Mathematical Analysis of Covid-19 with Double Dose Vaccination and Treatment

Abdassalam B. H. Aldaikh \ Department of Mathematics, University of Omar Al-Mukhtar, Libya \
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Abstract:
A compartmental model of covid-19 with double dose vaccine based on a system of non-linear ordinary differential equations is formulated and theoretically analyzed. The model is divided into eight compartmental classes, namely, susceptible (S), first dose vaccinated ($V_1$), second dose vaccinated ($V_2$), exposed (E), asymptomatic (A), symptomatic (I), hospitalized (H), and recovery (R). There are several kinds of approval vaccines, and each has a different efficacy and mechanism of action for reducing the outbreak of epidemic. Fortunately, there is a mathematical precise scale can be used as an indicator to determine whether the disease will be eradicated or persisted in the population, that is a basic reproduction number ($R_0$). The next generation method (NGM) is used to compute $R_0$ before vaccination, and after two doses were taken. Comparison the results shows -clearly- the positive effect of the intrinsic efficacy of vaccine on reducing $R_0$, and hence on eradication the epidemic.

Keywords: COVID-19, Next Generation Matrix, Basic Reproduction Number, Double Dose Vaccination, Treatment.
مصابون يتلقون العلاج ولا ينقلون العدوى إلى غيرهم نتيجة لعزلهم عن المجتمع (H).

مع تعدد أنواع اللقاحات المعتمدة من منظمة الصحة العالمية (WHO) ظهرت الحاجة للمفاضلة فيما بينها، وحسن الحظ فانه يوجد مقياس رياضي دقيق يمكن من خلاله توقع ما إذا كان المرض سيسيئ أو سينتشر وهو ما يعرف بـ رقم التكاثر الأساسي (R₀).

R₀ هو عدد متوسط الأشخاص الذين ي контактون باحترام بـ المرضى الرئيسيين، وسرعان ما تبين أن أرتفاع R₀ مشروحا في حالات سوء التزامات تطعيمات الجلاب القادمة، مما يؤدي إلى اصفرار المرض والسيطرة عليه.

كلمات مفتاحية: وداء الكورونا، مصفوفة الجيل القادمة، رقم التكاثر الأساسي، جرعتي تطعيم، تدخل علاجي.
Introduction
The December 2019 outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing COVID-19, was first reported in Wuhan, Hubei Province of China. Coronaviruses can be extremely contagious and spread easily from person to person. The disease, now a global pandemic, has spread rapidly worldwide, causing major public health concerns and economic crisis, having a massive impact on populations and economies and thereby placing an extra burden on health systems around the planet. In fact, all social levels of the society have suffered major disruptions due to the COVID-19 pandemic. [1]

The World Health Organization (WHO) first declared COVID-19 as a threat to the international community on January 30, 2020, and then as a pandemic on March 11, 2020 [2, 3, 4]. Today, April 04, 2022, there have been 492,271,251 confirmed cases worldwide with 6,178,291 deaths and 427,442,919 recovered (https://www.worldometers.info/coronavirus/). These numbers are exponentially growing day by day [5]

With the availability of COVID-19 vaccine and its known high efficacy, there is an urgent need to assess the impact of such vaccines with imperfect transmission-blocking effects [6] and potentially refine previous mathematical models of COVID-19 that incorporated the potential impact of an imperfect vaccine [1, 2, 7, 8].

Mathematical models, statistical analyses and computational techniques are very useful tools to study different processes, including testing hypotheses and understanding how factors affect the processes. For infectious disease processes, mathematical models can be used to perform in silico simulations of different potential scenarios, vaccination programs, and test different strategies to slow down epidemics [9–18].

It is widely accepted that using mathematical models can predict the occurrence of infectious diseases. In this way, it is possible to find the likely outcome of an outbreak that is beneficial for the purposes of public health initiatives. By using compartmental models as a basic mathematical framework, the complex dynamics of epidemiological processes can be studied, as stated in [19, 20].

Mathematical modeling plays a fundamental role in understanding, predicting, and controlling the transmission dynamics of infectious diseases. In this regard, its application has a long history, for example, in malaria [21–23], tuberculosis [24,25], and references cited

Mathematical modeling is useful and applicable to assess the sizes, peak and transmission dynamics of a contagious disease such as the novel SARS-CoV-2. For any pandemic of a contagious disease, it is essential to run its affecting parameters into a mathematical testing model to take further measures. There are many mathematical models for infectious diseases, including compartmental models, starting from the classical SIR to more sophisticated models. Such models play an important role in helping to quantify possible infectious disease control and mitigation strategies. Mathematical modeling has been used to analyze multiple characteristics of the disease and can provide the tools to predict the trends of transmission dynamics of a contagious disease such as COVID-19. Mathematical models estimate disease progress that can be helpful for public healthcare interventions and inspecting the momentum of disease outbreaks [5].

In this work, a deterministic mathematical model that assesses the impact of vaccination efficacy in controlling the disease, is presented, to study different scenarios. In particular, two doses and treatment are included.

**Main text**

Recently, a lot of research is being dedicated to study and monitoring the new covid-19 pandemic using mathematical modeling [33], and references cited therein. Most of these studies, however, deal with vaccination as one dose, and don’t devote particular compartment for each dose (i.e. $V_1, V_2 ...$). Having in mind that all of the recently approved vaccines for COVID-19 require at least two doses for increasing their average effectiveness, the proposed model takes this fact into account.

When a susceptible and an infectious individual comes into infectious contact, the susceptible individual contracts the disease and transitions to the latent compartment $E(t)$. Individuals in
compartment $E(t)$ are infected (carry the virus) but cannot spread the virus. Compartment $I(t)$ represents individuals who have been infected and show symptoms. The subpopulation $A(t)$ represents the number of individuals who have been infected and show symptoms. These individuals $I(t)$ and $A(t)$, are capable of infecting susceptible individuals after being in the $E(t)$ subpopulation. The variable $H(t)$ denotes the number of hospitalization individuals at time $t$. Hospitalized individuals are not able to transmit corona virus. Other section of those susceptible received a first dose of vaccination ($V_1$), at rate $\lambda S$, and they were also divided into two sections one of them infected according to efficacy of vaccine and transmitted to $E$, the second received a second dose of vaccination ($V_2$) once again some of them infected and transmitted to $E$, but less than before since the effectiveness becomes stronger, the majority of individuals in the ($V_2$), go to recovery class $R$, and, hence return to susceptible stage $S$, because the vaccine doesn’t give a permanent immunity. The model assumes that people in states $E(t)$, $H(t)$, and $R(t)$ do not transmit the infection. The mathematical model (1) is depicted graphically in Figure 1. Finally, symptom $I(t)$ and hospitalized $H(t)$, individuals can die due to the COVID-19 disease, in addition to normal reasons. This mathematical model that is similar to a SEIR-type epidemiological model is used to explain the dynamics of COVID-19 spread on the human population under a vaccination program, and has parameters that can be varied in order to study different possible scenarios. The parameters used in COVID-19 transmission model are given in Table 1. For instance, the pace of vaccination and efficacy of the vaccine can be modified. This is important since it is known that the efficacy of vaccines varies and they have different underlying mechanisms of action. Moreover, different countries and regions would apply the vaccines at different rates due to a variety of factors such as availability and resources [9].
The constructed mathematical model is given by

\[ S' = \Lambda + \sigma R - (\beta_2 + \lambda + \mu)S \]

\[ V_1' = \lambda S - [(1 - \varepsilon_1)\beta_2 + \eta + \mu]V_1 \]

\[ V_2' = \eta V_1 - [(1 - \varepsilon_2)\beta_2 + \omega + \mu]V_2 \]

\[ E' = \beta_2 S + (1 - \varepsilon_1)\beta_2 V_1 + (1 - \varepsilon_2)\beta_2 V_2 - (\alpha + \mu)E \]

\[ A' = \kappa \alpha E - (\phi + \gamma + \mu)A \]

\[ I' = (1 - k)\alpha E + \phi A - (\psi + h + \mu + \delta)I \]

\[ H' = hI - (\rho + \mu + \delta)H \]

\[ R' = \gamma A + \psi I + \rho H + \omega V_2 - (\sigma + \mu)R \]
### Table (1) Detailed description of state variables and relevant parameters of the proposed model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S(t)$</td>
<td>Susceptible</td>
</tr>
<tr>
<td>$V_1(t)$</td>
<td>First dose vaccinated</td>
</tr>
<tr>
<td>$V_2(t)$</td>
<td>Second dose vaccinated</td>
</tr>
<tr>
<td>$E(t)$</td>
<td>Exposed</td>
</tr>
<tr>
<td>$A(t)$</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>$I(t)$</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>$H(t)$</td>
<td>Hospitalized</td>
</tr>
<tr>
<td>$R(t)$</td>
<td>Recovered</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>Recruitment rate into susceptible population</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Rate of loss of immunity</td>
</tr>
<tr>
<td>$\beta_A$</td>
<td>Rate of transmission from $S$ to $E$ due to contact with $A$</td>
</tr>
<tr>
<td>$\beta_I$</td>
<td>Rate of transmission from $S$ to $E$ due to contact with $I$</td>
</tr>
<tr>
<td>$\beta_A + \beta_I$</td>
<td>Rate of vaccination with first dose</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Natural human death rate</td>
</tr>
<tr>
<td>$\varepsilon_1$</td>
<td>Efficacy of the first dose</td>
</tr>
<tr>
<td>$\varepsilon_2$</td>
<td>Efficacy of the second dose</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Rate of transmission from $V_1$ to $R$.</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Rate of transmission from $V_2$ to $R$.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Progression rate from $E$ to either $A$ or $I$</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Proportion of asymptomatic infectious people</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Rate of transmission from $A$ to $I$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Rate of recovery of the asymptomatic human population</td>
</tr>
<tr>
<td>$\psi$</td>
<td>Rate of recovery of the symptomatic population</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Rate of recovery due to treatment</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Rate of death due to the COVID-19 disease</td>
</tr>
</tbody>
</table>
Computation of Basic Reproduction Number $R_0$

The basic reproduction number $R_0$ is arguably the most important quantity in infectious disease epidemiology. It is among the quantities most urgently estimated for emerging infectious diseases in outbreak situations, and its value provides insight when designing control interventions for established infections. From a theoretical point of view $R_0$ plays a vital role in the analysis of, and consequent insight from, infectious disease models. There is hardly a paper on dynamic epidemiological models in the literature where $R_0$ does not play a role. $R_0$ is defined as the average number of new cases of an infection caused by one typical infected individual, in a population consisting of susceptible individuals only.[34]. If $R_0 < 1$, the disease free equilibrium is locally asymptotically stable; whereas if $R_0 > 1$, then it is unstable. Thus, $R_0$ is a threshold parameter for the model.[35]. Next Generation Matrix (NGM) is widely used to compute $R_0$, since Diekmann et al. (1990) [36], proposed to define $R_0$ as the dominant eigenvalue of it. Starting point is the ODE system that describes the production of new cases and the changes in infected states i.e. $E, A, I, H$. Assume that this set of ODEs, the infection subsystem, has been written in linearized form. Decompose the Jacobian matrix of the infection subsystem as $F$ and $M$ where $F$ is the transmission matrix, and $M$ the transition matrix, that is $F$ contains the entries corresponding to transmission events, where an epidemiological birth occurs, and $M$ contains the entries corresponding to all other changes of state (including death).[34].

\[
F = \begin{bmatrix}
\beta_2 S + (1 - \varepsilon_1) \beta_1 V_1 + (1 - \varepsilon_2) \beta_2 V_2 \\
0 \\
0 \\
0
\end{bmatrix},
\]

\[
M = \begin{bmatrix}
-(\alpha + \mu)E \\
\kappa\alpha E - [\varphi + \gamma + \mu]A \\
(1 - k)\alpha E + \varphi A - [\psi + h + \mu + \delta]I \\
hI - [\sigma + \mu + \delta]H
\end{bmatrix}
\]

Hence the Jacobian of this decomposition at the decease free equilibrium

\[
DFE(S_0, V_{10}, V_{20}, 0, 0, 0, 0); S_0 = \frac{\lambda}{\mu + \lambda}, V_{10} = \frac{\lambda S_0}{\mu + \eta}, V_{20} = \frac{\lambda}{\eta} \frac{\lambda}{\mu + \omega}, \frac{\lambda}{\mu + \omega} \frac{\lambda}{(\mu + \eta)(\mu + \lambda)}
\]
is

\[
F = \begin{bmatrix}
\beta_i S_0 + (1 - \varepsilon_1) \beta_i V_{10} + (1 - \varepsilon_2) \beta_i V_{20} & \beta_i S_0 + (1 - \varepsilon_1) \beta_i V_{10} + (1 - \varepsilon_2) \beta_i V_{20} & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
\]

\[
M = \begin{bmatrix}
-(\alpha + \mu) & 0 & 0 \\
\kappa \alpha & -(\varphi + \gamma + \mu) & 0 \\
(1 - k) \alpha & \varphi & -(\varphi + h + \mu + \delta) \\
0 & 0 & h \\
0 & 0 & -(\rho + \mu + \delta)
\end{bmatrix}
\]

\[
M^{-1} = \begin{bmatrix}
-1 & \frac{\alpha + \mu}{\alpha + \mu} & \frac{\kappa \alpha \varphi}{(\alpha + \mu)(\varphi + \gamma + \mu)} \\
\frac{1}{(1 - k) \alpha} & \frac{\kappa \alpha \varphi}{\alpha + \mu} + \frac{(\alpha + \mu)(\varphi + \gamma + \mu)}{(\alpha + \mu)(\varphi + \gamma + \mu)} & \frac{h}{\rho + \mu + \delta} \\
\frac{\varphi}{\psi + h + \mu + \delta} & \frac{\varphi}{\psi + h + \mu + \delta} & \frac{h}{\psi + h + \mu + \delta} \\
\frac{\varphi}{(\varphi + \gamma + \mu)(\psi + h + \mu + \delta)} & \frac{\varphi}{(\varphi + \gamma + \mu)(\psi + h + \mu + \delta)} & \frac{h}{(\varphi + \gamma + \mu)(\psi + h + \mu + \delta)} \\
0 & 0 & 0
\end{bmatrix}
\]

Since the matrix \(F\) has three zero rows, the next generation matrix of system (1) is taken by the spectral radius of \(NGM = -E^T F M^{-1} E\), where \(E = (1 \ 0 \ 0)^T\), which in this case reduces to single element, as follows,

\[
(-E^T F)(M^{-1} E) = -\begin{bmatrix}
\beta_i S_0 + (1 - \varepsilon_1) \beta_i V_{10} + (1 - \varepsilon_2) \beta_i V_{20} & \beta_i S_0 + (1 - \varepsilon_1) \beta_i V_{10} + (1 - \varepsilon_2) \beta_i V_{20} & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
\]
therefore the basic reproduction number of system (1) is given by

\[
R_0 = -[\beta_A S_0 + (1 - \varepsilon_1)\beta_A V_{10} + (1 - \varepsilon_2)\beta_A V_{20}] \left[ \frac{-k\alpha}{(\alpha + \mu)(\varphi + \gamma + \mu)} \right] - \beta_I S_0

+ (1 - \varepsilon_1)\beta_I V_{10}

+ (1 - \varepsilon_2)\beta_I V_{20} \left\{ \frac{-1}{\psi + h + \mu + \delta} \left[ \frac{(1 - k)\alpha}{\alpha + \mu} + \frac{k\alpha \varphi}{(\alpha + \mu)(\varphi + \gamma + \mu)} \right] \right\}

= \beta_A [S_0 + (1 - \varepsilon_1) V_{10} + (1 - \varepsilon_2) V_{20}] \left[ \frac{k\alpha}{(\alpha + \mu)(\varphi + \gamma + \mu)} \right] + \beta_I [S_0 + (1 - \varepsilon_1) V_{10}

+ (1 - \varepsilon_2) V_{20}] \left\{ \frac{(1 - k)\alpha}{(\psi + h + \mu + \delta)(\alpha + \mu)} + \frac{k\alpha \varphi}{(\psi + h + \mu + \delta)(\alpha + \mu)(\varphi + \gamma + \mu)} \right\}

= [S_0 + (1 - \varepsilon_1) V_{10} + (1 - \varepsilon_2) V_{20}] \left\{ \beta_A \left( \frac{k\alpha}{(\alpha + \mu)(\varphi + \gamma + \mu)} \right)

+ \beta_I \left( \frac{(1 - k)\alpha}{(\psi + h + \mu + \delta)(\alpha + \mu)} + \frac{k\alpha \varphi}{(\psi + h + \mu + \delta)(\alpha + \mu)(\varphi + \gamma + \mu)} \right) \right\}

R_0 = [S_0 + (1 - \varepsilon_1) V_{10} + (1 - \varepsilon_2) V_{20}] \left\{ \beta_A \left( \frac{k\alpha}{(\alpha + \mu)(\varphi + \gamma + \mu)} \right)

+ \beta_I \left( \frac{\alpha[(1 - k)(\gamma + \mu)]}{(\psi + h + \mu + \delta)(\alpha + \mu)(\varphi + \gamma + \mu)} \right) \right\}

\text{Computation of Basic Reproduction Number if there is no Vaccine (R}_0^0)\text{ }

In this case system (1) reduces to

\[
\begin{align*}
S' &= \Lambda + \sigma R - [\beta_x + \mu]S \\
E' &= \beta_x S - (\alpha + \mu)E \\
A' &= \kappa \alpha E - [\varphi + \gamma + \mu] A \\
I' &= (1 - k)\alpha E + \varphi A - [\psi + h + \mu + \delta] I
\end{align*}
\]
\[
\begin{align*}
\dot{H} &= \dot{h}I - [\rho + \mu + \delta]H \\
\dot{R} &= \gamma A + \psi I + \rho H - (\sigma + \mu)R
\end{align*}
\]
which can be composite to
\[
\mathcal{F}' = \begin{bmatrix}
\beta_2 S \\
0 \\
0
\end{bmatrix}
\]
which gives the Jacobian, \( F' = \begin{bmatrix}
0 & \beta_A S' \delta \\
0 & \beta_t S' \delta \\
0 & 0
\end{bmatrix} \), about the disease free equilibrium point \( DFE(S'_0, 0, 0, 0) \); \( S'_0 = \frac{\Lambda}{\mu} \) while the transition matrix \( \mathcal{M} \) doesn’t change, and hence – following the same process – the basic reproduction number in this case
\[
R'_0 = S'_0 \left\{ \beta_A \left( \frac{k\alpha}{(\alpha + \mu)(\phi + \gamma + \mu)} \right) + \beta_t \left( \frac{\alpha[\phi + (1 - k)(\gamma + \mu)]}{(\psi + h + \mu + \delta)(\alpha + \mu)(\phi + \gamma + \mu)} \right) \right\}
\]
From the formulas of \( R_0 \) and \( R'_0 \), the following relation could be found
\[
\frac{R_0}{R'_0} = \frac{S_0}{S'_0} = \frac{(1 - \varepsilon_1)\Lambda_{10} + (1 - \varepsilon_2)\Lambda_{20}}{\Lambda_{10}}.
\]
Substituting for \( S_0, S'_0, \Lambda_{10} \) and \( \Lambda_{20} \) gives
\[
\frac{R_0}{R'_0} = \frac{\Lambda}{\mu} + \frac{(1 - \varepsilon_1)\Lambda}{(\mu + \eta)(\mu + \lambda)} + \frac{(1 - \varepsilon_2)\eta}{\mu + \lambda}.
\]
Conclusion
In the last relation if \( \varepsilon_1 \) and \( \varepsilon_2 \rightarrow 1 \), the right-hand side tends to \( \frac{\mu}{\mu + \lambda} \) which is less than one, and hence \( R_0 < R'_0 \), so the higher the quality of the vaccine (smaller value of \( 1 - \varepsilon_1 \) and \( 1 - \varepsilon_2 \)), the smaller is the value of \( K = \frac{\mu}{(\mu + \eta)(\mu + \omega)(\mu + \lambda)} \). The parameter \( K \) represents the effect of vaccine implementation in reducing the initial basic reproduction number, which depends on \( \varepsilon_1 \) and \( \varepsilon_2 \) the efficacy of first and two dose of the vaccine respectively. Hence, it can be concluded that the implementation of double dose vaccination reduces the basic reproduction number by \( K \) percent.
References


