m, \beta_p$	transmission probabilities (unitless)	computed in Section 3.2		
ξ_s, ξ_m, ξ_p	infectiousness reduction factors (unitless)	defined by (9) and $\xi_p = 0.1$ [22]		
h_s, h_m, h_p	recovery rates per infection (days^{-1})	defined by (10)		
c, c_{\max}	percentage of contacts reduction and its upper bound	$c \in [0, c_{\max}]$, $c_{\max} = 0.95$ (assumed)		
γ_{dir}	mortality rate directly due to the COVID-19 (days^{-1})	[48]		
γ_{indir}	mortality rate indirectly due to the COVID-19 (days^{-1})	defined by (8)		
p	proportion of paucisymptomatic (unitless)	variable		
q	proportion of symptomatic requiring hospitalisation (unitless)	[48]		
B	cost of the control measure (unitless)	variable		
Specific parameters for each country				
Param.	Description (unit)	Burkina Faso	France	Vietnam
S_0	initial population of susceptible	[51]	[52, 53]	[54]
$I_0^{(*)}$	initial epidemic size	288 (WHO)**	130 [55]	217 (Ministry of Health)
μ_{nat}	natural death rate (days^{-1})	[56]	[57]	[58]
H_{sat}	maximal healthcare capacity (unitless)	11 [59]	5000 [55]	5932 (NIHE)**
K	matrix of social contacts (days^{-1})	[43]	[43]	[43]
Parameters and range for the global sensitivity analysis				
Param.	Description	Range		
Pop.Struc	population structure	{Burkina Faso, France, Vietnam}		
H_{sat}	maximal healthcare capacity	{10, 100, 500, 2000, 5000, 6000, 50000, 5e+05, 5e+06}		
p	proportion of paucisymptomatic	{0.05 to 0.95} by step of 0.1		
i_{sympt}	average time of symptoms onset	{1.2 to 9.2} by step of 2		
ξ_p	infectiousness reduction of I_p	{0.1, 0.3, 0.5, 0.7, 1}		

(*): corresponds to March, 1st, 2020 in France and April, 1st, 2020 in Burkina Faso and Vietnam.

(**): WHO: World Health Organisation, NIHE: National Institut of Hygiene and Epidemiology

Table 1: Model variables and parameters.

190 D_{dir}^{cum} , D_{indir}^{cum} being the cumulative number of deaths defined by (7), and $B(a)$ the cost associated with
 191 the implementation of such control c for the age class a . Our aim is to find the function c^* satisfying

$$J(c^*) = \min_{c \in \mathcal{U}} J(c) \quad (11)$$

wherein the set \mathcal{U} is defined by

$$\mathcal{U} = \{c \in L^\infty(\mathbb{R}_+ \times [0, a_{\max}]) : 0 \leq c(\cdot, \cdot) \leq c_{\max}\},$$

192 with $c_{\max} \leq 1$ a positive constant. That is to say, the function c^* will minimize the cumulative number
 193 of deaths during T days, as long as the cost of the control strategy is not too large.

194 Let (S, I_s, I_m, I_p, R) be a given solution of (3)-(5) then let λ and H be respectively defined by (2)
 195 and (4). After some computations (Appendix C), we find that the adjoint system of (5) reads as

$$\begin{pmatrix} \frac{\partial z_S}{\partial t}(t, a) \\ \frac{\partial z_R}{\partial t}(t, a) \\ \left(\frac{\partial z_{I_s}}{\partial t} + \frac{\partial z_{I_s}}{\partial i}\right)(t, a, i) \\ \left(\frac{\partial z_{I_m}}{\partial t} + \frac{\partial z_{I_m}}{\partial i}\right)(t, a, i) \\ \left(\frac{\partial z_{I_p}}{\partial t} + \frac{\partial z_{I_p}}{\partial i}\right)(t, a, i) \end{pmatrix} = \begin{pmatrix} \mu(a, H(t))z_S(t, a) - \mu_{add}(a, H(t)) \\ \mu(a, H(t))z_R(t, a) - \mu_{add}(a, H(t)) \\ (\mu(a, H(t)) + h_s(a, i))z_{I_s}(t, a, i) - \mu_{add}(a, H(t)) - \gamma(a, i, H(t))(1 - z_{I_s}(t, a, i)) \\ (\mu(a, H(t)) + h_m(a, i))z_{I_m}(t, a, i) - \mu_{add}(a, H(t)) \\ (\mu(a, H(t)) + h_p(a, i))z_{I_p}(t, a, i) - \mu_{add}(a, H(t)) \end{pmatrix} \\ - \begin{pmatrix} \zeta_2(t, a) \int_0^\infty \int_0^{a_{\max}} K(a, a')(\beta_s(a', i)I_s(t, a', i) + \beta_m(a', i)I_m(t, a', i) + \beta_p(a', i)I_p(t, a', i)) da' di \\ 0 \\ \zeta_1(t, a)\mathbf{1}_{[i_{\text{sympt}}, \infty)}(i) + \beta_s(a, i) \int_0^{a_{\max}} \zeta_2(t, a')S(t, a')K(a', a) da' + \zeta_3(t, a)h_s(a, i) \\ \beta_m(a, i) \int_0^{a_{\max}} \zeta_2(t, a')S(t, a')K(a', a) da' + \zeta_3(t, a)h_m(a, i) \\ \beta_p(a, i) \int_0^{a_{\max}} \zeta_2(t, a')S(t, a')K(a', a) da' + \zeta_3(t, a)h_p(a, i) \end{pmatrix} \quad (12)$$

with final conditions $z_S(T, a) = z_R(T, a) = 0$, $z_u(T, a, i) = 0$ and $\lim_{i \rightarrow \infty} z_u(t, a, i) = 0$, for any $u \in \{I_s, I_m, I_p\}$ and $(a, i) \in [0, a_{\max}] \times \mathbb{R}_+$, while ζ_k ($k \in \{1, 2, 3\}$) satisfy the system:

$$\begin{pmatrix} \zeta_1(t, a) \\ \zeta_2(t, a) \\ \zeta_3(t, a) \end{pmatrix} = \begin{pmatrix} \frac{\partial \mu}{\partial H}(a, H(t))(S(t, a)(1 - z_S(t, a)) + R(t, a)(1 - z_R(t, a))) \\ [1 - c(t, a)][(1 - p)(q(a)z_{I_s} + (1 - q(a))z_{I_m}) + pz_{I_p}](t, a, 0) - (1 - c(t, a))z_S(t, a) \\ z_R(t, a) \end{pmatrix} \\ + \begin{pmatrix} \int_0^\infty \frac{\partial \mu}{\partial H}(a, H(t))(I_s(t, a, i)(1 - z_{I_s}(t, a, i)) + I_m(t, a, i)(1 - z_{I_m}(t, a, i))) di \\ 0 \\ 0 \end{pmatrix} \\ + \begin{pmatrix} \int_0^\infty \left(\frac{\partial \mu}{\partial H}(a, H(t))I_p(t, a, i)(1 - z_{I_p}(t, a, i)) + \frac{\partial \gamma}{\partial H}(a, i, H(t))I_s(t, a, i)(1 - z_{I_s}(t, a, i)) \right) di \\ 0 \\ 0 \end{pmatrix}. \quad (13)$$

196 Finally, the Hamiltonian \mathcal{H} of (11) is given by (C.1). Then, solving $\frac{\partial \mathcal{H}}{\partial c} = 0$, it comes that

$$c^*(t, a) = \max(0, \min(\hat{c}(t, a), 1)), \quad (14)$$

for every $(t, a) \in [0, T] \times [0, a_{\max}]$, where

$$\hat{c}(t, a) = \frac{S(t, a)\lambda_0(t, a) [(1-p)(1-q(a))z_{I_m}(t, a, 0) + (1-p)q(a)z_{I_s}(t, a, 0) + pz_{I_p}(t, a, 0)]}{2B(a)},$$

197 with λ_0 defined by (B.4).

We also assume that the cost $B(a)$ of the control measure over individuals aged $a \in [0, a_{\max}]$ is proportional to their density in the initial susceptible population S_0 , *i.e.*

$$B(a) = \frac{B^* S_0(a)}{\int_0^{a_{\max}} S_0(u) du},$$

198 where $B^* \in \mathbb{R}_+$ is a variable parameter characterizing the relative cost in implementing the strategy.
 199 Additionally, one may consider the age distribution of the economic cost on the shape of the function
 200 B . For example, the economic cost can be assumed more important for the working population (*i.e.*
 201 age group 20 – 60) compared to the older, mostly retired, population. However, in absence of relevant
 202 references on this topic we stand with our primary assumption.

203 The state system (3)-(5) and the adjoint system (12)-(13) together with the control characteriza-
 204 tion (14) form the optimality system to be solved numerically. Since the state equations have initial
 205 conditions and the adjoint equations have final time conditions, we cannot solve the optimality system
 206 directly by only sweeping forward in time. Thus, an iterative algorithm, forward-backward sweep
 207 method, is used [8]. In other words, finding c^* numerically, involves first solving the state variables
 208 (3)-(5) forward in time, then solving the adjoint variables (12)-(13) backward in time, and then plug-
 209 ging the solutions for the relevant state and adjoint variables into (14), subject to bounds on the control
 210 function. Finally, the proof of the existence of such control is standard and is mostly based on the Eke-
 211 land's variational principle [62]. Therefore, existence of the optimal control to the above problem is
 212 assumed and we refer to [13] for more details.

213 5 Results

214 Here we consider three countries as case studies: Burkina Faso, France and Vietnam. They have quite
 215 contrasted age-structure and social contacts of their population (Figure 3). Indeed, in Burkina Faso
 216 the very large majority (96.1 %) of the population is under 60 while it is respectively 87.7 % and 73.4
 217 % in Vietnam and France (Figure 3 a,b). It shows that an higher proportion of the population is older
 218 than 60, hence at risk for COVID-19 infection, in France 26.6%, in comparison to Vietnam 12.3 %, or
 219 to Burkina Faso 3.9 % (Figure 3 a,b). Also, contacts are more frequent among the older population in
 220 France compared to Vietnam (Figure 3 d, e). By contrast, very few contacts are observed among older
 221 populations in Burkina Faso (Figure 3 c).

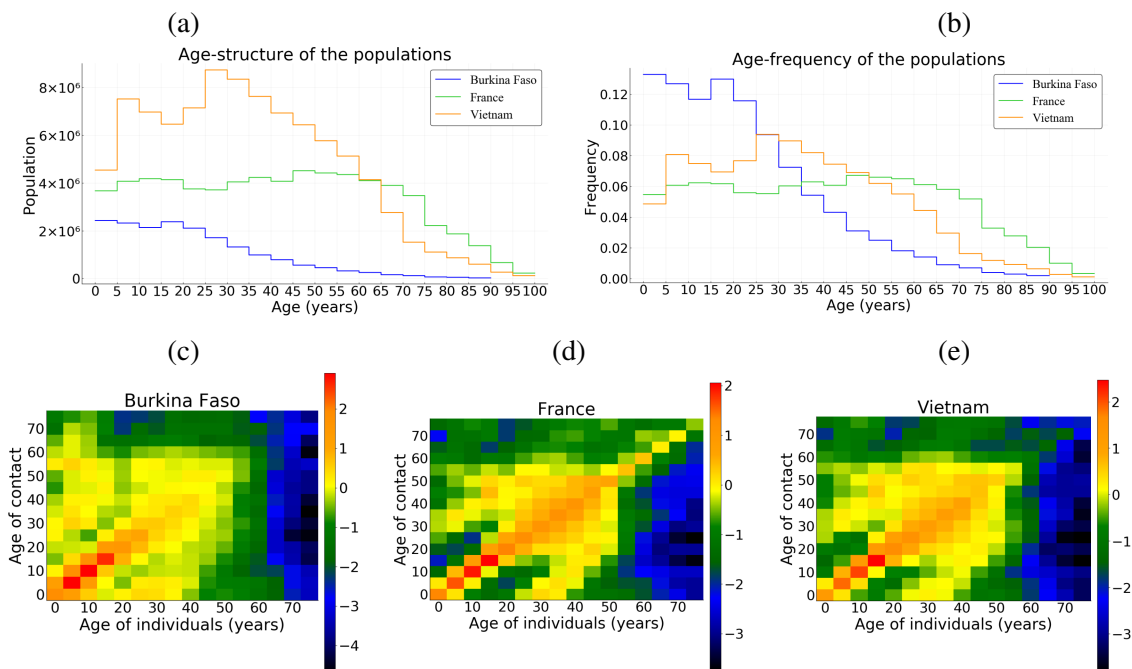


Figure 3: (a)-(b) The population age-structure of Burkina Faso, France and Vietnam. (c)-(e) Contact matrices in the three countries, in log scale where dark color intensities indicate less likely events *i.e.* smaller tendency of having a household member of that age, lower proclivity of making the age-specific contact.

222 5.1 Global sensitivity analysis

223 We study the sensitivity of infected individuals, hospitalizations and deaths to five parameters: pro-
 224 portion of paucisymptomatic (p), average time of symptoms onset (i_{sympt}), infectiousness reduction of
 225 paucisymptomatic infections (ξ_p), healthcare capacity (H_{sat}) and population structure (including the
 226 natural mortality, the size of the population, age-structure and social contacts). The variation range of
 227 above parameters is assigned in Table 1. Sensitivity indices are estimated by fitting an ANOVA (Anal-
 228 ysis Of Variance) linear model, including third-order interactions, to the data generated by simulation.
 229 Note that this ANOVA linear model fitted well with 99% of variance explained. Overall, the popula-
 230 tion structure is the main parameter highlighted by the sensitivity analysis with 70% of the variance
 231 explained for the number infected individuals, 40% for hospitalizations and deaths (Figure S1). The
 232 population structure is followed by ξ_p , p , and i_{sympt} which have quite similar importance on the num-
 233 ber infected individuals with a slight dominance of ξ_p (Figure S1). By contrast, for hospitalizations
 234 and deaths, the population structure is followed by p with 40% and 30% of the variance explained
 235 respectively; while ξ_p and i_{sympt} have very marginal impact (Figure S1). Finally, the importance of
 236 H_{sat} is strictly negligible on the three output variables, with however, a greater importance on deaths
 237 as compared to hospitalizations and infected (Figure S1).

238 **5.2 The basic reproduction number R_0**

239 An explicit expression of the R_0 of model (3)-(5) is difficult to obtain in general. We show in Ap-
 240 pendix B that it is possible to write $R_0 = \alpha \times r(\bar{U})$, where α is the scaling parameter introduced in
 241 Section 3.2, and $r(\bar{U})$ is the spectral radius of the next generation operator \bar{U} defined on $L^1(0, a_{\max})$
 242 by

$$\bar{U} : L^1(0, a_{\max}) \ni v \mapsto S_0(\cdot) \int_0^\infty \int_0^{a_{\max}} K(\cdot, a') \omega(a', i) v(a') da' di \in L^1(0, a_{\max}). \quad (15)$$

243 where S_0 is the initial susceptible population, K is the contact matrix and $\omega(a, i)$ is the infectiousness
 244 of individuals of age a infected since time i (Appendix B). It follows that

$$\alpha = \frac{R_0}{r(\bar{U})}. \quad (16)$$

245 Setting $R_0 = 3.3$ [63, 64] for all three countries and using a numerical approach and corresponding
 246 values for S_0 and K for each country, we successively determine $r(\bar{U})$ and α by (15) and (16) respec-
 247 tively.

248 **5.3 Uncontrolled epidemic**

249 We first use the model (3)-(5) to describe the outbreak of the epidemics for all three countries, without
 250 any public health measure (*i.e.* $c \equiv 0$), with $R_0 = 3.3$ and other parameters defined in Section 3 and
 251 summarized in Table 1.

252 The peak of the epidemics is reached approximately at day $t = 51$ for hospitalised people, and day
 253 $t = 46$ for non-hospitalised people without any control measures in the France scenario (Figure 4 e).
 254 Such times to peaks for hospitalised and non-hospitalised people are 47 and 41 (resp. 50 and 45) for
 255 Burkina Faso (resp. Vietnam) scenario (Figure 4 a, resp. Figure 4 i). The delay between the two peaks
 256 is due to the latency time i_{sympt} for symptoms onset (Table 1).

257 In absence of control measures, the healthcare capacity is quickly exceeded, about twenty days
 258 for France scenario (Figure 4 e), and the number of deaths increases sharply from then on. Such
 259 configuration is similar for Vietnam scenario (Figure 4 i). By contrast, due to a very low healthcare
 260 capacity in Burkina Faso, the health system is exceeded only after a few days compared to France
 261 and Vietnam (Figure 4 a). However, this overloading of the health system does not have the same
 262 consequences in terms of mortality in Burkina Faso compared to France and Vietnam. This is partially
 263 explained on the one hand by the fact that less than 4% of the population is above 60 years in Burkina
 264 Faso (Figure 3 a) and on the other hand by the fact that very few contacts are observed with older
 265 population in Burkina Faso compared to France or Vietnam (Figure 3 b-d).

266 At the end of the simulation ($t = 150$ days), without any control measures, the herd immunity
 267 threshold ($1 - 1/R_0 \approx 69.7\%$) is reached in Burkina Faso, France and Vietnam (Figure 5). Indeed,
 268 the average size of the epidemic (severe, mild, and paucisymptomatic infections) is close to 90% in
 269 France and Vietnam but only 78% in Burkina Faso (Figure 5). Interestingly, in all three countries,

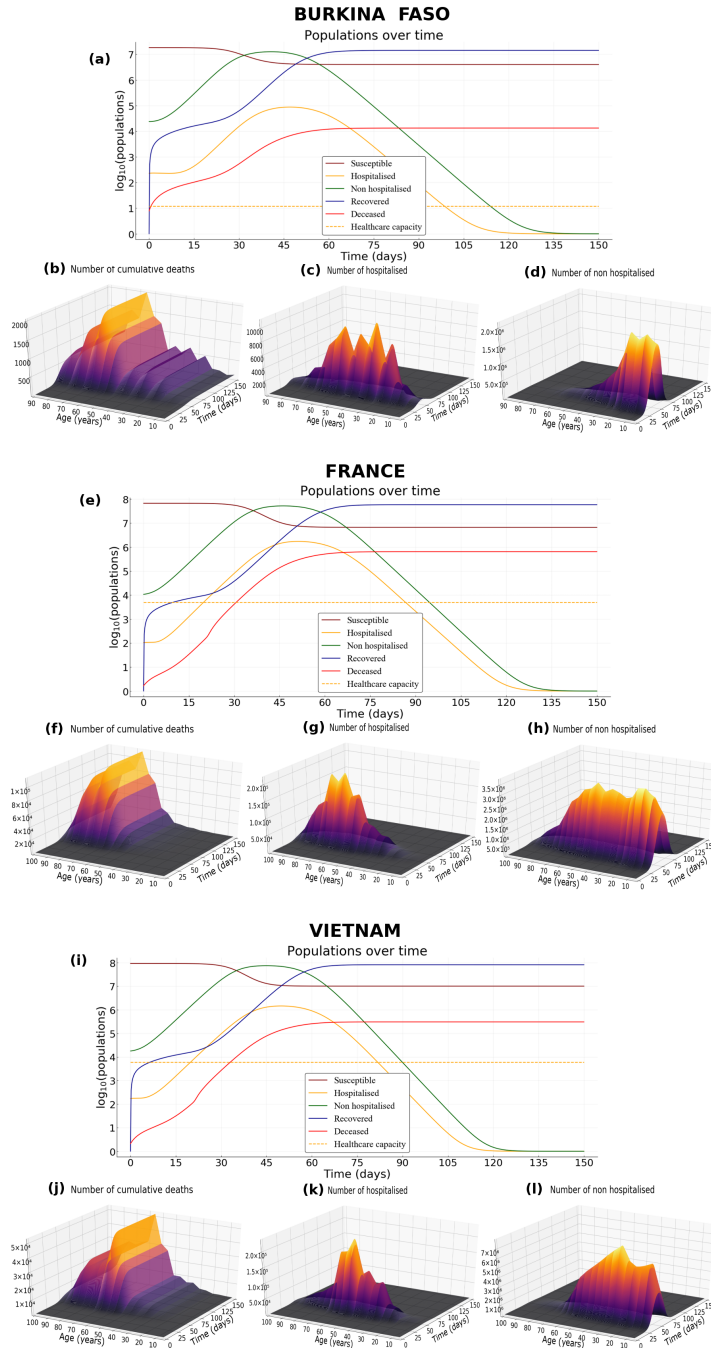


Figure 4: **Epidemic scenario without any control measures.** (a) Dynamics of epidemiological outputs, (b) number of cumulative deaths, (c) number of hospitalised and (d) non-hospitalised people in Burkina Faso. (e-h) As for (a-d) but in France. (i-l) As for (a-d) but in Vietnam. Parameter values are default in Table 1, $R_0 = 3.3$ and the proportion of paucisymptomatic infections is $p = 0.5$.

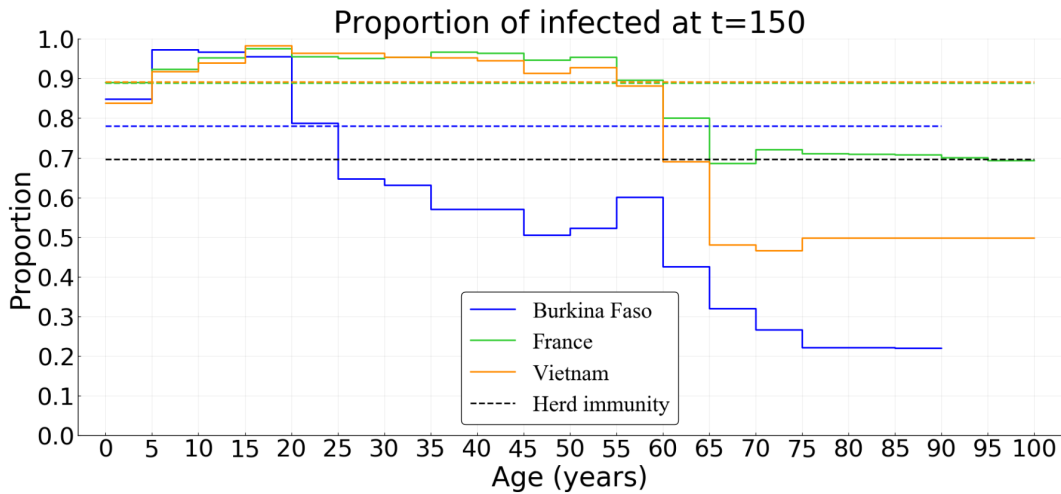


Figure 5: **Simulated age distribution of the proportion of the population infected in Burkina Faso, France, and Vietnam in absence of control measures.** Parameter values are default, $R_0 = 3.3$ and the proportion of paucisymptomatic infections is $p = 0.5$.

270 the proportion of the population less than 20 that have been infected is around 93%. While almost
 271 the same proportion of the group [20 – 60] was infected in France and Vietnam (94%), only 65% was
 272 infected in Burkina Faso. This proportion then decreases for the population older than 60, more or less
 273 quickly depending on the country, and is around 73% in France, 56% in Vietnam and 33% in Burkina
 274 Faso. Further, among the infected population, more than 98% are less than 60 in Burkina Faso, while
 275 this proportion is 92% in Vietnam and 76% in France. This age structure of infected populations is
 276 particularly important since most of the infections that occur in the young population do not require
 277 hospitalisation (Figures 4g, 4 c, 4 k) while people older than 60 represent the age class with the highest
 278 cumulative number of deaths (Figures 4 f, 4 b, 4 j).

279 5.4 Optimal intervention

280 We now investigate the result of implementing an optimal intervention that accounts for the age struc-
 281 ture of the population. Strategies performances are here compared in terms of cumulative number of
 282 deaths for three costs of control measures (low $B^* = 10^2$, intermediate $B^* = 10^3$, and high $B^* = 10^4$).

283 The optimal control strategy varies in time and depends on host age. In general, regardless of
 284 the country (Burkina Faso, France or Vietnam), the control is stronger early in the epidemic and for
 285 older populations (Figures 6, S2, S3). Overall, the level of optimal control is lower in Burkina Faso
 286 compared to France and Vietnam (Figures 6, S2, S3). If the cost of implementing the measures B^* is
 287 intermediate or high, the optimal control is almost restricted to individuals above 55 and to the first
 288 third of the time interval considered, with a significant reduction in deaths (Figures 6 d, e, Figure S2
 289 d, e and Figure S3 d, e). In France, the relative performance of the optimal control c^* compared to a

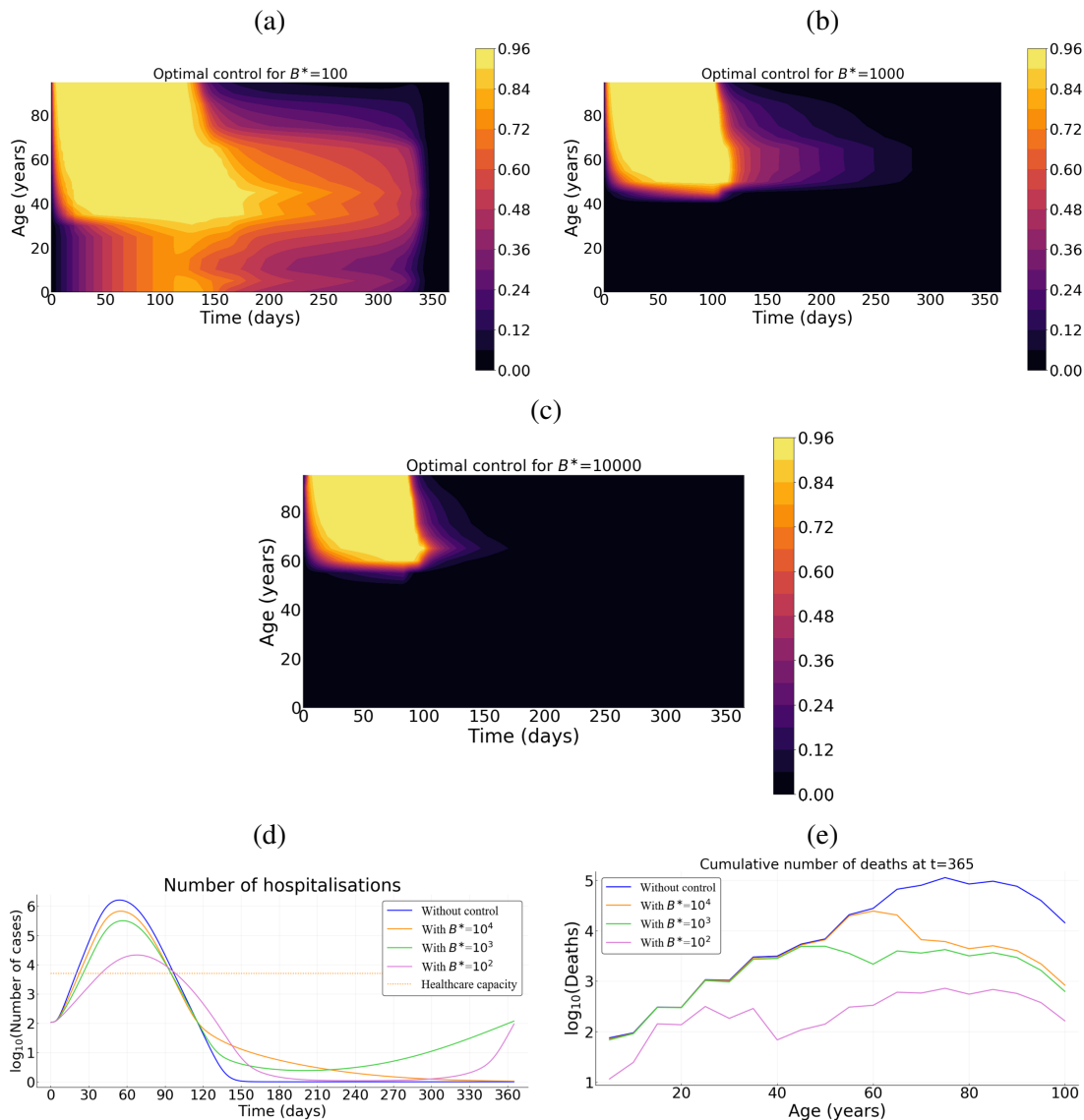


Figure 6: **Optimal control strategy (c^*) as a function of the cost of the control measures in France.**

Intensity of the control as a function of time and host for for (a) relatively low $B^* = 10^2$, (b) an intermediate $B^* = 10^3$, and (c) a high $B^* = 10^4$ cost. (d) Prevalence of hospitalized patients as a function of the strategy and the cost. (e) Cumulative deaths per age at the end of the time interval (when $T = 365$ days). Parameter values not related to the control are identical to Figure 4. Cases of Burkina Faso and Vietnam are given by Figures S2, S3.

290 ‘doing nothing’ scenario ($\Delta(c^*, 0)$) is at least 92% (resp. 82%) when the cost is $B^* = 10^3$ (resp. 10^4).
 291 For Burkina Faso, $\Delta(c^*, 0)$ is at least 50% (resp. 4%) when $B^* = 10^3$ (resp. 10^4). Finally, for Vietnam
 292 $\Delta(c^*, 0)$ is at least 87% (resp. 62%) when $B^* = 10^3$ (resp. 10^4). In the case of Burkina Faso, note that
 293 the level of the optimal control is quite low when the cost of implementation is high (Figure S2 c),

294 and as a result, the effect of this control in reducing mortality at the population level is negligible. This
295 is due to the relatively small number of deaths in the whole population in Burkina Faso without any
296 control measures (Figure 4 a).

297 If the implementation of the control measure comes at a low cost ($B^* = 10^2$), the optimal control
298 significantly extends to younger populations in all three countries (Figures 6 a, S2 a, S3 a), with
299 a maximum intensity reached near the 4th month of the epidemics and a steady decrease until the
300 end of the control period. Overall, the optimal control lasts less longer in Burkina Faso (Figure S2 a)
301 compared to the cases of France and Vietnam (Figures 6 a, S3 a). At first, the control is mainly applied
302 to people above 35 in all three countries (Figures 6 a, S2 a, S3 a). But, while the control extends to
303 people less than 35 in France and Vietnam after 2 or 3 months (Figures 6 a, S3 a), such an extension
304 is very moderate (or even negligible) in Burkina Faso (Figure S2 a). The resulting reduction in the
305 number of deaths is very pronounced with a relative performance $\Delta(c^*, 0)$ of at least 80% (resp. 99%,
306 97%) in Burkina Faso (resp. France, Vietnam).

307 5.5 Performance and practical implementation

308 To illustrate how the strategy identified using optimal control theory outperforms “classical” optimi-
309 sation approaches, we derive optimal strategies that do not vary in time and use the same amount of
310 “resources” (that is the same cumulative cost). Assuming a relatively high cost $B^* = 10^3$, we first
311 investigate a control strategy that targets the younger fraction of the population (Figure 7 a), a second
312 strategy that uniformly targets the whole population (Figure 7 b). Both strategies have a control level
313 $c_{\max} = 0.95$ and vary in duration (the total amount of resource used being constant).

314 In France, when targeting the population uniformly, the epidemic is under control during approxi-
315 mately 60 days. However, once the control resources are exhausted, the epidemic reemerges (Figure 7
316 c). With the (longer) control over the younger fraction of the population, the first epidemic peak is
317 slightly delayed and the epidemic appears to be under control for a longer time period (180 days). Un-
318 fortunately, resources also become exhausted and a second peak appears a few months later (Figure 7
319 c). Whether it is for a uniform control of the whole population or over its younger fraction, the cu-
320 mulative mortality over the time period of interest is comparable to that without any control measure
321 (Figure 7 d). The performance of the optimal control relatively to the uniform control of the whole
322 population or over its younger fraction, is approximately 92%; and at the end, 55% of the whole popu-
323 lation has been infected with the optimal control and at least 85% with control of the whole population
324 or over its younger fraction (Figure 7 e). A such configuration is quite similar for the case of Vietnam
325 (Figure S4).

326 By contrast, for the case of Burkina Faso, regardless the control strategy (optimal, uniform or
327 over the younger fraction) the proportion of infected population is approximately the same as without
328 control (78%). The herd immunity threshold ($1 - 1/R_0 \approx 69.7\%$) is then reached for all the three con-
329 trol measures and the epidemic cannot restart (Figure 8 e). The cumulative mortality with a uniform
330 control of the whole population or over its younger fraction is comparable to that without any control

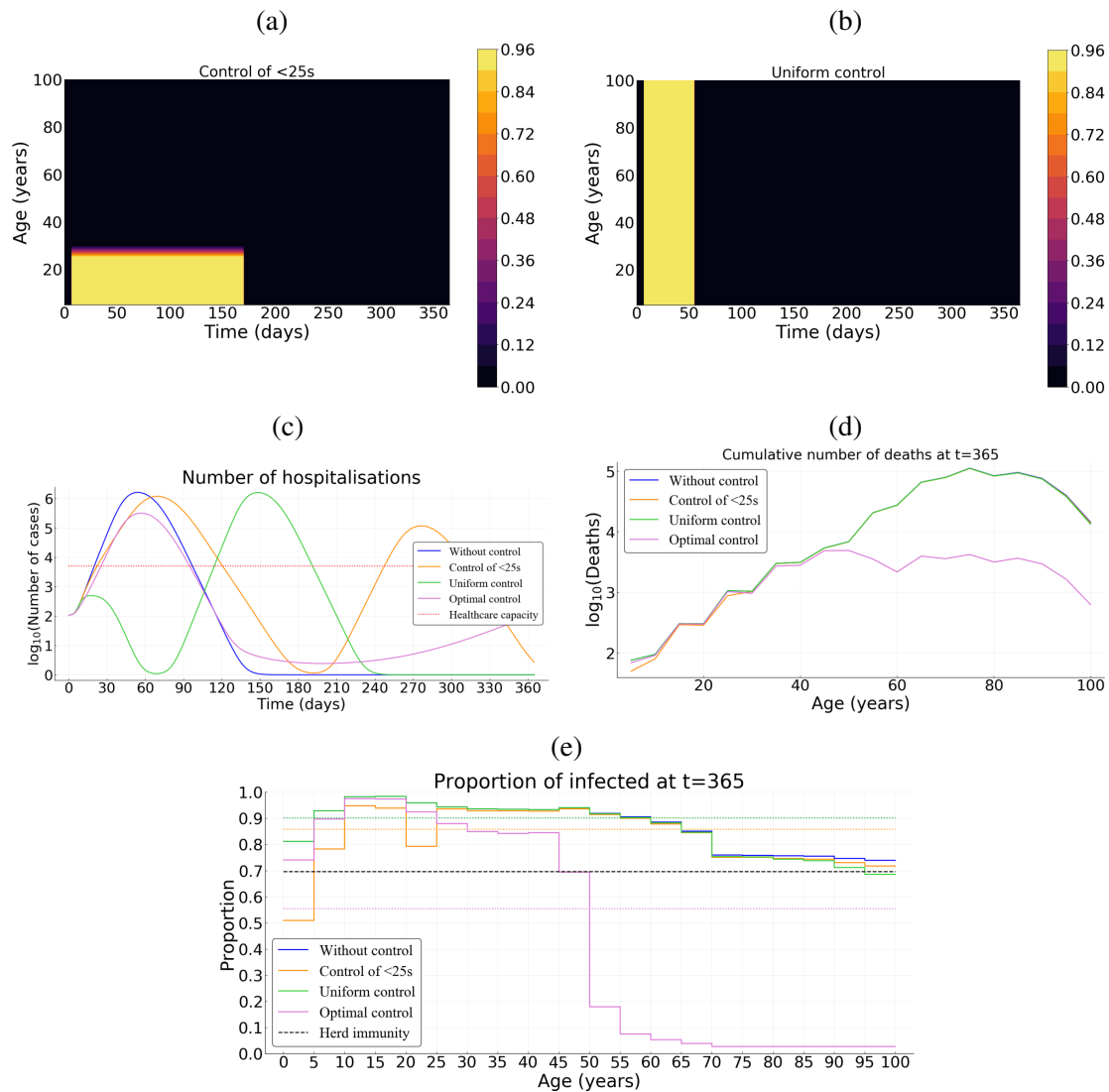


Figure 7: **Comparing optimal control with uniform control of the whole population of over its younger fraction in France.** (a) Illustration of the control over the young population and (b) uniform control of the whole population. (c) Number of hospitalizations. (d) Cumulative deaths per age at final time $T = 365$ days. (e) Age distribution of the proportions of the population that have been infected before one year. Here, we assume $B^* = 10^3$ and $p = 0.5$.

331 measure (Figure 8 d). However, despite their same proportion of infected individuals, the performance
 332 of the optimal control relatively to the uniform control of the whole population or over its younger
 333 fraction, is at least 50%.

334 A practical issue regarding the implementation of such optimal control strategy is the fact that
 335 it is a continuous function. One possibility to address this problem is to derive step functions. For
 336 instance, in Supplementary Figure S5, we subdivided the population into 10-year amplitude classes

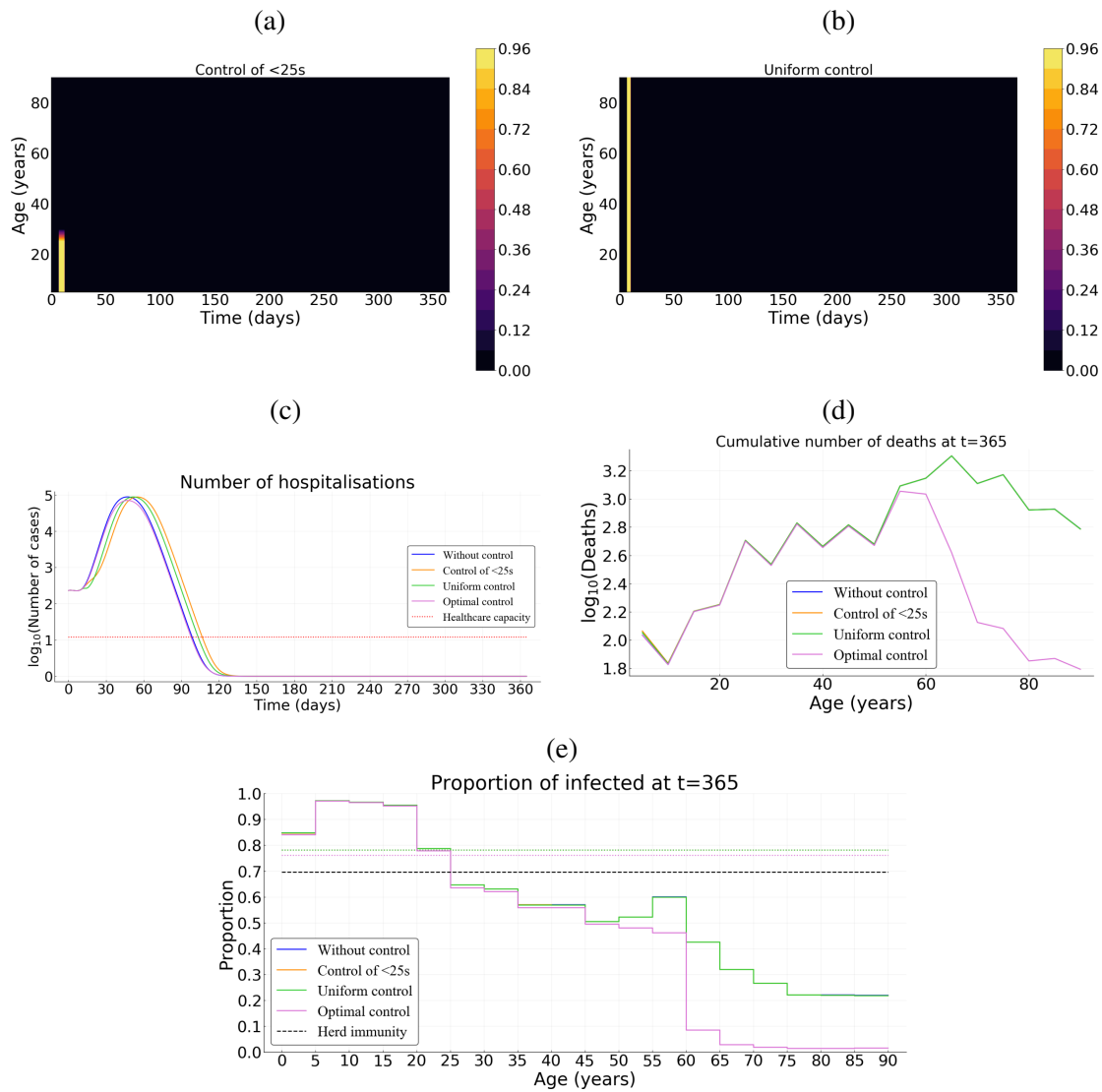


Figure 8: **Comparing optimal control with uniform control of the whole population or over its younger fraction in Burkina Faso.** (a) Illustration of the control over the young population and (b) uniform control of the whole population. (c) Number of hospitalizations. (d) Cumulative deaths per age at final time $T = 365$ days. (e) Age distribution of the proportions of the population that have been infected before one year. Here, we assume $B^* = 10^3$ and $p = 0.5$.

337 and updated the control every 3-weeks. Importantly, even though it is assumed to be constant during
 338 each 3-weeks period for each age-class, the control intensity directly originates from the results of
 339 the continuous optimal control strategy. This discrete implementation of the optimal strategy achieve
 340 similar efficiencies (Figure S5), with a relative performance of 91% compared to a doing nothing
 341 scenario.

342 6 Discussion

343 Non-pharmaceutical public health interventions can be implemented either to mitigate the COVID-19
344 epidemic wave, and rely on natural immunisation, or to suppress the wave long enough to develop
345 and implement a vaccine or a treatment. Here, we explicitly factor in the age heterogeneity of the
346 host population in the identification of the optimal allocation of the control efforts in three countries
347 (Burkina Faso, France, Vietnam) which have quite contrasted age-structure of their population and
348 social contacts (Figure 3).

349 We use optimal control theory to characterize an optimal strategy that significantly reduces the
350 number of deaths, while being sustainable at the population level. Our formulation assumes a quadratic
351 cost for the control effort. Overall, the optimal control lasts less shorter in Burkina Faso compared to
352 cases of France and Vietnam. We find that, with this strategy, the intensity of the control is always
353 relatively high on the older fraction of the population during at least a hundred days, before decreasing
354 more or less rapidly depending on the cost associated to the control and the social structure of the host
355 population. The control over the younger fraction of the population is weak and only occurs when
356 the cost associated with the optimal control is relatively low and, while the control extends to the
357 younger population in France and Vietnam after 2 or 3 months, such extension is very moderate (or
358 even negligible) in Burkina Faso. This late control over the younger part of the population actually
359 mimics the results [10] where the control did not peak right away. Intuitively, if control strategies
360 come at a high cost for the population, it is best to focus on the age classes that are the most at risk.
361 Conversely, if the control measures are more acceptable to the population, the optimal strategy is to
362 aim wide in order to completely suppress the epidemic wave.

363 Information on the natural history of paucisymptomatic infections of COVID-19 remains rela-
364 tively little-known [65, 66]. It is estimated that a proportion p of infected individuals will remain
365 asymptomatic throughout the course of infection. However, this proportion remains largely unspeci-
366 fied in the literature [65, 66]. We explored effects of the proportion p on the optimal control strategy
367 c^* . Overall, the proportion of paucisymptomatic infections has marginal effects on the optimal control
368 strategy (Figure S6). The optimal control remains strong over the older population from the begin-
369 ning of the epidemic, before being progressively relaxed. The control over the younger population is
370 weaker and occurs only if the control cost itself is low. But, the level of control over the younger frac-
371 tion increases when the proportion of paucisymptomatic infections decreases. Further, for high values
372 of B^* (10^3 or 10^4), the shape of the optimal control is qualitatively the same when the proportion p
373 varies, except for extreme high values of $p = 0.9$ and $B^* = 10^4$ for which the control becomes naturally
374 low for the whole population (Figure S6). Indeed, the epidemics cannot be stopped and the strategy
375 is then to reduce mortality by protecting the population the most at risk (here the older population).
376 However, with low value of B^* (10^2), different shape of the optimal control give the same result since
377 there are enough resources to stop the epidemics.

378 Given the leverage represented by school and university closure, we investigated the effect of

379 control measures over individuals aged under 25. Our results show that NPIs targeting the younger
 380 fraction of the population are not very efficient in reducing cumulative mortality, unless they can be
 381 implemented strongly and for a relatively long period. Indeed, the number of deaths with a control
 382 only over the younger population is similar to a doing nothing scenario for cases of Burkina Faso,
 383 France and Vietnam (Figures 7, 8, S4 a, c). Thus, this result does not seem to depend on the age-
 384 structure and social contacts of the population considered. However, the variation of the transmission
 385 probability with age (discussed below) can potentially impact such a result.

386 The formulation of the objective functional considered here searches for the optimal control effort
 387 the cumulative number of deaths. However, other objective functions can be considered including for
 388 example, long-term hospitalizations and long-term health consequences. It is equivalent to consider-
 389 ing the number of hospitalizations as the variable to be minimized and costs associated to long-term
 390 hospitalizations and long-term health consequences. This formulation may indeed be interesting to
 391 look at in details but would deserve to be considered independently in another study.

The model proposed here is an extension of the classical models based on ordinary differential
 equations that tackled the issue of the optimal control of COVID-19 outbreak [9–12]. Here, the whole
 population is structured by age (a) and additionally by the time since infection (i) for infectious indi-
 viduals, which echoes the model developed in [64] using a discrete-time formulation of the infection.
 With our continuous structure, we show that the number of new cases $I_N(t, a)$ at time t in individuals
 of age a is given by the renewal equation

$$I_N(t, a) = S_0(a) \int_0^\infty \int_0^{a_{\max}} K(a, a') \omega(a', i) I_N(t - i, a') da' di,$$

392 where K is the contact matrix and $\omega(a, i)$ is the infectiousness of individuals aged a which are in-
 393 fected since time i (Appendix B). For parameterisation purposes, we assume that $\omega(a, i)$ is the product
 394 between the proportion of individuals of age a in the whole population and the infectiousness $\bar{\beta}(i)$
 395 of individuals infected since time i . This is potentially a limitation —not in the model formulation
 396 proposed here, but rather in parameterisation perspective in relation to the existing literature— since
 397 infectiousness $\bar{\beta}$ could depend on the age a thereby creating an additional heterogeneity in addition
 398 to that since the time since infection i . This issue can be particularly important since some studies
 399 suggest a low risk of transmission in the young population (*e.g.* [67]). On the other hand, although
 400 superspreading events (of young people) have been documented, there is still much uncertainty about
 401 their relative role in the spread of the epidemic and about their origin (superspreading could be linked
 402 to environmental conditions, such as massive gatherings, rather than individual properties). Therefore,
 403 assuming independence from age seems the most parsimonious assumption given the current data.

404 Another potential limitation is the lack of gender structure and comorbidities in the model for-
 405 mulation. Given the observed male bias in mortality during the COVID-19 pandemic, it has been
 406 suggested that males are more at risk of developing severe infections [68]. This heterogeneity could
 407 readily be introduced in the model.

408 Contact networks have an important role in transmission dynamic models. Epidemic models that

409 determine which interventions can successfully prevent an outbreak may benefit from accounting
410 for social structure and mixing patterns. Contacts are highly assortative with age across a given
411 country, but regional differences in the age-specific contacts is noticeable [43]. The current model
412 could be modified to explore epidemiological dynamics in a spatially structured population with non-
413 homogeneous mixing, *e.g.* by using a meta-population model [69].

414 Another potential extension of the model would be to allow for the isolation of symptomatic cases
415 and their contacts, following the method developed in [70] and applied recently to digital contact
416 tracing [22]. Indeed, these measures strongly depend on the relative timing of infectiousness and
417 the appearance of symptoms, and the formulation of the presented model seems suitable for that.
418 However, this also raises technical challenges due to the double continuous structure. Being able to
419 identify age classes to follow in priority with contact tracing could be, though, an asset in controlling
420 epidemic spread.

421 **Code availability**

422 The code (with the Julia Programming Language) used to simulate the model can be accessed through
423 the Zenodo platform <http://doi.org/10.5281/zenodo.4288144>

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589 **A** Supplementary Figures

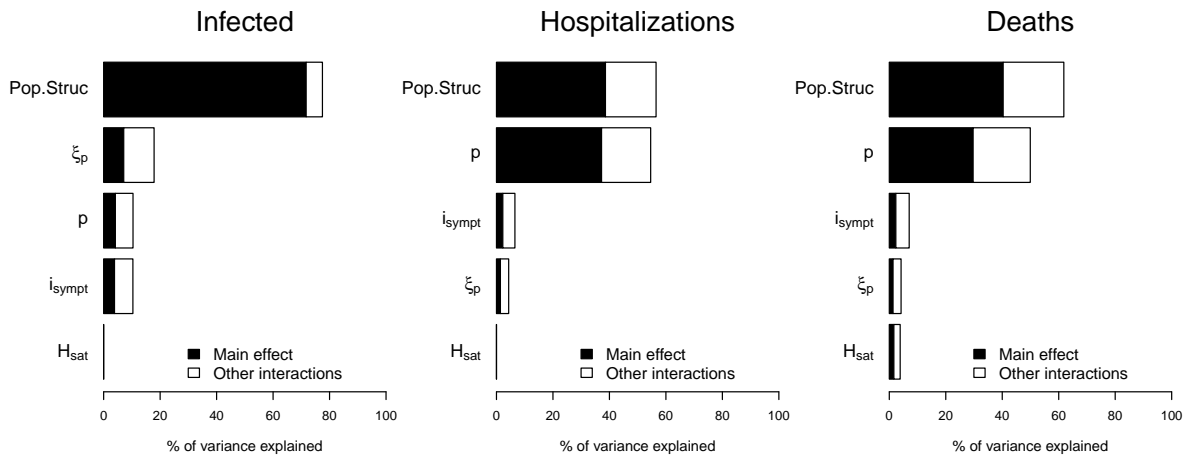


Figure S1: **Global sensitivity analysis.** Sensitivity of infected individuals, hospitalizations and deaths to the proportion of paucisymptomatic (p), average time of symptoms onset (i_{sympt}), infectiousness reduction of paucisymptomatic (ξ_p), healthcare capacity (H_{sat}) and population structure –Pop.Struc– (including the natural mortality, the size of the population, age-structure and social contacts).

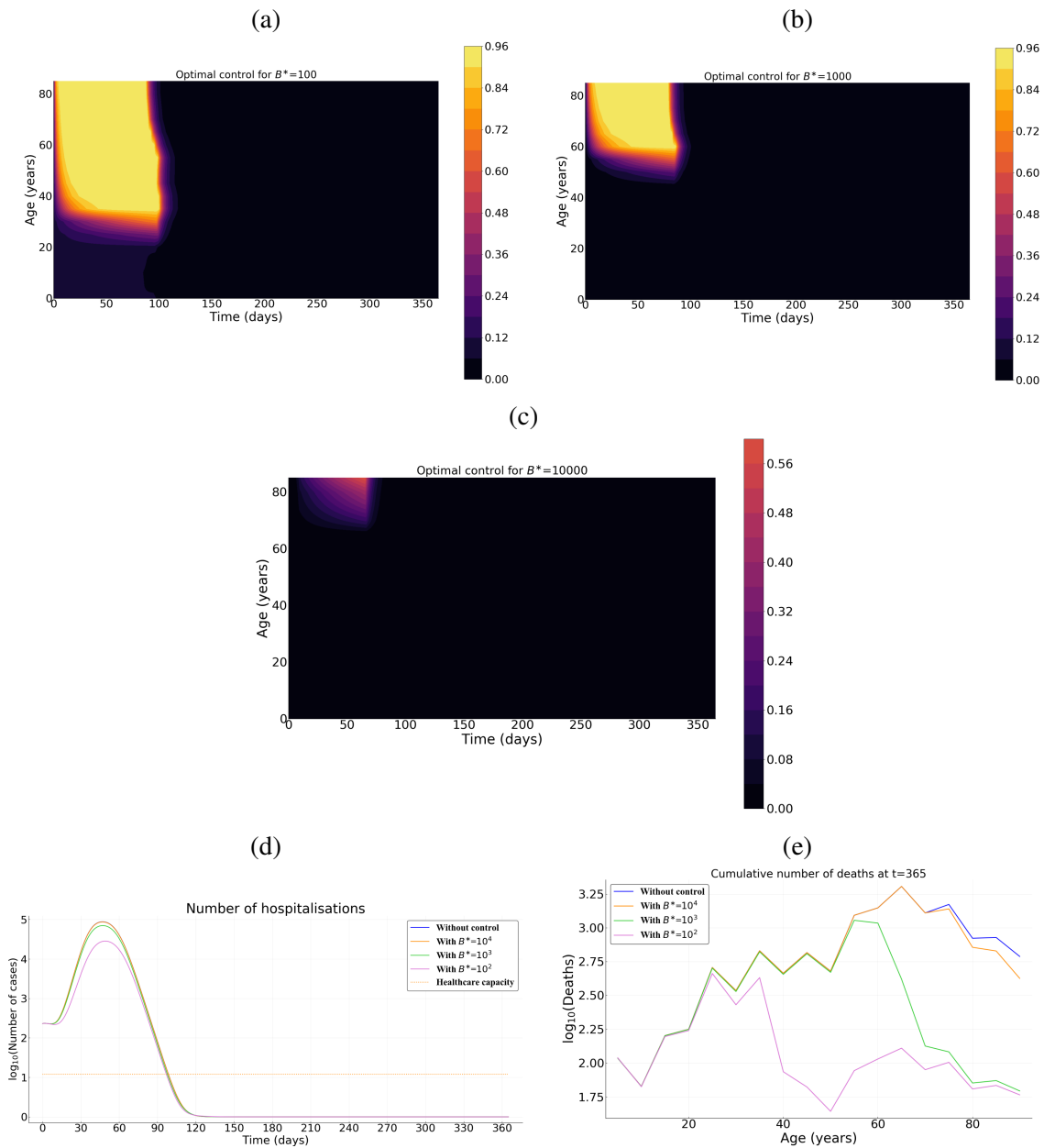


Figure S2: **Optimal control strategy (c^*) as a function of the cost of the control measures in Burkina Faso.** Intensity of the control as a function of time and host for for (a) relatively low $B^* = 10^2$, (b) an intermediate $B^* = 10^3$, and (c) a high $B^* = 10^4$ cost. (d) Prevalence of hospitalized patients as a function of the strategy and the cost. (e) Cumulative deaths per age at the end of the time interval (when $T = 365$ days). Parameter values not related to the control are identical to Figure 4.

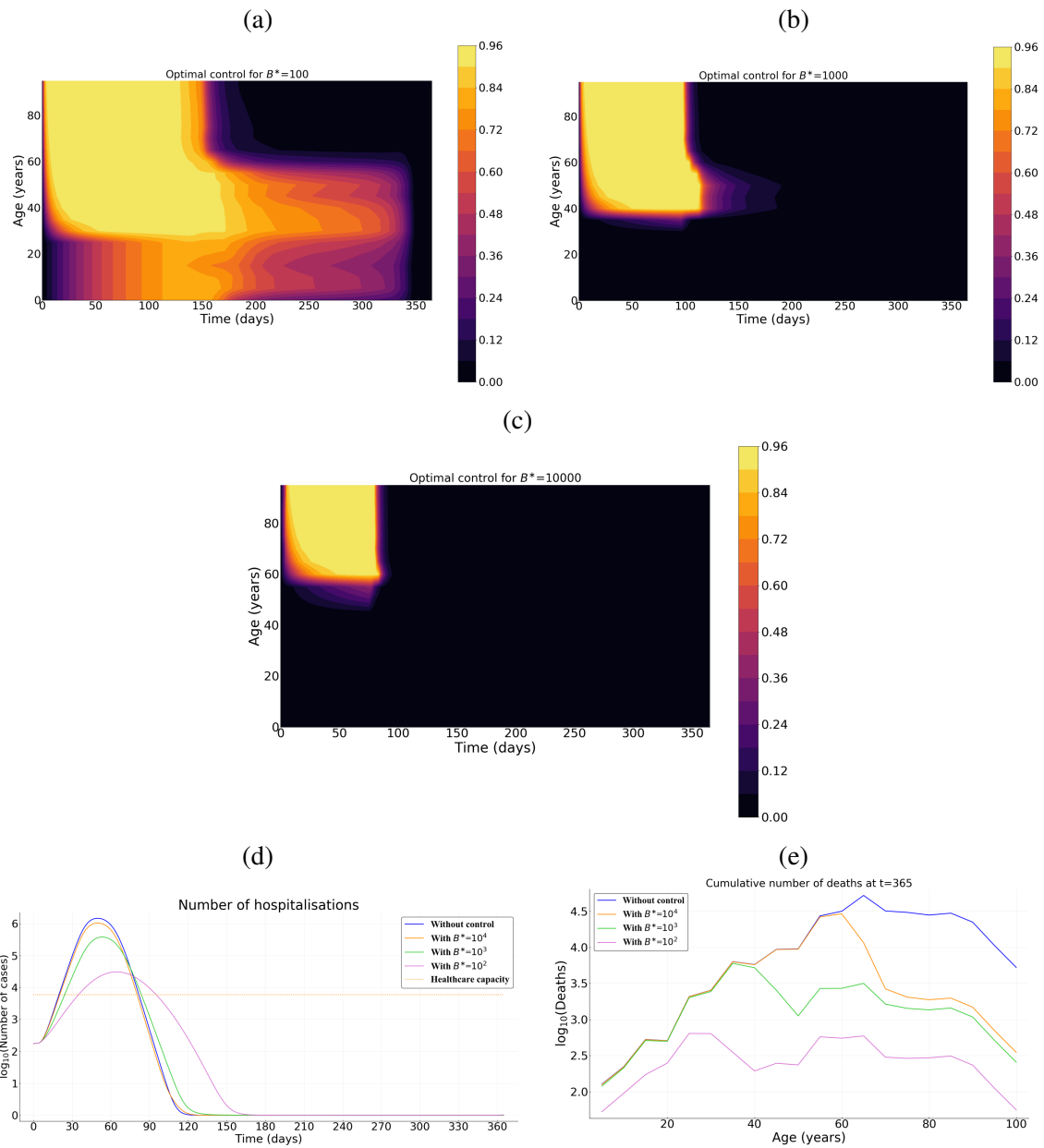


Figure S3: **Optimal control strategy (c^*) as a function of the cost of the control measures in Vietnam.** Intensity of the control as a function of time and host for for (a) relatively low $B^* = 10^2$, (b) an intermediate $B^* = 10^3$, and (c) a high $B^* = 10^4$ cost. (d) Prevalence of hospitalized patients as a function of the strategy and the cost. (e) Cumulative deaths per age at the end of the time interval (when $T = 365$ days). Parameter values not related to the control are identical to Figure 4.

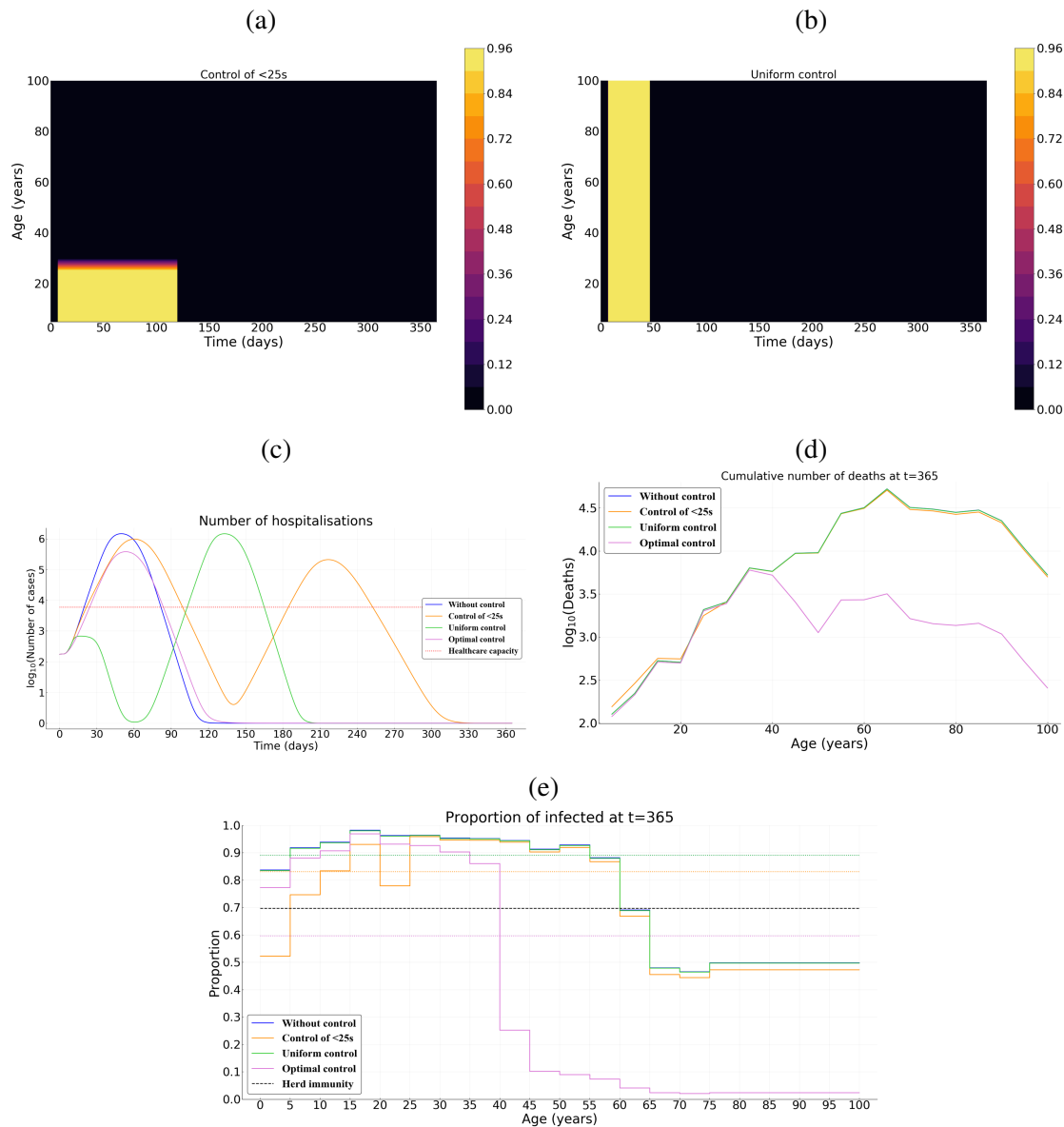


Figure S4: **Comparing optimal control with uniform control of the whole population or over its younger fraction in Vietnam.** (a) Illustration of the control over the young population and (b) uniform control of the whole population. (c) Number of hospitalizations. (d) Cumulative deaths per age at final time $T = 365$ days. (e) Age distribution of the proportions of the population that have been infected before one year. Here, we assume $B^* = 10^3$ and $p = 0.5$.

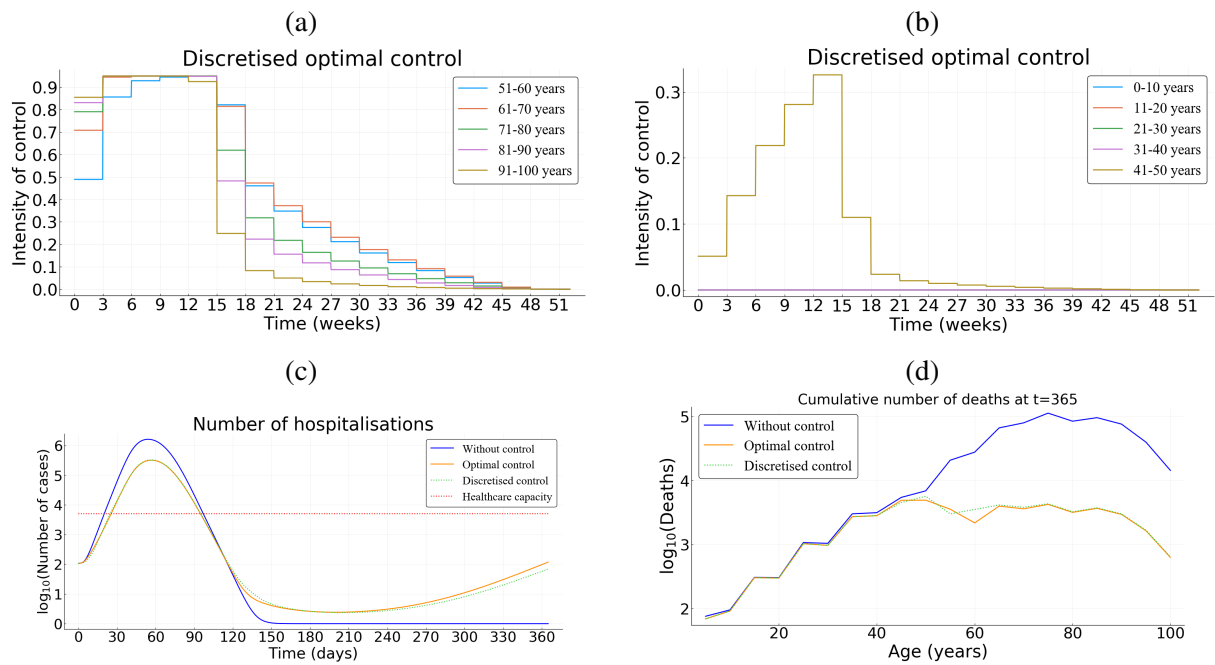


Figure S5: **Practicability of the age-structured optimal control.** (a)-(b) Step optimal controls with a 3-weeks update over the older and younger populations. The corresponding optimal is given by Figure 6 b. (c)-(d) Cumulative deaths per age at final time $T = 365$ days.

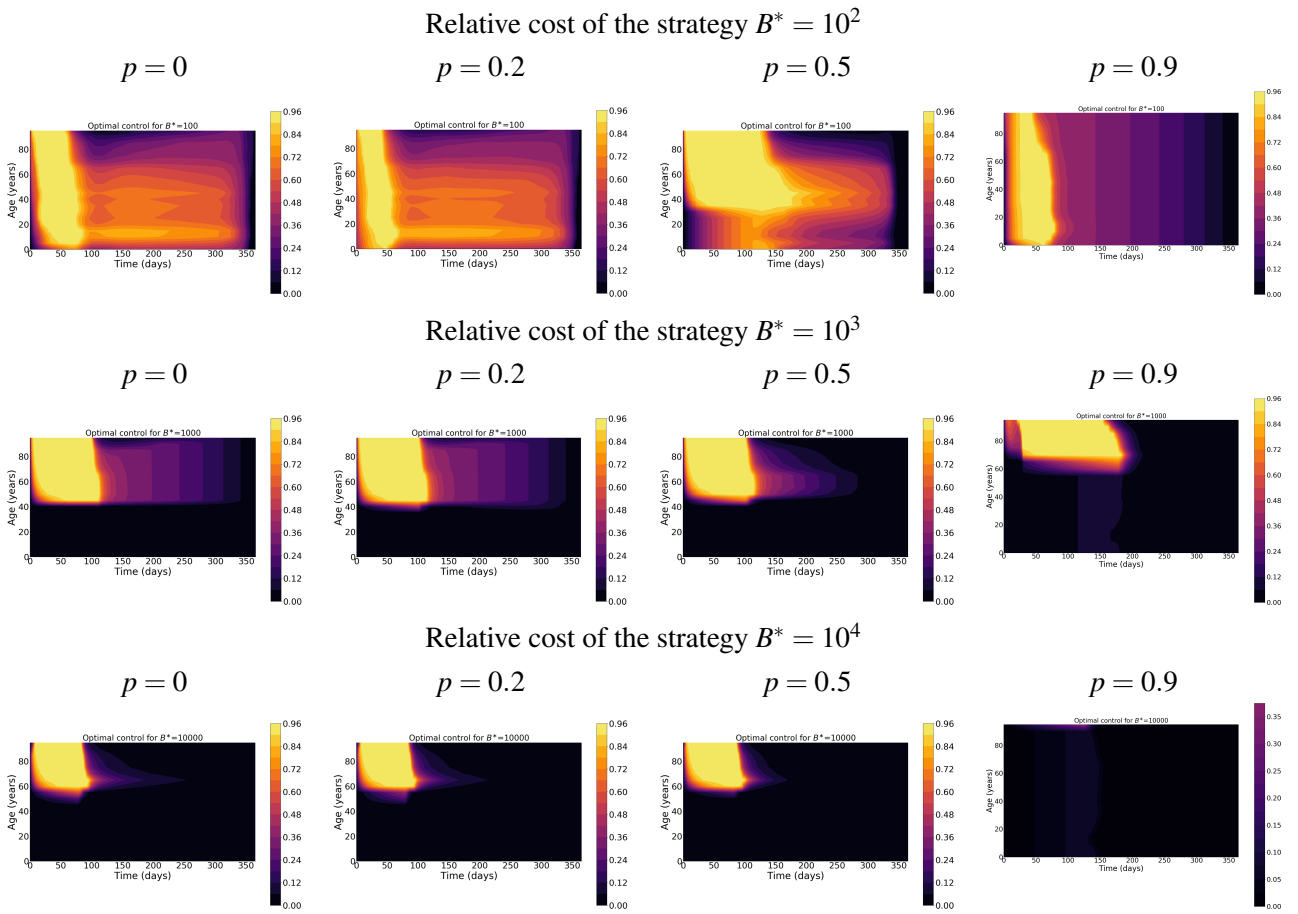


Figure S6: The effect of paucisymptomatic infections, through their proportion p , on the optimal control c^* .

593 B Basic reproduction number

Here we compute the basic reproduction number R_0 of the model (3)-(5). First let us set for $i \geq 0$ and $a \in [0, a_{\max}]$ the following functions

$$\begin{aligned}\pi_s(a, i) &= \exp\left(-i\mu_{nat}(a) - \int_0^i [\gamma_{dir}(a)\mathbf{1}_{[i_{sympt}, i_{\max}]}(\sigma) + h_s(a, \sigma)]d\sigma\right), \\ \pi_m(a, i) &= \exp\left(-i\mu_{nat}(a) - \int_0^i h_m(a, \sigma)d\sigma\right), \\ \pi_p(a, i) &= \exp\left(-i\mu_{nat}(a) - \int_0^i h_p(a, \sigma)d\sigma\right),\end{aligned}$$

594 that describe the survival probability of infected individuals (in the respective compartment), with age
595 a , from their infection until the time since infection i , in case of no hospitalisation (*i.e.* $H \equiv 0$). We
596 get the following Volterra formulation of the linearized system of (3)-(5):

$$I_s(t, a, i) = \begin{cases} I_{s,0}(a, i-t) \frac{\pi_s(a, i)}{\pi_s(a, i-t)}, & \text{for } t \in [0, i), \\ (1-p)q(a)\lambda_0(t-i, a)S_0(a)\pi_s(a, i), & \text{for } t \geq i, \end{cases} \quad (\text{B.1})$$

597

$$I_m(t, a, i) = \begin{cases} I_{m,0}(a, i-t) \frac{\pi_m(a, i)}{\pi_m(a, i-t)}, & \text{for } t \in [0, i), \\ (1-p)(1-q(a))\lambda_0(t-i, a)S_0(a)\pi_m(a, i), & \text{for } t \geq i \end{cases} \quad (\text{B.2})$$

598 and

$$I_p(t, a, i) = \begin{cases} I_{A,0}(a, i-t) \frac{\pi_p(a, i)}{\pi_p(a, i-t)}, & \text{for } t \in [0, i), \\ p\lambda_0(t-i, a)S_0(a)\pi_p(a, i), & \text{for } t \geq i \end{cases} \quad (\text{B.3})$$

599 where $\lambda_0 = \lambda(\cdot, \cdot, 0)$ is defined by

$$\lambda_0(t, a) = \int_0^{a_{\max}} K(a, a') \int_0^\infty (\beta_s(a', i)I_s(t, a', i) + \beta_m(a', i)I_m(t, a', i) + \beta_p(a', i)I_p(t, a', i)) di da', \quad (\text{B.4})$$

where $\beta_k, k \in \{s, m, p\}$ are defined in Section 3.2. Let $I_N(t, a) = \lambda_0(t, a)S_0(a)$ be the density of newly infected of age a at time t , with $c \equiv 0$. Then (B.1)-(B.2)-(B.3) can be rewritten as the following Volterra formulation:

$$I_N(t, a) = S_0(a) \int_0^t \int_0^{a_{\max}} K(a, a') \omega(a', i) I_N(t-i, a') da' di + f(t, a),$$

where

$$\omega(a', i) = \beta_s(a', i)(1-p)q(a')\pi_s(a', i) + \beta_m(a', i)(1-p)(1-q(a'))\pi_m(a', i) + \beta_p(a', i)p\pi_p(a', i)$$

and $f(t, a)$ is the density of new infections produced by the initial population. Therefore, the basic reproduction number R_0 is the spectral radius, denoted by $r(U)$, of the next generation operator U defined on $L^1_+(0, a_{\max})$ by

$$U : L^1(0, a_{\max}) \ni v \longmapsto S_0(\cdot) \int_0^\infty \int_0^{a_{\max}} K(\cdot, a') \omega(a', i) v(a') da' di \in L^1(0, a_{\max})$$

600 As explained in Section 3.2, it is estimated in [22] that each average infectiousness β_k ($k \in \{s, m, p\}$)
 601 takes the form of a Weibull distribution $W(3, 5.65)$ so that the mean and median are equal to 5.0
 602 days while the standard deviation is 1.9 days. Based on this estimation, we assume that $\beta_k(a, i) =$
 603 $\alpha \bar{\beta}(i) \xi_k(i)$ where $\bar{\beta} \sim W(3, 5.65)$ and α is a positive parameter to be determined. Consequently, it
 604 follows that α is given by

$$\alpha = \frac{R_0}{r(\bar{U})}, \quad (\text{B.5})$$

where \bar{U} is the operator defined by

$$\bar{U} : L^1(0, a_{\max}) \ni v \mapsto S_0(\cdot) \int_0^\infty \int_0^{a_{\max}} K(\cdot, a') \bar{\omega}(a', i) v(a') da' di \in L^1(0, a_{\max})$$

with

$$\bar{\omega}(a', i) = \bar{\beta}(i) [\xi_s(i)(1-p)q(a')\pi_s(a', i) + \xi_m(i)(1-p)(1-q(a'))\pi_m(a', i) + \xi_p(i)p\pi_p(a', i)].$$

We see that \bar{U} can be rewritten as

$$\bar{U}v(a) = S_0(a) \int_0^{a_{\max}} K(a, a') \bar{\Omega}(a') v(a') da', \quad \forall v \in L^1_+(0, a_{\max}) \quad \text{where} \quad \bar{\Omega}(a') = \int_0^\infty \bar{\omega}(a', i) di.$$

605 Now, in order to compute the spectral radius $r(\bar{U})$, we first make the following assumptions:

606 **Assumption B.1** *We suppose that functions $S_0, K, \bar{\Omega}$ are bounded and positive almost everywhere.*

Then, we can show that $r(\bar{U})$ is given by the spectral radius of the following linear operator:

$$L^1(0, a_{\max}) \ni v \mapsto \int_0^{a_{\max}} K(\cdot, a') \bar{\Omega}(a') S_0(a') v(a') da' \in L^1(0, a_{\max})$$

607 which can be easily computed since the age a is numerically divided into N classes, so that the term
 608 inside the integral of the latter equation is a $N \times N$ matrix. Finally, we obtain α from (B.5).

In addition to Assumption B.1, if the function K is symmetric, we can define the positive self-adjoint operator S by

$$S : L^2(0, a_{\max}) \ni v \mapsto \sqrt{S_0(\cdot) \bar{\Omega}(\cdot)} \int_0^{a_{\max}} K(\cdot, a') \sqrt{S_0(a') \bar{\Omega}(a')} v(a') da' \in L^2_+(0, a_{\max}).$$

609 We then deduce the following

Proposition B.2 *Let K be symmetric and Assumption B.1 be satisfied. Then, operators \bar{U} and S are positive and compact, their spectra $\sigma(\bar{U}) \setminus \{0\}$ and $\sigma(S) \setminus \{0\}$ are composed of isolated eigenvalues with finite algebraic multiplicity. Moreover, we have $\sigma(\bar{U}) = \sigma(S) \subset \mathbb{R}_+$ and the following Rayleigh formula holds:*

$$r(\bar{U}) = r(S) = \sup_{\substack{v \in L^2(0, a_{\max}) \\ \|v\|_{L^2(0, a_{\max})} = 1}} \int_0^{a_{\max}} \int_0^{a_{\max}} K(a, a') \sqrt{S_0(a') \bar{\Omega}(a')} \sqrt{S_0(a) \bar{\Omega}(a)} v(a') v(a) da' da.$$

Proof. The compactness of both integral operators follows from the fact that $a_{\max} < \infty$ by assumption (see Table 1), hence their spectra are punctual. Now we prove that $\sigma(\bar{U}) = \sigma(S)$. Let $\nu \in \sigma(\bar{U})$ be an eigenvalue of \bar{U} and $\phi \in L^1(0, a_{\max})$ be the associated eigenvector, *i.e.*

$$\bar{U}\phi(a) = S_0(a) \int_0^{a_{\max}} K(a, a') \bar{\Omega}(a') \phi(a') da' = \nu \phi(a), \quad \forall a \in [0, a_{\max}]$$

so that $\phi \in L^\infty(0, a_{\max}) \subset L^2(0, a_{\max})$. Defining the function

$$\psi = \frac{\phi \sqrt{\bar{\Omega}}}{\sqrt{S_0}} \in L^2(0, a_{\max})$$

leads to

$$\nu \psi(a) = \sqrt{S_0(a) \bar{\Omega}(a)} \int_0^{a_{\max}} K(a, a') \sqrt{\bar{\Omega}(a') S_0(a')} \psi(a') da' = S\psi(a), \quad \forall a \in [0, a_{\max}]$$

i.e. $\nu \in \sigma(S)$ is an eigenvalue of S associated to the eigenvector ψ , so that $\sigma(\bar{U}) \subset \sigma(S)$. For the reverse inclusion, let $\nu \in \sigma(S)$ and $\psi \in L^2(0, a_{\max}) \subset L^1(0, a_{\max})$ be the associated eigenvector for S . It follows that the function

$$\phi = \frac{\psi \sqrt{S_0}}{\sqrt{\bar{\Omega}}} \in L^1(0, a_{\max})$$

610 is an eigenvector of \bar{U} related to the eigenvalue $\nu \in \sigma(\bar{U})$, whence $\sigma(\bar{U}) = \sigma(S)$. In particular,
 611 both spectral radius are equal. Finally, the Rayleigh formula is classical for positive and symmetric
 612 operators. ■

613 C Computations of the adjoint system

In order to deal with the necessary optimality conditions, we use some results in [61]. Next, we detail the computations of the adjoint system (12)-(13). To this end, we first define the functions $y_1, Q : [0, T] \times [0, a_{\max}] \rightarrow \mathbb{R}$ and $y_2 : [0, T] \times [0, a_{\max}] \times \mathbb{R}_+$ by:

$$y_1(t, a) = \begin{pmatrix} S(t, a) \\ R(t, a) \end{pmatrix}, \quad y_2(t, a, i) = \begin{pmatrix} I_s(t, a, i) \\ I_m(t, a, i) \\ I_p(t, a, i) \end{pmatrix}, \quad Q(t, a) = \begin{pmatrix} H(t) & E(t, a) & b(t, a) \end{pmatrix}$$

614 wherein

$$g_H(i, y_2(t, a, i)) = I_s(t, a, i) 1_{[i_{\text{symp}}, \infty)}(i), \quad g_R(i, y_2(t, a, i)) = \sum_{k \in \{s, m, p\}} h_k(a, i) I_k(t, a, i),$$

$$g_\lambda(a, i, y_1, y_2) = S(t, a) \int_0^{a_{\max}} K(a, a') (\beta_s(a', i) I_s(t, a', i) + \beta_m(a', i) I_m(t, a', i) + \beta_p(a', i) I_p(t, a', i)) da',$$

$$H(t) = \int_0^\infty \int_0^{a_{\max}} g_H(i, y_2(t, a, i)) da di, \quad E(t, a) = \int_0^\infty g_\lambda(a, i, y_1(t, a, i), y_2(t, a, i)) di,$$

$$b(t, a) = \int_0^\infty g_R(i, y_2(t, a, i)) di.$$

The model (5) thus rewrites as

$$\begin{cases} \partial_t y_1(t, a) &= F_1(a, Q(t, a), c(t, a), y_1(t, a)), \\ (\partial_t + \partial_i) y_2(t, a, i) &= F_2(a, i, Q(t, a), c(t, a), y_2(t, a, i)), \\ y_2(t, a, 0) &= \Phi(a, c(t, a), E(t, a)), \end{cases}$$

with

$$F_1(a, Q(t, a), c(t, a), y_1(t, a)) = \begin{pmatrix} -\mu(a, H(t))S(t, a) - (1 - c(t, a))E(t, a) \\ -\mu(a, H(t))R(t, a) + b(t, a) \end{pmatrix},$$

$$F_2(a, i, Q(t, a), c(t, a), y_2(t, a, i)) = \begin{pmatrix} -(\mu(a, H(t)) + \gamma(a, i, H(t)) + h_s(a, i))I_s(t, a, i) \\ -(\mu(a, H(t)) + h_m(a, i))I_m(t, a, i) \\ -(\mu(a, H(t)) + h_p(a, i))I_p(t, a, i) \end{pmatrix},$$

and

$$\Phi(a, c(t, a), Q(t, a)) = \begin{pmatrix} (1 - p)q(a)(1 - c(t, a))E(t, a) \\ (1 - p)(1 - q(a))(1 - c(t, a))E(t, a) \\ p(1 - c(t, a))E(t, a) \end{pmatrix}.$$

We now rewrite the functional J as

$$J(c) = \int_0^T \int_0^{a_{\max}} \left(\mathcal{J}_1(a, c(t, a), Q(t, a), y_1(t, a)) + \int_0^\infty \mathcal{J}_2(a, i, Q(t, a), y_2(t, a, i)) di \right) da dt$$

which is decomposed into

$$\mathcal{J}_1(a, c(t, a), Q(t, a), y_1(t, a)) = \mu_{add}(a, H(t))(S(t, a) + R(t, a)) + B(a)c^2(t, a)$$

and

$$\mathcal{J}_2(a, i, Q(t, a), y_2(t, a, i)) = \gamma(a, i, H(t))I_s(t, a, i) + \mu_{add}(a, H(t))(I_s(t, a, i) + I_m(t, a, i) + I_p(t, a, i)).$$

We denote by $z_k, \zeta_k : [0, T] \times [0, a_{\max}] \rightarrow \mathbb{R}$ (for $k \in \{1, 2, 3\}$) the following adjoint functions

$$z_1(t, a) = (z_S(t, a), z_R(t, a)), \quad \zeta(t, a) = (\zeta_1(t, a), \zeta_2(t, a), \zeta_3(t, a)),$$

and we denote by $z_2 : [0, T] \times [0, a_{\max}] \times \mathbb{R}_+$ the following adjoint function

$$z_2(t, a, i) = (z_{I_s}(t, a, i), z_{I_m}(t, a, i), z_{I_p}(t, a, i)),$$

satisfying $\lim_{i \rightarrow \infty} z_2(t, a, i) = 0$ and $z_1(T, a) = z_2(T, a, i) = 0$. We get

$$\nabla_{y_1} \mathcal{J}_1(a, c(t, a), Q(t, a), y_1(t, a)) = \begin{pmatrix} \mu_{add}(a, H(t)) \\ \mu_{add}(a, H(t)) \end{pmatrix}^T$$

$$\nabla_{y_2} \mathcal{J}_2(a, i, Q(t, a), y_2(t, a, i)) = \begin{pmatrix} \mu_{add}(a, H(t)) + \gamma(a, i, H(t)) \\ \mu_{add}(a, H(t)) \\ \mu_{add}(a, H(t)) \end{pmatrix}^T$$

$$\nabla_{y_1} F_1(a, Q(t, a), c(t, a), y_1(t, a)) = \begin{pmatrix} -\mu(a, H(t)) & 0 \\ 0 & -\mu(a, H(t)) \end{pmatrix}$$

and

$$\nabla_{y_2} F_2 = \begin{pmatrix} -\mu(a, H(t)) - \gamma(a, i, H(t)) - h_s(a, i) & 0 & 0 \\ 0 & -\mu(a, H(t)) - h_m(a, i) & 0 \\ 0 & 0 & -\mu(a, H(t)) - h_p(a, i) \end{pmatrix},$$

615 where $\nabla_y F$ denotes differentiation of F with respect to the variable y .

Then

$$(z_1 \cdot \nabla_{y_1} F_1)(t, a) = \begin{pmatrix} -\mu(a, H(t))z_S(t, a) & -\mu(a, H(t))z_R(t, a) \end{pmatrix}$$

and

$$(z_2 \cdot \nabla_{y_2} F_2)(t, a, i) = \begin{pmatrix} -(\mu + \gamma + h_s)z_{I_s}(t, a, i) & -(\mu + h_m)z_{I_m}(t, a, i) & -(\mu + h_p)z_{I_p}(t, a, i) \end{pmatrix}.$$

Setting

$$g_1(a, y_1, y_2) = \begin{pmatrix} \int_0^\infty g_H(i, y_2(t, a, i)) di \\ E(t, a) \\ b(t, a) \end{pmatrix}, \quad g_2(a, i, y_1, y_2) = \begin{pmatrix} g_H(i, y_2(t, a, i)) \\ g_\lambda(a, i, y_1(t, a, i), y_2(t, a, i)) \\ g_R(i, y_2(t, a, i)) \end{pmatrix},$$

we see that

$$\nabla_{y_1} g_1(a, y_1, y_2) = \begin{pmatrix} 0 & 0 & 0 \\ \int_0^\infty \int_0^{a_{\max}} K(a, a') (\beta_s(a', i) I_s(t, a', i) + \beta_m(a', i) I_m(t, a', i) + \beta_p(a', i) I_p(t, a', i)) da' di & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$\nabla_{y_2} g_2(a, i, y_1, y_2) = \begin{pmatrix} \mathbf{1}_{[i_{\text{sympt}}, \infty)}(i) & 0 & 0 \\ S(t, \cdot) \beta_s(a, i) K(\cdot, a) & S(t, \cdot) \beta_m(a, i) K(\cdot, a) & S(t, \cdot) \beta_p(a, i) K(\cdot, a) \\ h_s(a, i) & h_m(a, i) & h_p(a, i) \end{pmatrix}.$$

From there, we deduce that

$$(\zeta \cdot \nabla_{y_1} g_1)(t, a) = \left(\zeta_2(t, a) \int_0^\infty \int_0^{a_{\max}} K(a, a') (\beta_s(a', i) I_s(t, a', i) + \beta_m(a', i) I_m(t, a', i) + \beta_p(a', i) I_p(t, a', i)) da' di \quad 0 \right)$$

and

$$(\zeta \cdot \nabla_{y_2} g_2)(t, a, i) = \begin{pmatrix} \zeta_1(t, a) \mathbf{1}_{[i_{\text{sympt}}, \infty)}(i) + \beta_s(a, i) \int_0^{a_{\max}} \zeta_2(t, a') S(t, a') K(a', a) da' + \zeta_3(t, a) h_s(a, i) \\ \beta_m(a, i) \int_0^{a_{\max}} \zeta_2(t, a') S(t, a') K(a', a) da' + \zeta_3(t, a) h_m(a, i) \\ \beta_p(a, i) \int_0^{a_{\max}} \zeta_2(t, a') S(t, a') K(a', a) da' + \zeta_3(t, a) h_p(a, i) \end{pmatrix}^T.$$

The adjoint system is given by

$$\begin{cases} -\frac{\partial z_1}{\partial t}(t, a) & = \nabla_{y_1} \mathcal{J}_1(t, a) + (z_1 \cdot \nabla_{y_1} F_1)(t, a) + (\zeta \cdot \nabla_{y_1} g_1)(t, a) \\ -\left(\frac{\partial z_2}{\partial t} + \frac{\partial z_2}{\partial i}\right)(t, a, i) & = \nabla_{y_2} \mathcal{J}_2(t, a) + (z_2 \cdot \nabla_{y_2} F_2)(t, a, i) + (\zeta \cdot \nabla_{y_2} g_2)(t, a, i) \end{cases}$$

which is equivalent to (12). Next, we see that

$$\nabla_Q \Phi(t, a) = \begin{pmatrix} 0 & (1-p)q(a)(1-c(t, a)) & 0 \\ 0 & (1-p)(1-q(a))(1-c(t, a)) & 0 \\ 0 & p(1-c(t, a)) & 0 \end{pmatrix}$$

whence

$$(z_2(\cdot, \cdot, 0) \cdot \nabla_Q \Phi)(t, a) = \left(0 \quad [1-c(t, a)][(1-p)(q(a)z_{I_s} + (1-q(a))z_{I_m}) + pz_{I_p}](t, a, 0) \quad 0 \right).$$

Further, we have

$$\nabla_Q \mathcal{J}_1(t, a) = \left(\frac{\partial \mu}{\partial H}(a, H(t))(S(t, a) + R(t, a)) \quad 0 \quad 0 \right)$$

and

$$\nabla_Q \mathcal{J}_2(t, a, i) = \left(\frac{\partial \mu}{\partial H}(a, H(t))(I_s(t, a, i) + I_m(t, a, i) + I_p(t, a, i)) + \frac{\partial \gamma}{\partial H}(a, i, H(t))I_s(t, a, i) \quad 0 \quad 0 \right).$$

We also see that $\nabla_Q g_1 \equiv 0$, $\nabla_Q g_2 \equiv 0$,

$$\nabla_Q F_1(t, a) = \begin{pmatrix} -\frac{\partial \mu}{\partial H}(a, H(t))S(t, a) & -(1-c(t, a)) & 0 \\ -\frac{\partial \mu}{\partial H}(a, H(t))R(t, a) & 0 & 1 \end{pmatrix}$$

and

$$\nabla_Q F_2(t, a, i) = \begin{pmatrix} -\left(\frac{\partial \mu}{\partial H}(a, H(t)) + \frac{\partial \gamma}{\partial H}(a, i, H(t))\right)I_s(t, a, i) & 0 & 0 \\ -\frac{\partial \mu}{\partial H}(a, H(t))I_m(t, a, i) & 0 & 0 \\ -\frac{\partial \mu}{\partial H}(a, H(t))I_p(t, a, i) & 0 & 0 \end{pmatrix}$$

whence

$$(z_1 \cdot \nabla_Q F_1)(t, a) = \begin{pmatrix} -\frac{\partial \mu}{\partial H}(a, H(t))S(t, a)z_S(t, a) - \frac{\partial \mu}{\partial H}(a, H(t))R(t, a)z_R(t, a) \\ -(1-c(t, a))z_S(t, a) \\ z_R(t, a) \end{pmatrix}^T$$

and

$$(z_2 \cdot \nabla_Q F_2)(t, a, i) = \left(-\left(\frac{\partial \mu}{\partial H} + \frac{\partial \gamma}{\partial H}\right)I_s z_{I_s} - \frac{\partial \mu}{\partial H}I_m z_{I_m} - \frac{\partial \mu}{\partial H}I_p z_{I_p} \quad 0 \quad 0 \right).$$

Finally, the adjoint functions ζ must satisfy the following equation:

$$\begin{aligned} \zeta(t, a) &= (z_2(\cdot, \cdot, 0) \cdot \nabla_Q \Phi)(t, a) + (\nabla_Q \mathcal{J}_1)(t, a) + (z_1 \cdot \nabla_Q F_1)(t, a) + (\zeta \cdot \nabla_Q g_1)(t, a) \\ &\quad + \int_0^\infty ((\nabla_Q \mathcal{J}_2)(t, a, i) + (z_2 \cdot \nabla_Q F_2)(t, a, i) + (\zeta \cdot \nabla_Q g_2)(t, a, i)) di \end{aligned}$$

which is equivalent to (13). Finally by [61], the Hamiltonian is given by

$$\mathcal{H}(t, a, c) = z_2(t, a, 0) \cdot \Phi(t, a, c, Q) + \mathcal{J}_1(a, c, Q, y_1) + \int_0^\infty \mathcal{J}_2(a, i, Q, y_2) di$$

which leads to

$$\begin{aligned} \mathcal{H}(t, a, c) &= E(t, a)[1-c(t, a)][(1-p)(q(a)z_{I_s} + (1-q(a))z_{I_m}) + pz_{I_p}](t, a, 0) \\ &\quad + \mu_{add}(a, H(t))(S(t, a) + R(t, a)) + B(a)c^2(t, a) \\ &\quad + \int_0^\infty (\gamma(a, i, H(t))I_s(t, a, i) + \mu_{add}(a, H(t))(I_s(t, a, i) + I_m(t, a, i) + I_p(t, a, i))) di. \end{aligned} \quad (\text{C.1})$$