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RECEIVED 30 January 2023

ACCEPTED 14 April 2023

PUBLISHED 18 May 2023

## CITATION

Caga-anan RL, Macalisang JM, Dalisay JLM,  
Raza MN, Martinez JGT and Arcede JP (2023)  
Optimal vaccination control for COVID-19 in a  
metapopulation model: a case of the  
Philippines. *Front. Appl. Math. Stat.* 9:1154634.  
doi: 10.3389/fams.2023.1154634

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# Optimal vaccination control for COVID-19 in a metapopulation model: a case of the Philippines

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We investigate a contextual problem of how to distribute a limited supply of vaccines over a period of time in a country where different regions have its own vaccination capacities. Considering that daily vaccination will affect future disease progression, we aim to find a distribution strategy over time that can minimize the total infection and implementation costs. Lagrangian and Eulerian migrations connect our multi-patch COVID-19 model, and vaccination is added as a control measure. An optimal control problem with an isoperimetric constraint is formulated and solved using the Adapted Forward–Backward Sweep Method. In distributing 5 million vaccines in 50 days, simulations showed that the optimal control strategy could lead to a difference of reducing two hundred thousand infections in just one region.

## KEYWORDS

metapopulation, vaccination, optimal, control, COVID-19, Philippines

## 1. Introduction

The rapid development of COVID-19 vaccines, which began less than a year after the emergence of the SARS-CoV-2 virus, has made vaccination arguably the most effective method for preventing the spread of COVID-19 [1–3]. Despite the numerous problems with the COVID-19 vaccine, global communities applauded its introduction and accelerated mass vaccination. The Philippines have administered 166,138,040 vaccinations as of 8 December 2022 since vaccinations began in March 2021. It includes the first and second doses (71 million and 73 million, respectively) and more than 21 million booster doses administered to frontline workers, senior citizens, and the immunocompromised<sup>1</sup>. In the second quarter of 2020–2021, the government's gross domestic product (GDP) increased by 12.1% due to the expansion of economic activities made possible by vaccination mandates and the strengthening of minimum health protocols. This is in stark contrast to the –16.6% GDP recorded at the height of the pandemic [4]. In addition, the unemployment rate decreased from 8.8 percent in 2021 to 6.4 percent in 2022.

1 National COVID-19 Vaccination Dashboard | Department of Health Website. Available online at: <https://doh.gov.ph/covid19-vaccination-dashboard>.

By the end of 2022, however, approximately 36 percent of the country's population still remained not fully vaccinated. In some areas of the region, vaccination participation is low. Vaccine hesitancy is endemic in every nation. In the Philippines, the decision to vaccinate can be influenced by differing factors, including individuals (i.e., perceptions of vaccine effectiveness and also inefficiency and inflexibility of the system), the community (i.e., vaccine hesitancy for religious reasons and social networks), and the health system (politics and policy) [5]. On a global level, countries with large vaccine industries reserve their own supplies for their own populations. Moreover, global manufacturing capabilities remain far below what is required, which leads to vaccine politics or global competition over a limited supply. The longer the vaccinations are delayed, the greater the likelihood that new virus strains will emerge and undermine the efficiency of vaccines.

Since the early stages of the pandemic, mathematical modeling has assisted the Philippines in its response, and a number of studies [6–8], including regional ones [9, 10], have been published. In addition, it has been used extensively in many countries to evaluate pandemic control strategies such as lockdown, social distancing, testing, face mask use, and public awareness [11–21].

With the introduction of COVID-19 vaccines, numerous modeling studies on vaccine allocation are available worldwide, based on age or risk group [22–25], space [26], and dose timing [27, 28]. However, there are few mathematical modeling studies on the optimal control of vaccine prioritization against COVID-19 at the regional level. Molla et al. [29] introduced an SEIR-type compartmental model with vaccination that accounts for heterogeneity across age groups and mobility across geographic regions. To optimize the allocation of vaccines in Italy, Lemaitre et al. [30] evaluated a second spatially explicit COVID-19 epidemiological model of the SEIR type, which proposes prioritizing precise targeting over delivery speed to increase the number of doses distributed in provinces where the impact of vaccines is anticipated to be greater.

In light of the fact that the Philippines is an archipelagic nation with vaccine supply and distribution issues, an effective spatial vaccination prioritization strategy must be developed to optimize the use of the limited vaccine supply. Thus, the objective of this paper is to use optimal control theory to determine time-dependent optimal vaccine allocation strategies that could minimize infections with associated intervention costs under various epidemiological scenarios, including mobility, supply level, infected individuals, and vaccination capacity. See our problem setup below.

In support of the “last mile” program of the Philippines, [31], we hope that the findings of this paper will help improve COVID-19 vaccine uptake and reach.

## 2. Problem setup

There are 17 regions in the Philippines. The nation's vaccine supply arrived in large quantities, and it should be distributed to the regions over a period of time. Since there is definitely a very limited supply, a methodical approach to distributing it over time to the various regions is required. The distribution of the vaccines should minimize both the implementation expenditure

and the country's overall risk of infection. Each region has a daily cap on the number of people it can immunize, which restricts the distribution. Additionally, it is conceivable that each day that vaccines are administered will impact the disease's progression in the following days. One may consider using a linear program right at the beginning of the distribution. This, however, will not be able to take the effects of vaccination over time into account. One option is to use a dynamic linear program to solve it every day while also resolving how the disease develops in relation to the impact of vaccinations from the day before. This is technically feasible but very computationally demanding. Here, we demonstrate how to use optimal control theory to address these constraints and resolve the distribution problem, with an emphasis on the Philippines.

We do not intend to evaluate the vaccination policy choices made by the Philippine government in this article. With the constraints and goal discussed above, this study aims to demonstrate the viability of using mathematical optimization, more specifically optimal control theory, to resolve the distribution problem.

## 3. Mathematical model

In [32], a modeling concept of the progression of COVID-19 disease was presented. This modeling concept serves as the basis for the base model, which represents a single region. The structure of the model makes it possible to estimate the hidden untested infection figure, which is also sometimes referred to as the dark figure of the pandemic. This estimate can be obtained by using the model. Instead of having a separate compartment for the vaccinated people in this study, we incorporate the effect of vaccination by the flow from the susceptible to the removed compartment. This allows us to account for the full scope of the phenomenon. During the process of applying the base model to every region of the country, we take into account the possibility that some infected individuals may travel between regions, which has the effect of influencing the transmission rate of the regions.

The population in region  $i$  is divided into four compartments: Susceptible ( $S_i$ ), Infected ( $I_i$ ), Tested positive ( $T_i$ ), and Removed ( $R_i$ ). The natural birth and death rates, as well as the effect of reinfection, are not accounted for in the model because the simulations used in this study are conducted over a relatively short period of time. We denote by  $N_{0i}$  the total population in region  $i$ . The flowchart of the model is given in Figure 1.

The model is governed by the following system of  $4n$  ordinary differential equations:

For  $i = 1, 2, \dots, n$ ,

$$\frac{dS_i}{dt} = -\alpha_i \beta_{0i} S_i \left( I_i + \sum_{j \neq i} c_{ji} q_j I_j \right) - \Lambda_i, \quad (1)$$

$$\frac{dI_i}{dt} = \alpha_i \beta_{0i} S_i \left( I_i + \sum_{j \neq i} c_{ji} q_j I_j \right) - \sum_{j \neq i} m_{ij} I_i + \sum_{j \neq i} m_{ji} I_j - (\gamma_i + \rho_i) I_i, \quad (2)$$

$$\frac{dT_i}{dt} = \rho_i I_i - \delta_i T_i, \quad (3)$$

$$\frac{dR_i}{dt} = \gamma_i I_i + \delta_i T_i + \Lambda_i, \quad (4)$$

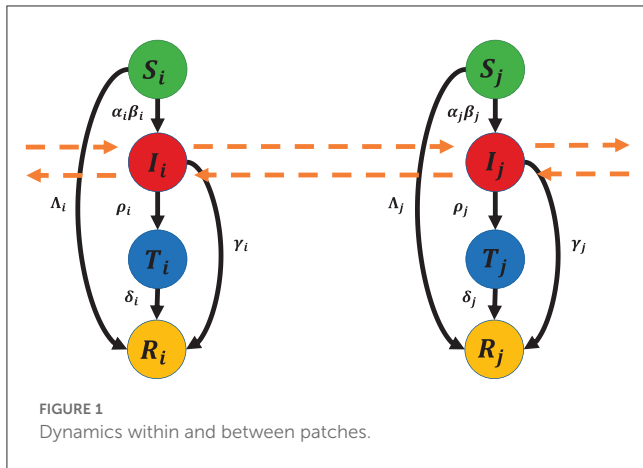


FIGURE 1 Dynamics within and between patches.

TABLE 1 Parameters of the model.

Parameter	Description	Unit
$\Lambda_i$	Vaccination rate in region $i$	Persons/day
$\beta_i$	Transmission rate in region $i$	1/day
$\alpha_i$	Transmission reduction control in region $i$	Dimensionless
$\rho_i$	Detection rate in region $i$	1/day
$\delta_i$	Removal rate from $T_i$ to $R_i$	1/day
$\gamma_i$	Removal rate from $I_i$ to $R_i$	1/day
$q_i$	Proportion of infected individuals in region $i$ that are traveling to other regions	Dimensionless
$c_{ij}$	Proportion of those traveling infected individuals from region $i$ to region $j$	Dimensionless
$m_{ij}$	Migration rate from region $i$ to region $j$	1/day

where  $j \in \{1, 2, \dots, n\}$ ,  $\beta_{0i} = \beta_i/N_{0i}$ , and  $\sum_{j=1}^n c_{ij} = 1$ . The time domain is only up to time  $t_f$ , where  $\Lambda_i < S_i(t_f)$ , for all  $i = 1, 2, \dots, n$ . The description of the parameters is given in Table 1.

### 4. Parameter values

The Philippines' Department of Health (DOH) has made data on confirmed cases available to the public<sup>2</sup>, so ethical approval is unnecessary. The parameter calibration was set up with the help of such information. The data spans the period of 1 June 2021 to 31 October 2021. We chose this time frame for our simulations since it represents the Philippines' first notable peak, the vaccination campaign has just recently started to gain traction, and there is a dearth of vaccines. To determine the fitted values for the parameters  $\beta$ ,  $\alpha$ ,  $\rho$ , and  $I_0$ , we minimized a non-linear least squares function that is given by the sum of the squares of the differences between the output of the model and the data. To solve the optimization problem, the Levenberg-Marquardt algorithm and approximate Bayesian computation are used [33–35]. This was done for every region. The results are presented in Table 2, where the last column displays the relative error of the fitting technique for each region.

### 5. Optimal control problem

In this study, we consider the vaccination controls  $v_i$  for each region  $i$ , where  $0 \leq v_i \leq 1$ . The system with the regions' vaccination controls is given by:

For  $i = 1, 2, \dots, n$ ,

$$\frac{dS_i}{dt} = -\alpha_i \beta_{0i} S_i \left( I_i + \sum_{j \neq i} c_{ji} q_j I_j \right) - v_i(t) \Lambda_i, \tag{5}$$

$$\frac{dI_i}{dt} = \alpha_i \beta_{0i} S_i \left( I_i + \sum_{j \neq i} c_{ji} q_j I_j \right) - \sum_{j \neq i} m_{ij} I_i + \sum_{j \neq i} m_{ji} I_j - (\gamma_i + \rho_i) I_i, \tag{6}$$

$$\frac{dT_i}{dt} = \rho_i I_i - \delta_i T_i, \tag{7}$$

$$\frac{dR_i}{dt} = \gamma_i I_i + \delta_i T_i + v_i(t) \Lambda_i, \tag{8}$$

where  $j \in \{1, 2, \dots, n\}$ ,  $\beta_{0i} = \beta_i/N_{0i}$ , and  $\sum_{j=1}^n c_{ij} = 1$ . Our time domain is only up to time  $t_f$  such that  $\Lambda_i < S_i(t_f)$ , for all  $i = 1, 2, \dots, n$ .

Our objective is to determine the vaccine distribution to the regions over time so that the total number of infections for a given period and the associated cost are minimized. We take note of the fact that our options are constrained by the vaccines that are on hand and the daily vaccination capacity of each region.

Letting  $B$  be the total number of available vaccines, the objective functional to be minimized is given by

$$J(v_1, v_2, \dots, v_n) = \int_{t_0}^{t_f} \sum_{i=1}^n \left( I_i(t) + \frac{A_i}{2} v_i^2(t) \right) dt \tag{9}$$

such that

$$\int_{t_0}^{t_f} \sum_{i=1}^n v_i(t) \Lambda_i dt = B. \tag{10}$$

Equation (10) is an isoperimetric constraint, and we will do the trick discussed in [37]. We let  $Z(t)$  be an additional state variable such that

$$Z'(t) = \sum_{i=1}^n v_i(t) \Lambda_i, \tag{11}$$

<sup>2</sup> Department of Health Website (2022). Available online at: <https://doh.gov.ph/vaccines>.

TABLE 2 Parameter values.

Region	$N_0$	$\Lambda$	$\alpha$	$\beta$	$\rho$	$S_0$	$I_0$	$T_0$	$R_0$	Relative Error
BARMM	4938539	2041	0.73745	0.14484	0.01191	4899821	3201	803	8879	0.00127
CAR	1791121	3374	0.40973	0.41859	0.01475	1638328	1132	1130	37915	0.00093
CARAGA	2795340	3524	0.62258	0.21379	0.02383	2721089	3678	1828	17643	0.00284
NCR	13484462	37430	0.44696	0.43619	0.01187	11381077	12888	7750	522624	0.00047
I	5292297	9381	0.53773	0.37148	0.07376	5186246	1538	1538	26128	0.00059
II	3679748	6231	0.26216	0.58817	0.01612	3481905	3290	3093	48638	0.00108
III	12387811	21689	0.61213	0.27342	0.04340	11911136	6451	6451	117556	0.00105
IV-A	16139770	26269	0.77467	0.18224	0.01192	15154262	29444	7361	239016	0.00123
IV-B	3212287	3498	0.50935	0.24775	0.02030	3161034	2860	1051	12098	0.00104
V	6067290	7616	0.65418	0.18829	0.01629	5994377	4840	1723	17018	0.00191
VI	7935531	11656	0.55571	0.23127	0.02464	7691631	17239	4310	56665	0.00048
VII	8046285	8744	0.76742	0.32960	0.13779	7769337	2244	2244	68676	0.00040
VIII	4531512	6544	0.45094	0.30247	0.04173	4432464	5236	1309	23453	0.00065
IX	3862588	4958	0.71558	0.18237	0.01973	3776561	3122	2117	20726	0.00173
X	5007798	6624	0.47553	0.38723	0.07454	4898426	2888	2888	26621	0.00161
XI	5223802	8383	0.51928	0.25595	0.02418	5083999	10598	2758	32301	0.00136
XII	4351773	5317	0.78857	0.21662	0.00129	4275821	8356	2089	16899	0.00835

The population  $N_0$  for each region is based on the 2020 Census of Population and Housing by the Philippine Statistics Authority of the Philippines [36]. The initial values of the other compartments are estimated using  $N_0$ , the fitted  $I_0$ , and data from DOH. The vaccination capacity ( $\Lambda$ ) is the per day average of the full dosed vaccines delivered in the Philippines in 2021<sup>1</sup>. We assumed  $q = 0.01$ , and for  $\gamma$  and  $\delta$ , we used the values 1/12 and 1/7, respectively, from [32].

where  $Z(t_0) = 0$  and  $Z(t_f) = B$ . Note that then we will have satisfied (10).

The Hamiltonian  $H$  is then given by

$$H = \sum_{i=1}^n \left( I_i(t) + \frac{A_i}{2} v_i^2(t) + \lambda_{Si} G_{Si} + \lambda_{Ii} G_{Ii} + \lambda_{Ti} G_{Ti} + \lambda_{Ri} G_{Ri} \right) + \lambda_Z G_Z,$$

where  $G_{Si}$ ,  $G_{Ii}$ ,  $G_{Ti}$ ,  $G_{Ri}$ , and  $G_Z$  are the right hand sides of Equations (5), (6), (7), (8), and (11), respectively, for  $i = 1, 2, \dots, n$ . Applying Pontryagin’s maximum principle, there exist adjoint variables  $\lambda_{Si}, \lambda_{Ii}, \lambda_{Ti}, \lambda_{Ri}, \lambda_Z, i = 1, 2, \dots, n$ , which satisfy the following system of ordinary differential equations:

for  $i = 1, \dots, n$ ,

$$\begin{aligned} \frac{\partial \lambda_{Si}}{\partial t} &= (\lambda_{Si} - \lambda_{Ii}) \alpha_i \beta_{0i} (I_i + \sum_{j \neq i} c_{ji} q_j I_j), \\ \frac{\partial \lambda_{Ii}}{\partial t} &= -1 + (\lambda_{Si} - \lambda_{Ii}) \alpha_i \beta_{0i} S_i + (\lambda_{Ii} - \lambda_{Ri}) \gamma_i + (\lambda_{Ii} - \lambda_{Ti}) \rho_i \tau_i, \\ &\quad + \sum_{j \neq i} [(\lambda_{Ii} - \lambda_{Ij}) m_{ij} + (\lambda_{Sj} - \lambda_{Ij}) c_{ij} q_i \alpha_j \beta_{0j} S_j], \\ \frac{\partial \lambda_{Ti}}{\partial t} &= (\lambda_{Ti} - \lambda_{Ri}) \delta_i, \\ \frac{\partial \lambda_{Ri}}{\partial t} &= 0, \\ \frac{\partial \lambda_Z}{\partial t} &= 0, \end{aligned}$$

with transversality conditions  $\lambda_{Si}(t_f) = \lambda_{Ii}(t_f) = \lambda_{Ti}(t_f) = \lambda_{Ri}(t_f) = 0$ , for  $i = 1, 2, \dots, n$ .

For  $i = 1, \dots, n$ , optimal controls  $v_i(t)$  are derived by the following optimality conditions:

$$\frac{\partial H}{\partial v_i} = v_i(t) A_i - (\lambda_{Si} - \lambda_{Ri} - \lambda_Z) \Lambda_i = 0. \tag{12}$$

We thus have the following theorem.

**Theorem 5.1.** *Problem (9)-(10) has a solution and the optimal control variables are given by, for  $i = 1, \dots, n$*

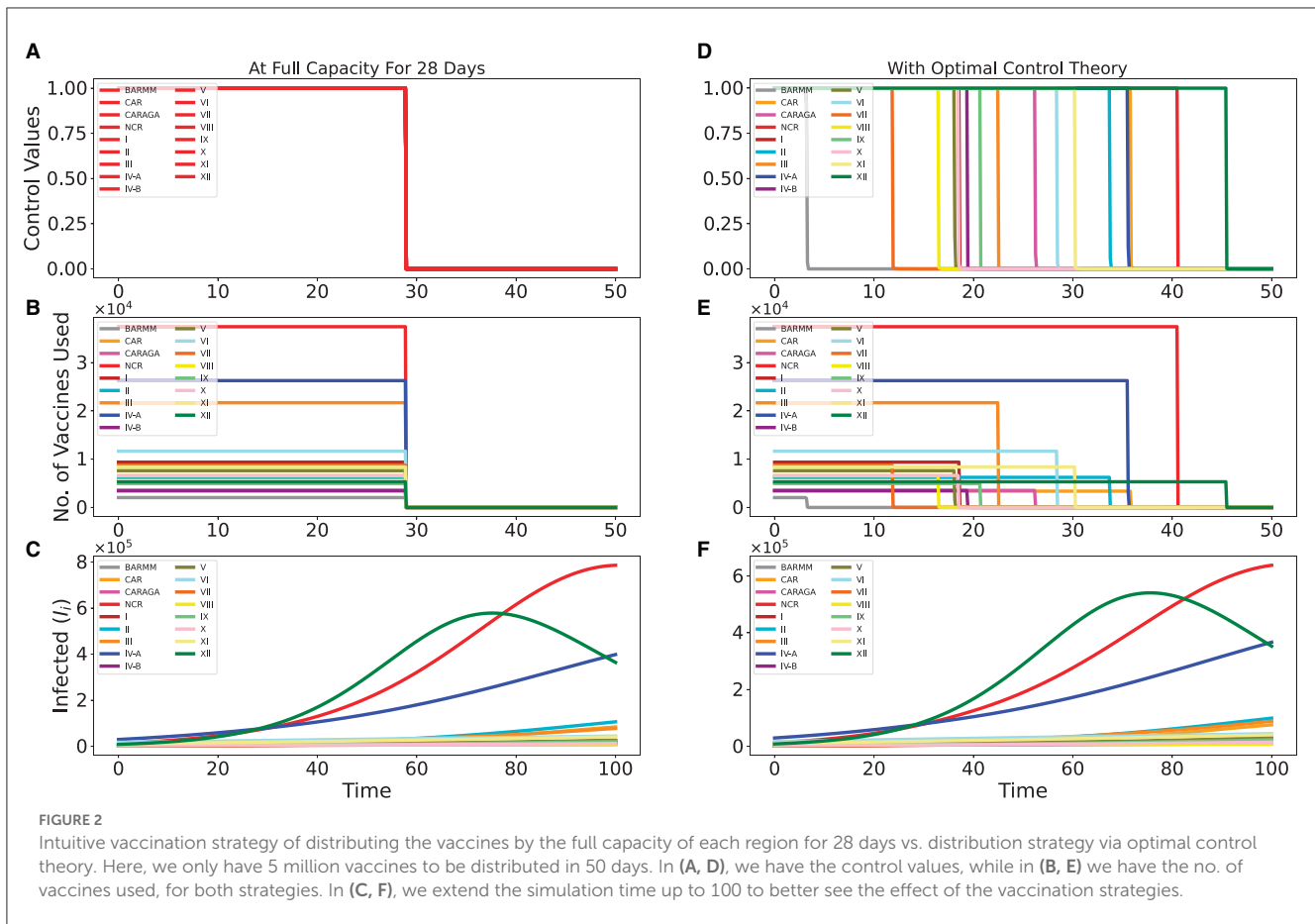
$$v_i(t) = \max \left( 0, \min \left( \frac{(\lambda_{Si} - \lambda_{Ri} - \lambda_Z) \Lambda_i}{A_i}, 1 \right) \right).$$

## 6. Simulations

Using the adapted forward-backward sweep method, which is used to solve isoperimetric problems [37], we numerically solved the optimization problem. This is a combination of the forward-backward sweep method and the shooting method, which is a variation of Newton’s method for finding zeros. In the simulations, we consider distributing 5 million vaccines over a period of 50 days, subject to the limitations described in Section 2. Thus, we anticipated the arrival of the next batch of vaccines in 50 days.

### 6.1. Intuition vs. optimal control

Table 2 lists the daily vaccination capacity for each region. Our intuition would lead us to recommend administering each region’s



full daily allotment of vaccines until they are all consumed. This suggests that all 5 million vaccine doses will be consumed in just 28 days. Figures 2A, B show this strategy. Figure 2A displays the control values for all regions, which are 100% for 28 days, and Figure 2B displays the number of vaccines each region uses based on their daily vaccination capacity.

The Philippines has implemented lockdowns and border control between regions during the simulation’s time frame (1 June 2021 to 31 October 2021). We assume these precautions are sufficient to prevent infected people from traveling between different regions. The impact of infected people moving between regions is not included in this simulation. During this time, every region urgently needs vaccination; therefore, implementation costs are not a concern. Therefore, the implementation cost for each region in this simulation is set at the same value. However, these values can be modified easily if necessary.

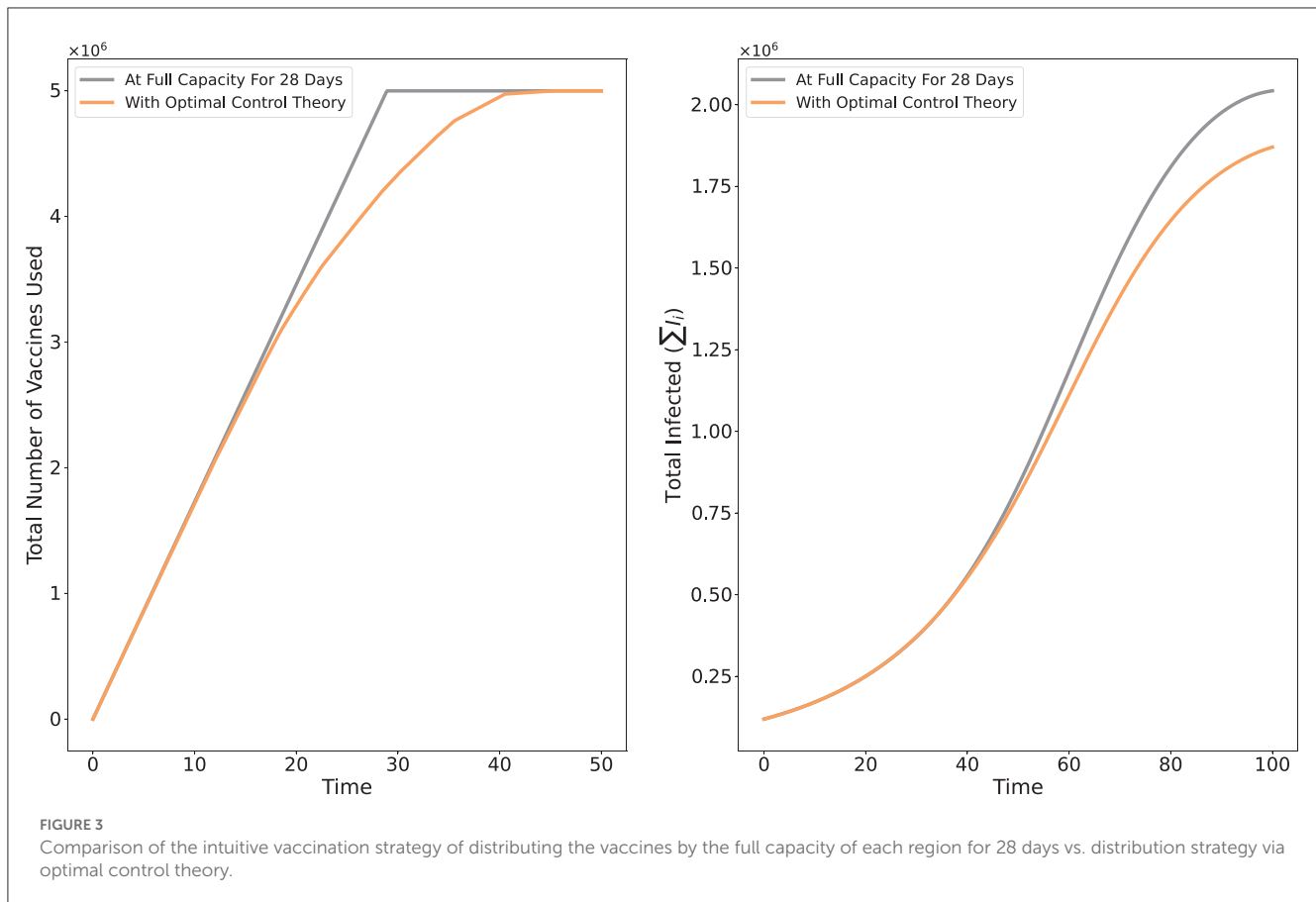
Figure 2C illustrates how this intuitive strategy affected the disease progression in each region. This is compared to the distribution strategy derived from optimal control theory shown in Figures 2D, E, with the effect on disease progression given in Figure 2F. One can observe that it did not advocate using all of each region’s resources for 28 days. The NCR, III, and IV-A regions received higher priority under the strategy. Since infection rates were much higher in these areas, especially in the three regions XII, NCR, and IV-A, which could be seen clearly in Figures 2C, F, this strategy can be explained by the need to control the progression of the disease there.

Even though the progression of the disease looks the same for both strategies, the optimal control strategy is better at stopping infections than the other one. This is evident when comparing the y-axes of Figures 2C, F, which compare the two strategies. As an illustration, for NCR, the infected reached approximately  $8 \times 10^5$  using the intuitive strategy but only approximately  $6 \times 10^5$  using the optimal control strategy.

Information about the overall infection can be found in Figure 3. According to the intuitive strategy shown in the left figure, all 5 million vaccines were used up by Day 28, compared to that to the non-linear, more gradual approach of the optimal control strategy. The total number of infected people over time in each of the 17 regions is shown in the right figure. The simulation is carried out through Day 100 to clearly demonstrate how the sums vary (with no additional vaccination after Day 50).

### 6.2. Limited vs. unlimited vaccines

In this simulation, we assume that lockdowns and border controls are not working that well, and so there is mobility of infected individuals between regions. There are no publicly available statistics on interregional movement, particularly for infected people. Based on our knowledge of the regions of the Philippines and their relationships with one another, we estimate the values of the mobility parameters  $q_i$ ,  $c_{ij}$ , and  $m_{ij}$  for the purpose of demonstration. The used values are listed in Table 3.



This situation is comparable to the later stages of the pandemic when lockdowns are not used, and only lax border controls are in place. We contrast the scenario where vaccine supply is limited, just like in the preceding simulation (Section 6.1), and the scenario where vaccine supply is seemingly unlimited, or where there is always enough vaccine to meet each region's vaccination capacity over the course of the simulation.

Figures 4A, B depict the simulation for the scenario where vaccine supply is limited. In contrast, Figures 4C, D depict the simulation for the scenario where vaccine supply is presumptively limitless. In the unlimited case, optimal control theory also recommends providing all the regions with their full vaccination capacity, as is intuitively expected. Figure 4E depicts the variation in the overall number of vaccines used, while Figure 4F depicts the anticipated variation in the overall infections (sum of the infected in the 17 regions), for both cases.

## 7. Discussion and conclusion

Our simulations showed how important it is to use optimal control theory to figure out how to give out a limited amount of vaccine over a certain amount of time in a country with different regions and a daily vaccination limit for each region. The advantage of this approach is that it seeks to determine the most efficient distribution plan while accounting for the influence that daily vaccination rates have on the progression of the disease in the days that follow in each region. In Section 6.1, we clearly saw that the optimal control formulation's solution minimizes the overall

infection in the country better than the intuitive approach of simply distributing the supply to all the regions based on their vaccination capacity. We also demonstrated the effectiveness of our method even when individual mobility between infected regions is considered.

We could also point out some drawbacks though. For instance, we did not take political and social factors into account. Due to lower reported cases or higher infection rates in other regions that needed to be prioritized, an optimal control strategy might, for instance, recommend against administering vaccines to a specific region. Although we can be mathematically confident that the strategy will reduce the overall infection of the country more effectively, it could be easily interpreted as simple discrimination. These things can also be taken into account when developing our formulation. As an illustration, we could stipulate that the lower limit for the controls  $v_i$  must be 30%.

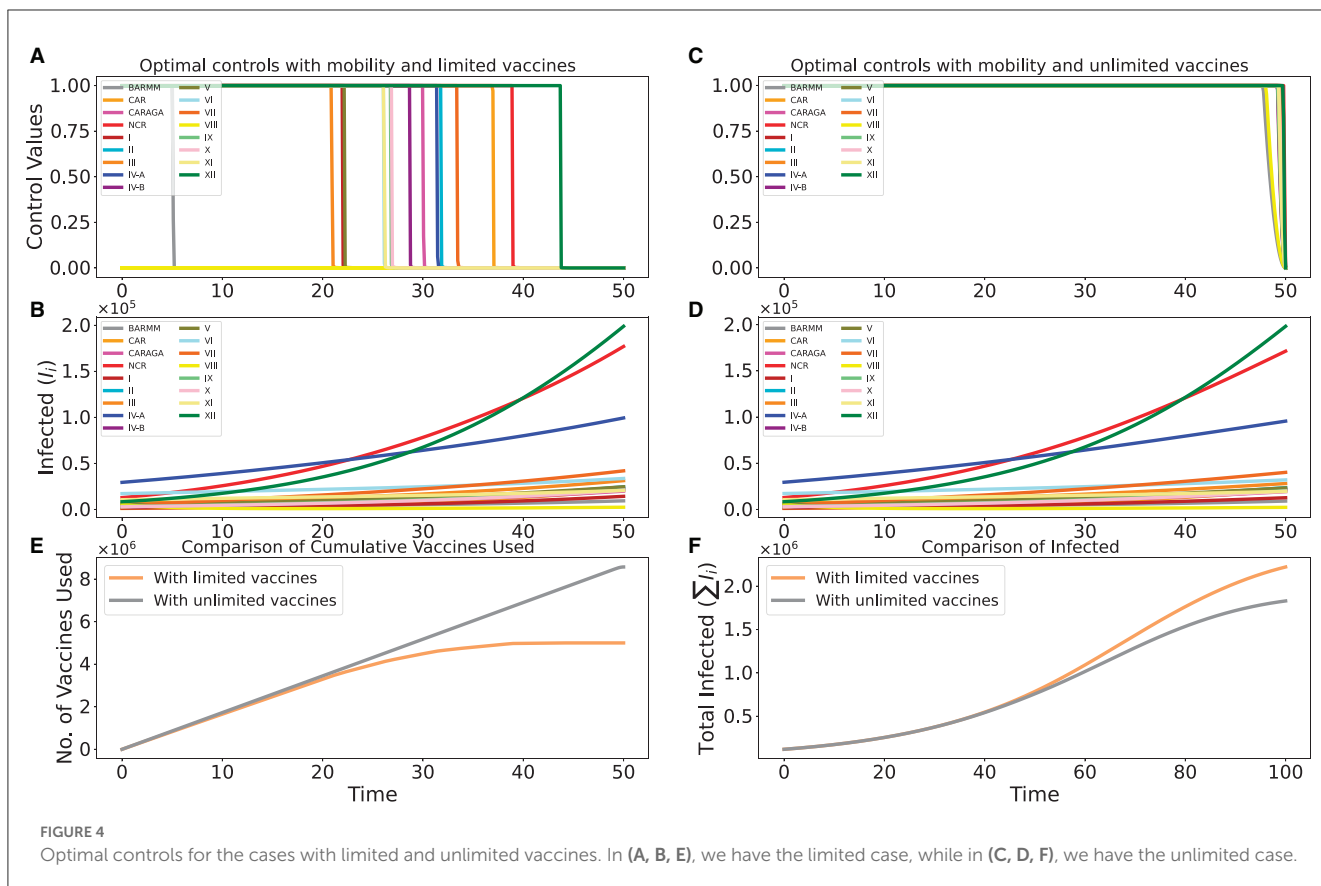
We note here that the method presented in this study can be easily extended or adapted to consider more divisions of the country. For instance, instead of the 17 regions, we could also consider more than 7,000 islands of the country. However, this would entail a much higher computational cost. Alternatively, we could zoom in on one city and consider the distribution problem for its barangays, which are the smallest administrative divisions in the country.

As stated in Section 2, we do not intend to assess the government's distribution initiative here. Instead, we propose a different strategy for administering the vaccines that we have mathematically demonstrated to be more effective with regard to our goal of reducing the overall infection rate in the country.

TABLE 3 Mobility values used.

	BARMM	CAR	CARAGA	NCR	I	II	III	IV-A	IV-B	V	VI	VII	VIII	IX	X	XI	XII
BARMM	0	0	0	1	0	0	0	0	0	0	0	1	0	2	2	2	2
CAR	0	0	0	3	2	1	2	1	0	0	0	1	0	0	0	0	0
CARAGA	1	0	0	1	0	0	0	1	1	1	1	1	1	1	1	0	0
NCR	0	1	1	0	1	1	1	1	1	1	0	1	0	0	1	0	0
I	0	2	0	2	0	2	1	1	1	1	0	0	0	0	0	0	0
II	0	1	0	2	1	0	1	1	1	1	1	1	0	0	0	0	0
III	0	1	0	2	1	1	0	1	1	1	1	1	0	0	0	0	0
IV-A	0	0	0	2	0	0	1	0	1	1	1	1	1	1	1	0	0
IV-B	0	0	0	2	0	0	1	1	0	1	1	1	1	1	1	0	0
V	0	0	1	1	0	0	1	1	1	0	1	1	1	1	1	0	0
VI	0	0	1	2	0	0	0	1	1	1	0	2	1	1	0	0	0
VII	0	0	1	2	0	0	0	1	1	1	2	0	1	1	0	0	0
VIII	0	0	1	1	0	0	0	1	1	1	1	2	0	1	1	0	0
IX	1	0	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1
X	1	0	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1
XI	1	0	1	1	0	0	0	0	0	1	1	1	1	1	1	0	1
XII	1	0	1	1	0	0	0	0	1	0	1	1	1	1	1	1	0

The values for  $c_{ij}$  and  $m_{ij}$  are obtained from this table by multiplying the cells by  $10^{-1}$  and  $10^{-3}$ , respectively. Note that  $\sum_{j=1}^{17} c_{ij} = 1$ , for all  $i = 1, \dots, 17$ .



## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

RC-a and JA contributed to the conception and design of the study and wrote the first draft of the manuscript. JMM and MR provided mathematical analysis and calculation. JD handled data collection and processing. JGM provided biological expertise. RC-a carried out the numerical simulations. All authors discussed the results and implications, and reviewed and approved the final version of the manuscript.

## Funding

The authors would like to thank DOST through PCHRD and ASTHRDP, MSU-IIT's OVCRE through PRISM, and CSU's MSCRC for the funding support.

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## Acknowledgments

The authors would like to thank W. Bock for a fruitful discussion.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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