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Research article

Analyzing the relationship between the vitamin D deficiency and COVID-19 mortality rate and modeling the time-delay interactions between body's immune healthy cells, infected cells, and virus particles with the effect of vitamin D levels

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Abstract: This paper presents some recent views on the aspects of vitamin D levels in relation to the COVID-19 infections and analyzes the relationship between the prevalence rates of vitamin D deficiency and COVID-19 death rates per million of various countries in Europe and Asia using the data from the PubMed database. The paper also discusses a new mathematical model of time-delay interactions between the body's immune healthy cells, infected cells, and virus particles with the effect of vitamin D levels. The model can be used to monitor the timely progression of healthy immune cells with the effects of the levels of vitamin D and probiotics supplement. It also can help to predict when the infected cells and virus particles free state can ever be reached as time progresses. The consideration of the time delay in the modeling due to effects of the infected cells or virus particles and the growth of healthy cells is also an important factor that can significantly change the outcomes of the body's immune cells as well as the infections.

Keywords: Vitamin D deficiency; immune system; virus particles; COVID-19; infected cell; delay differential equation

1. Introduction

The COVID-19 pandemic has made a significant impact on the global economy and the daily life of almost each household around the globe. With recent developments of COVID-19 vaccines

that significantly help to prevent the severe of infected virus, people cannot wait and are in the mood to get back to a normal pre-COVID state, yet many people would still take caution since the spread of the COVID-19 virus is still at an alarming rate due to increased global travel and some drastic changes in the environments [1,2]. The COVID-19 symptoms such as sore throat, headache or shortness of breath, of infected persons are the same for both unvaccinated and vaccinated people but generally milder and lesser severe to vaccinated person [3,4].

COVID-19 has killed at least 1 million people and infected more than 82 million in the United States since the pandemic began [5]. Authorities in at least 220 countries have reported over500 million COVID-19 cases and more than 6 million global deaths since the COVID-19 pandemic beginning in December 2019 [6]. Many researchers around the world [7–8] have developed models to estimate the COVID-19 deaths [9–11] and its effects due to various restrictions and changes including social distancing, reopening schools, vaccines and face mask mandates in their cities and states [12–14].

Some recent studied has observed that infected people with COVID increase the risk of severe infection if they had lower vitamin D levels. Several other studies [15], however, found no association between vitamin D levels and COVID-19 infected cases. Similarly, other clinical studies have observed that vitamin D may reduce the COVID-19 infection rates and the mortality but the evidence for vitamin D prevention of the COVID virus will still need further studies.

Vitamin D is one of many vitamins our bodies need to stay healthy and assisting in promoting bone growth and supporting body's immune system. The immune system needs vitamin D to fight off invading bacteria and viruses. Vitamin D deficiency or hypovitaminosis D (i.e. "25(OH)D") is a serum 25-hydroxyvitamin D concentrations ≤20 ng/mL (50 nmol/L). It is typically diagnosed by measuring the concentration of the "25(OH)D"- in the blood, which is the most accurate measure of vitamin D status in the body. The classifications of the vitamin D levels are shown in Table 1. People can measure vitamin D intake in micrograms (mcg) or international units (IU) where one microgram of vitamin D is equivalent to 40 IU. Vitamin D is fat-soluble, meaning that if you take more than your body can immediately use, the excess is stored in your body and is not excreted in urine (as many vitamins are).

Table 1. Levels of Vitamin D.

Classification	Vitamin D deficiency "25(OH)D"
Severe deficiency	<12 ng/mL (or ≤ 30 nmol/L)
Deficiency	<20 ng/mL (or ≤ 50 nmol/L)
Insufficient	20–29 ng/mL (or 50–75 nmol/L)
Normal	30–50 ng/mL (or 75–125 nmol/L)

Notation: ng = nanogram; mL = millilitre; nmol = nanomoles; L = litre; 1 ng/mL = 2.5 nmol/L

In this paper, we discuss in section 2 some recent views about the relationship between the levels of vitamin D and disease infections related to COVID-19 pandemic. We then present a correlation analysis result between the prevalence rates of the deficiency levels of vitamin D and COVID-19 death rates per million among the population of 23 countries in Europe continent and 24 countries in Asia and all 47 countries in both continents Europe and Asia as will be discussed in section 3. We also develop a mathematical model of time-delay interactions between body's immune healthy cells,

infected cells, and virus particles with consideration of vitamin D deficiency levels as will be discussed in section 4. Section 5 discusses brief conclusion and findings.

2. On the Aspects of Vitamin D and the COVID-19

Some recent studies have shown vitamin D deficiency has been linked to colorectal cancer [16], diabetes mellitus [17], infection [18], prostate cancer, heart disease, breast cancer [19], depression [20], postural instability [21], and weight gain. Several recent studies have also shown that people with sufficient levels of vitamin D have a lower risk of infection although they do not definitively prove due to the lack of vitamin D that causes disease, or that vitamin D supplements would lower risk. Some studies in recent years especially during the COVID-19 pandemic period showed with a sufficient vitamin D3 level, it likely can help to cure some of the human diseases [22–24] caused by a weak immune system [25–27] including various types of disease infections [28–31], infections related vitamin D [32–34] and lung infections [35–37] that cause acute respiratory distress syndrome (ARDS) [38–40], as well as autoimmune diseases [41,42].

Although some new findings with recommendations about the levels of vitamin D3 have discussed in recent years, many researchers in the medical community still want to keep the existing one established 100 years ago [43]. In addition, many recommendations for vitamin D3 supplementation are in the range of 5 to 20 mcg per day (200 to 800 international units (IU)), which is much too low to guarantee the optimal blood level of 40–60 ng/mL [22,44]. Various studies [44] in the past decades have shown there has been a significant association between the vitamin D deficiency and the occurrence of infectious diseases including sepsis [45], respiratory infection [46], seasonal influenza [47–49], adaptive immune responses [50–52].

Some recent reviews [53–58], observations [59–64], clinical tests [65–68] and empirical studies [69–71] have shown there was a significant association between the vitamin D deficiency patients and the high risk of death related to COVID-19 compared to with patients who have sufficient vitamin D levels. Some empirical designed studies [72–74] have observed that vitamin D supplementation can help to reduce symptoms for patient at high risk of respiratory infection. Several recent findings based on observational studies have illustrated a strong correlation between high COVID-19 mortality rate and vitamin D deficiency in most European countries [68,75–77] such as Italy and Spain.

Many researchers [78–82] have actively studied and widely discussed with various guidelines [83–87] about the sufficient vitamin D levels in some countries [88–92] in the past decades but there is yet consent on what will be the best level of vitamin D [93–97].

Vitamin D deficiency is a common health problem [98–101] of most countries around the world where risk factors may due to lack of sun exposure [102–104], wearing long clothing or lack of outdoor activities or due to some social cultural groups to wear long clothing outdoors [105,106].

3. Prevalence rates analysis of Vitamin D deficiency in European and Asian Countries

The prevalence rates of severe vitamin D deficiency (i.e., 25(OH)D <30 nmol/L) and vitamin D deficiency (i.e 25(OH)D < 50nmol/L), have reported of, respectively, 5.9% and 24% in US [107], 7.4% and 37% in Canada [108], and 13% and 40% in Europe [109,110]. Both the vitamin D deficiency insufficiency levels have shown strongly related with various health outcomes and

increased risk for COVID-19-related severity and high mortality rate [52] based on related mortality distributions [111]. Recent study by Dror et al [112] has demonstrated that people with lower vitamin D levels are more likely to have severe COVID-19 infections than people with higher vitamin D levels based on the data records of 1176 patients from the Galilee Medical Center (GMC) in Nahariya, Israel, between April 7, 2020 and February 4, 2021, with positive tests for COVID-19.

In this section, we discuss the correlation analysis of the vitamin D deficiency and COVID-19 death rates per million among the people of 23 countries in Europe continent, 24 countries in Asia and all 47 countries in both continents Europe and Asia. The number of COVID-19 reported cases (see column 7, Table 2) and deaths (column 8, Table 2) per one million as of January 15th, 2022 by countries in Asia and Europe were obtained from the Worldometer website [5]. The corresponding prevalence of vitamin D deficiency of 23 countries in European and 24 countries in Asia were obtained from the PubMed database [52] as shown in Table 2.

We observe that among European countries, the lowest and highest prevalence of vitamin D deficiency were reported in Finland and Ukraine with vitamin D deficiency values ranging from 6.9 to 81.8%, respectively, as shown in Table 2. The lowest and highest number of COVID-19 infected cases per million of the country population in Europe were from Finland (66,824 deaths per million) and Slovenia (253,591 cases per million) accordingly where the lowest and the highest number of COVID-19 deaths per million were from Norway (252 deaths per million) and Bulgaria (4,660 per million), respectively. Figure 1 shows the data that represent the vitamin D deficiency levels with respect to European countries (x-Axis), COVID-19 deaths (y-axis), and COVID-19 cases (z) for European countries. Figure 2 shows the vitamin D deficiency levels with respect to European countries (x-axis), the COVID-19 deaths between 1000 and 2500 deaths (Axis y) and the COVID-19 cases between 100,000 and 300,000 cases (z-axis).

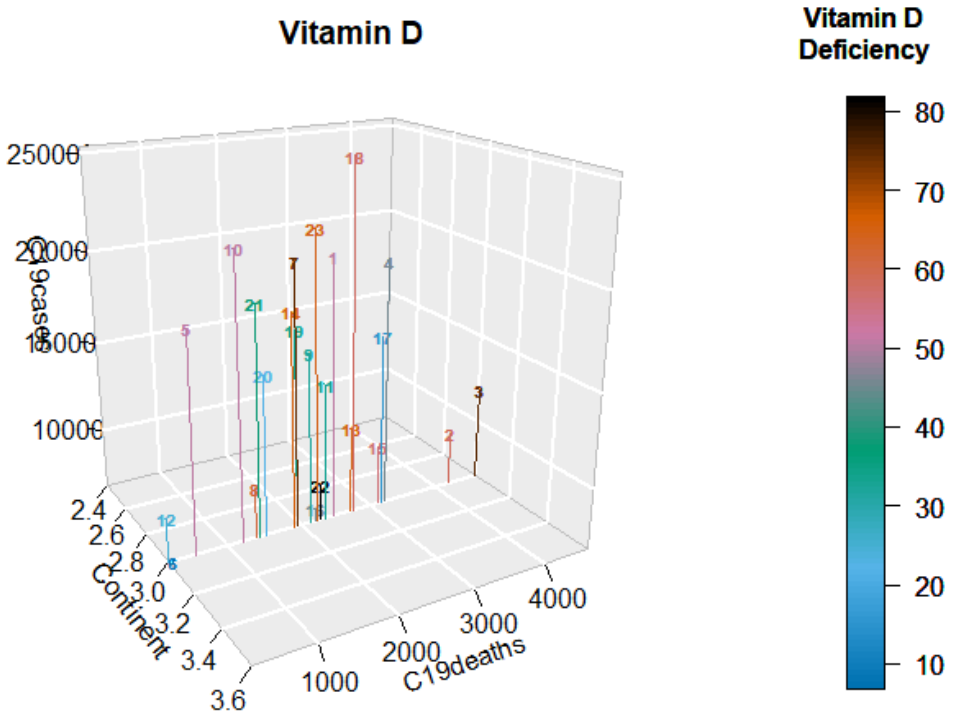


Figure 1. Vitamin D deficiency levels with respect to Continent (x-axis); COVID-19 deaths (y), and COVID-19 cases (z) among 23 countries in Europe.

Table 2. The Prevalence of Vitamin D Deficiency and COVID-19 Death Rateof 47 Countries*.

No.	Country	Continent	ref	Sample	Age(yrs)	VitDdef	C19cases per million	C19 deaths per million
				Europe				
1	Belgium	3	Hoge et al 2015	697	20-69	51.1	206627	2452
2	Bosnia	3	Sokolovic 2016	2483	>18	58.7	96380	4229
3	Bulgaria	3	Borissova 2013	2016	20-80	75.8	118495	4660
4	Croatia	3	Baric 2016	791	45.5	46.1	199613	3215
5	Denmark	3	Hansen 2018	2565	18-69	51.5	183639	598
6	Finland	3	Adebayo 2020	798	30-64	6.9	66824	310
7	France	3	Deplanque 2017	297	18-65	75.1	207186	1935
8	Germany	3	Rabenberg 2018	6995	18-79	61.5	94020	1380
9	Greece	3	Dimakopou 2019	1084	>18	32.4	159508	2116
10	Ireland	3	Griffin 2020	17590	>18	51.5	217571	1202
11	Italy	3	Giuliani 2019	74235	>18	33.3	141515	2335
12	Norway	3	Petrenya 2020	4465	40-69	24.7	90464	252
13	Poland	3	Pludowshi 2016	5775	16-90	65.8	113765	2707
14	Portugal	3	Duarte 2020	3092	>18	66.6	182513	1898
15	Romania	3	Niculescu 2017	812	>21	56.5	99568	3110
16	Russia	3	Karonova 2016	1544	18-75	45.7	73781	2196
17	Slovakia	3	Sebekova 2016	578	>5	15	160413	3158
18	Slovenia	3	Hribar 2020	125	18-64	58.2	253591	2739
19	Spain	3	Gonzalez-M. 2011	1262	20-83	33.9	172992	1940
20	Sweden	3	Nalsen 2020	268	18-80	22.4	153038	1517
21	Switzerland	3	Guessous 2012	367	25-70	38.2	189587	1435
22	Ukrain	3	Povoroznyuk 2012	1575	20-95	81.8	86500	2266
23	United Kingdom	3	Jolliffe 2016	222	48-94	64.9	221341	2220
				Asia				
1	Bahrain	1	Almesri 2020	314	>30	79.9	168999	780
2	Bangladesh	1	Acherjya 2019	160	<70	63.7	9644	168
3	Brunei	1	Leong 2016	446	>18	52	35480	221
4	China	1	Jiang 2020	14302	18-65	50.3	73	3
5	India	1	Mechenro 2018	424	>18	55.2	26499	347
6	Iran	1	Esmaelli 2019	7504	18-65	65.3	72613	1542
7	Iraq	1	Al-Hilali 2016	300	25-70	75.3	50730	583
8	Japan	1	Asakura 2020	107	20-69	28.2	14539	146
9	Jordan	1	Khasawneh 2018	3007	<83	67.9	105948	1252
10	Kazakhstan	1	Gromava 2019	1347	>18	70	54200	683
11	Kuwait	1	Zhang 2016	960	>20	83	104480	566
12	Lebanon	1	Saad 2020	142131	>19	35.5	119291	1380
13	Malaysia	1	Shafinaz 2016	858	>18	67.4	84911	962
14	Mongolia	1	Bromage 2016	320	20-58	35.5	120499	620
15	Nepal	1	Sherchand 2018	300	>18	51.3	28363	388
16	Oman	1	Abiaka 2013	206	18-55	87.5	58492	776
17	Pakistan	1	Kandhro 2019	1255	<84	36	5803	128
18	Qatar	1	Zainel 2019	102342	18-65	71.4	105143	222
19	Saudi Arabia	1	Altowijri 350	20-40	74.6		17112	250
20	Singapore	1	Bi 2016 114	21-100	42.1		48984	142
21	Thailand	1	Rajatanavin 2019	120	25-60	19.1	33059	313
22	Turkey	1	Gotkas 2020	11734	>18	70.6	121344	987
23	UAE	1	Al Zarooni 2019	12346	>18	72	79631	217
24	Vietnam	1	Ho-Pham 2011	637	18-87	2	20347	360

* "1" in the category indicates Asian countries; '3" indicates European countries.

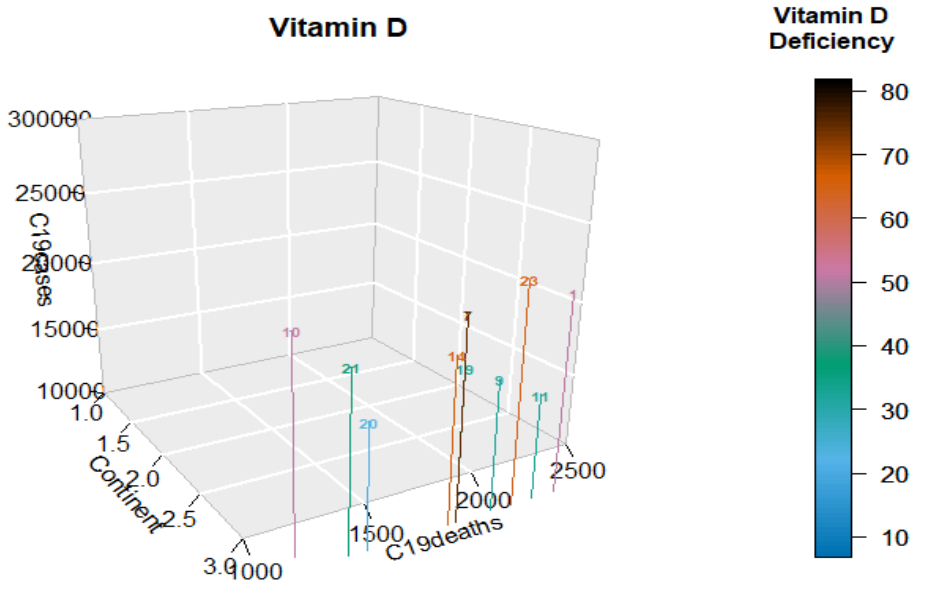


Figure 2. Vitamin D deficiency levels with respect to continent (x-axis), COVID-19 deaths (y-axis) between 1000 and 2500 deaths, and COVID-19 cases (z) between 100,000 and 300,000 in Europe.

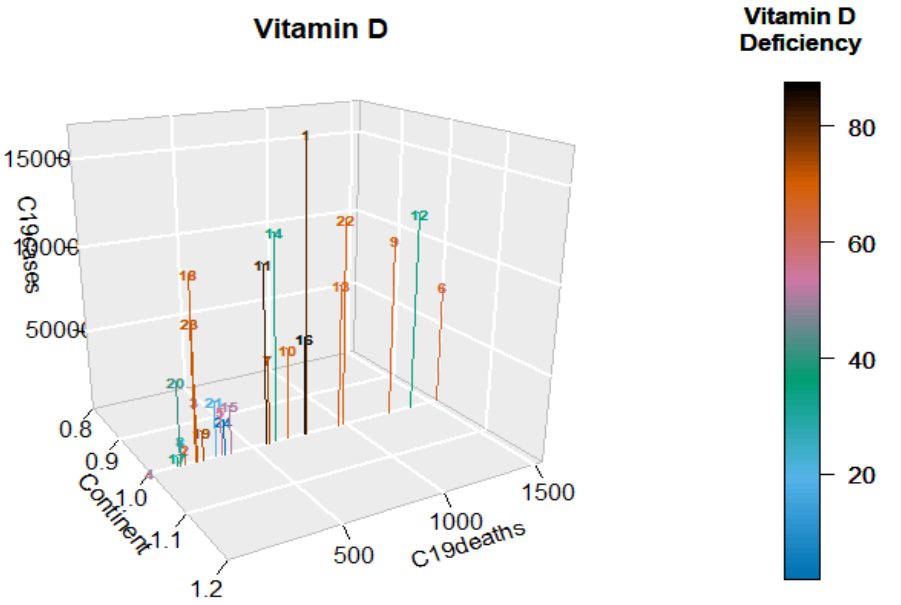


Figure 3. Vitamin D deficiency levels with respect to Continent (x-axis); COVID-19 deaths (y), and COVID-19 cases (z) among 24 countries in Asia.

Similarly, the lowest and highest prevalence of vitamin D deficiency in Asia were reported in Vietnam and Oman with vitamin D deficiency values ranging from 2.0 to 87.5%, respectively. The lowest and the highest number of COVID-19 infected cases per million of the country population among Asian countries were from Vietnam (20,347 cased per million) and Bahrain (168,999 cases per million) respectively where the lowest and the highest number of COVID-19 deaths per million of the total population were from Vietnam (360 deaths per million) and Iran (1542 per million),

respectively. Figure 3 shows the vitamin D deficiency levels with respect to Asian countries (x-Axis), COVID-19 deaths (y-axis), and COVID-19 infected cases (z) for Asian countries. Figure 4 shows the vitamin D deficiency levels with respect to Asian countries (x-axis), the COVID-19 deaths between 1000 and 2500 deaths (Axis y) and the COVID-19 cases between 100,000 and 300,000 cases (z-axis). Figures 5 and 6 are similar to Figures 3 and 4 when both European and Asian continents were combined.

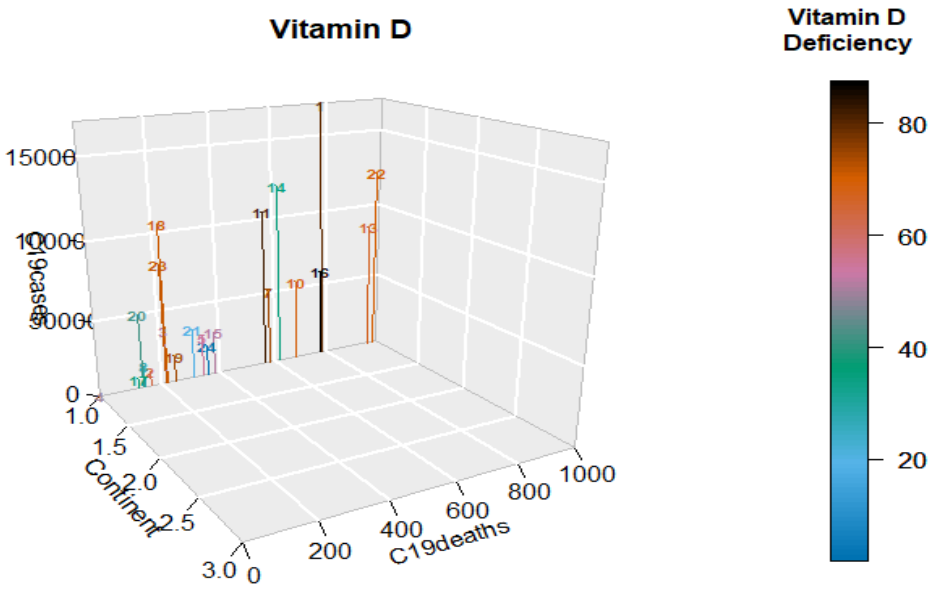


Figure 4. Vitamin D deficiency levels with respect to continent (x-axis), COVID-19 deaths (y-axis) between 1000 and 2500 deaths, and COVID-19 cases (z) between 100,000 and 300,000 among countries in Asia.

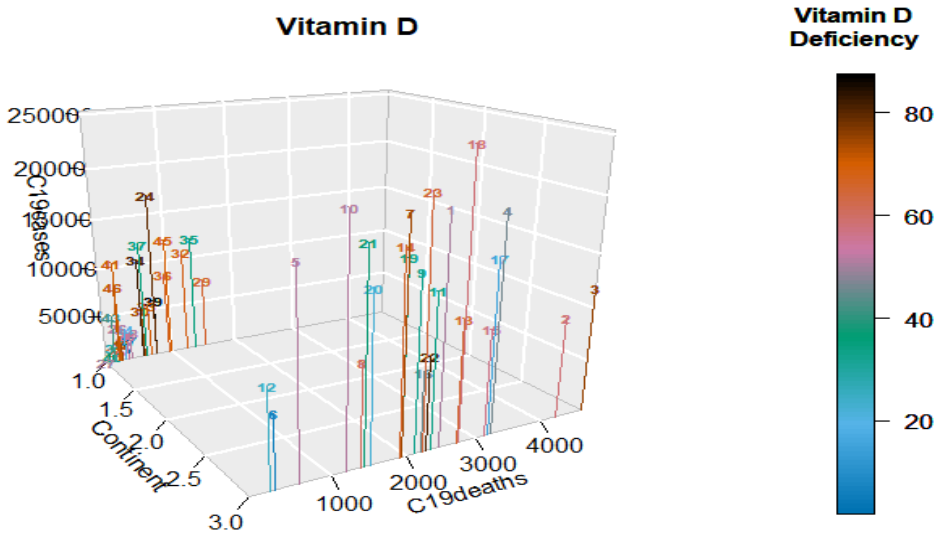


Figure 5. Vitamin D deficiency levels with respect to Continent (x-axis); COVID-19 deaths (y), and COVID-19 cases (z) among countries in Asia and Europe.

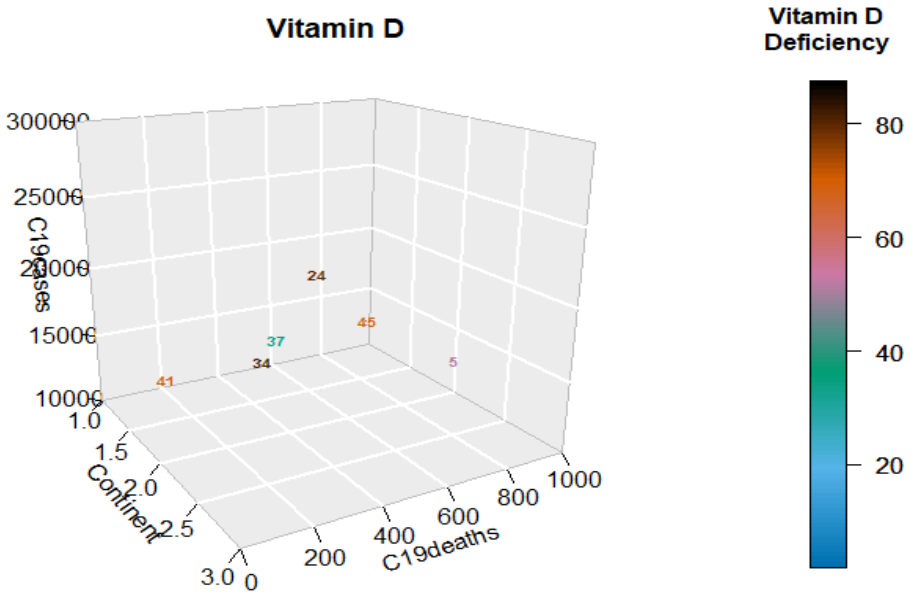


Figure 6. Vitamin D deficiency levels with respect to continent (x-axis), COVID-19 deaths (y-axis) between 1000 and 2500 deaths, and COVID-19 cases (z) between 100,000 and 300,000 among countries in Asia and Europe.

Table 3. Correlation values with the prevalence of vitamin D deficiency.

Continent	Deaths (per million)	Infected Cases (per million)
Europe continent	0.4151	0.1347
Asia continent	0.2655	0.3901
Europe & Asia continents	0.0949	0.0589

Table 3 presents the results of the correlation analysis of the prevalence of vitamin D deficiency, COVID-19 death, and infected cases rates per million in European and Asian continents. We observe the following:

- The prevalence of vitamin D deficiency has a strong positive correlation with the COVID-19 deaths in European continent (i.e. correlation value ('cv') = 0.4151) as shown in Figure 7. The results of linear regression model as shown in Figure 8 can be used to support this finding that COVID-19 death rate (per million) increases in European continent as the prevalence of vitamin D deficiency increases.
- The prevalence of vitamin D deficiency also has a strong positive correlation with the COVID-19 deaths in Asian continent with cv = 0.2655 as shown in Figure 9. The results of linear regression model as shown in Figure 10 can be used to support such finding that COVID-19 death rate (per million) increases in Asian continent as the prevalence of vitamin D deficiency increases.
- When both European and Asian continents were combined there seems to be no correlation between the prevalence of vitamin D deficiency and the COVID-19 death rate with cv = 0.0949 as shown in Figure 11.

- The prevalence of vitamin D deficiency has a strong positive correlation with the COVID-19 infection cases in Asian continent (cv = 0.3901) but has a weak positive correlation in European continent with cv = 0.1347 and has no correlation when both the continents were combined.

It is worth to note that the COVID-19 death rate (per 1 million population) had a strong positive correlation with the COVID-19 infected cases in Asian continent (cv = 0.6302) and when both European and Asian continents were combined (cv = 0.5608) but not in European continent alone (cv = 0.0085).

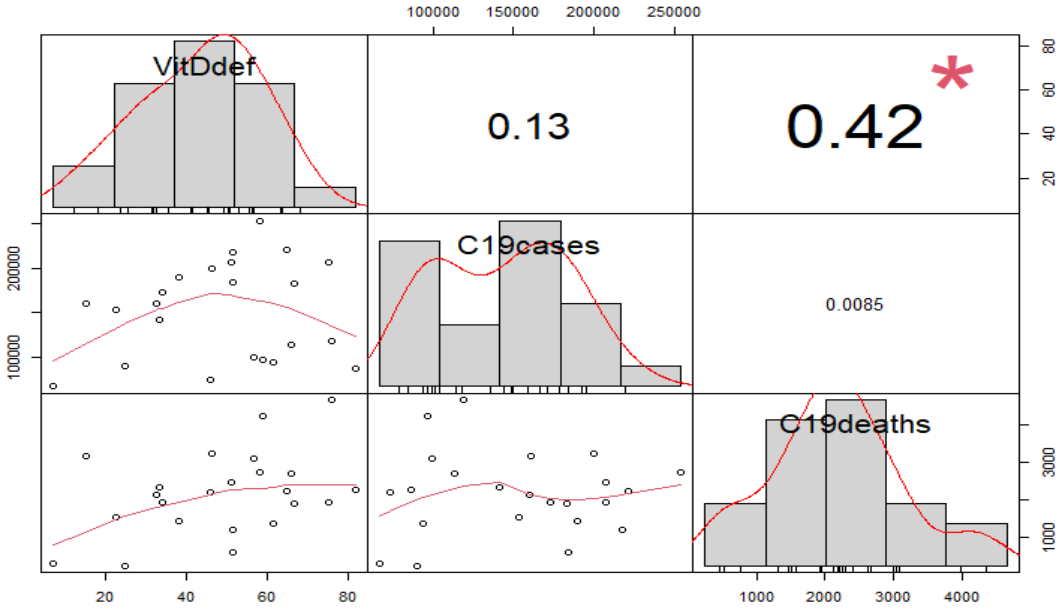


Figure 7. Correlation analysis of prevalence of vitamin D deficiency, COVID-19 death rate and infection rate in European continent.

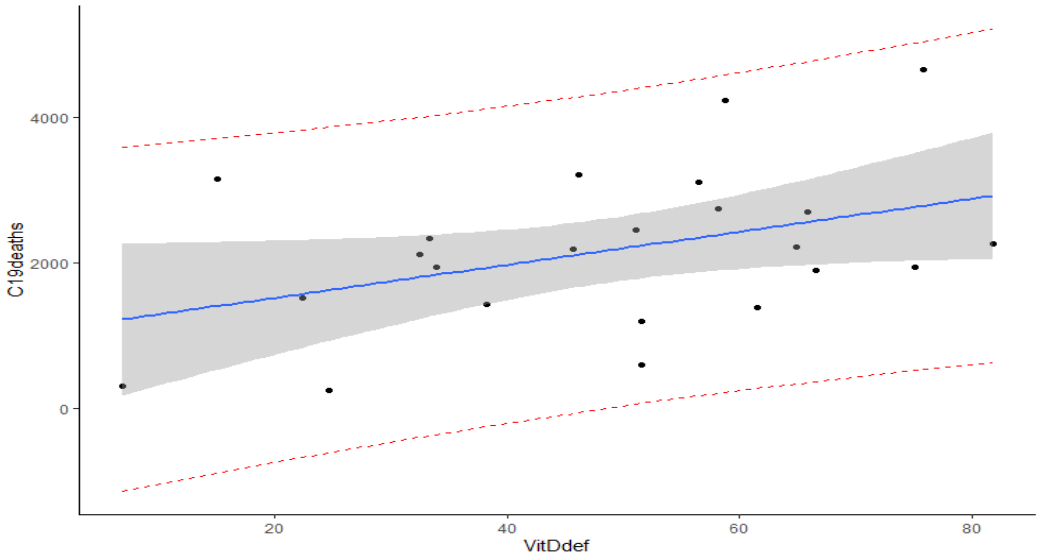


Figure 8. Regression analysis ofCOVID-19 death rate versus prevalence of vitamin D deficiency in European continent.

This result is agreed with recent study by Dror et al [112] that there was an association between vitamin D deficiency and the COVID-19 deaths and COVID-19 infected cases and the lower vitamin D levels were associated with greater COVID-19 deaths. As suggested by many researchers [15,22,44–50,83–84], supplementation with vitamin D might be recommended to the people who are currently in vitamin D deficient and insufficient levels.

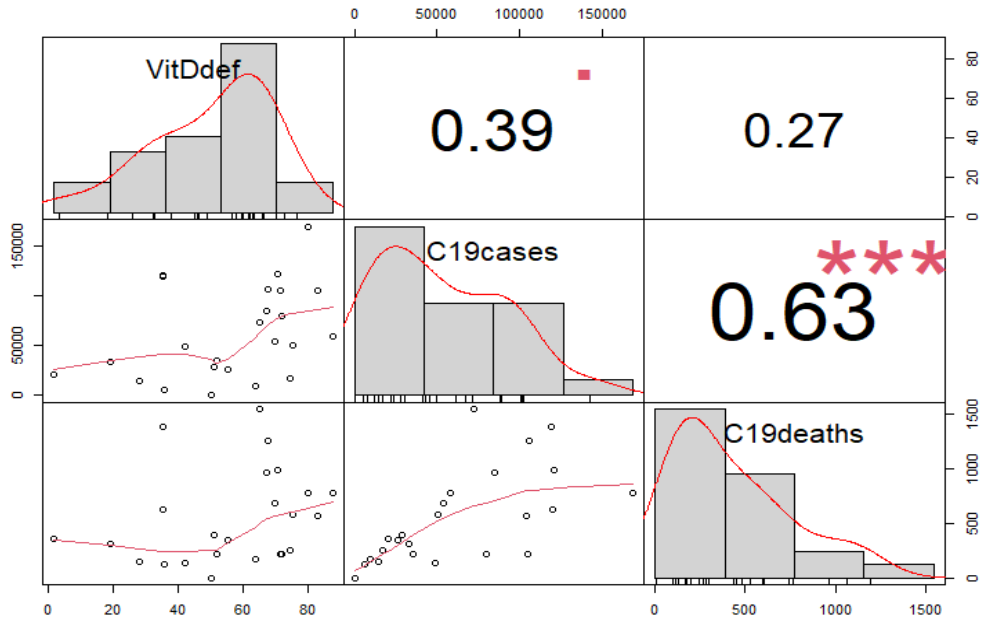


Figure 9. Correlation analysis of prevalence of vitamin D deficiency, COVID-19 death rate and infection rate in Asian continent.

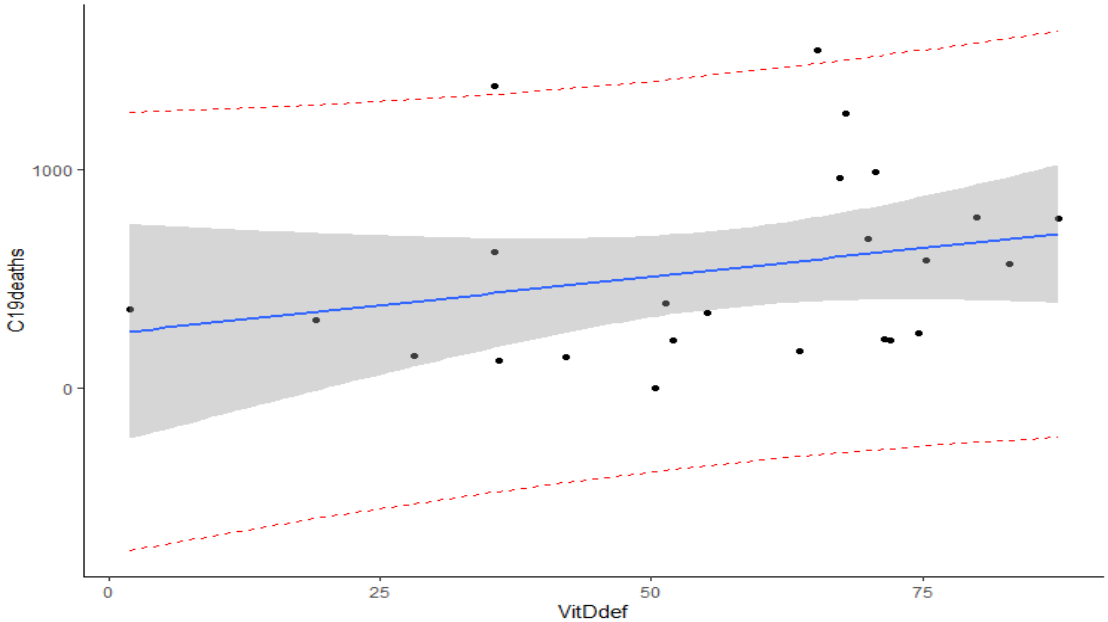


Figure 10. Regression analysis of COVID-19 death rate versus prevalence of vitamin D deficiency in Asian continent.

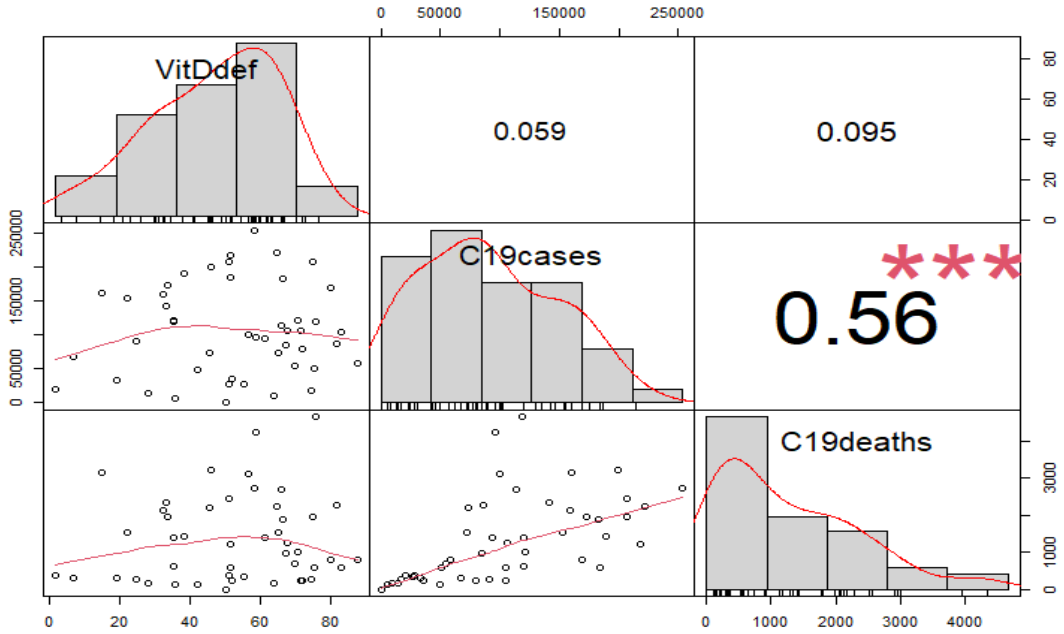


Figure 11. Correlation analysis of prevalence of vitamin D deficiency, COVID-19 death rate and infection rate in both European and Asian continents.

4. Mathematical model development

Vitamin D is a fat-soluble vitamin which plays an important function in supporting immune response that enhances the function of immune healthy cells to protect the body against pathogens. As we discussed in previous sections, lower vitamin D levels such as vitamin D deficiency have been associated with increased susceptibility to infection, disease, and autoimmunity. In other words, vitamin D deficiency is linked to immune disorders and increased the risk of infections and COVID-19 mortality rate.

The immune system needs vitamin D to fight off invading bacteria and viruses. Recent research shows with high levels of vitamin D status can help to keep body's immune system healthy and likely protect against respiratory illnesses. Hospitalized patients with COVID-19 infections who had sufficient vitamin D levels has a decreased risk of adverse outcomes and death [112]. The immune system provides all the protective mechanisms needed to fight off infections or other dangerous agents [7].

Developing mathematical models to assess the growth of disease infections and immune healthy cells have been of interest in the area of cancer epidemiology [113,114], tumor growth [115–117] and infectious disease [118,119] in the past few decades. Many models [118–120] have been studied in the past decades using the ordinary differential equations to characterize the tumor-immune dynamic growth of virus-infected cells of immune system [120]. Lestari et al. [121] studied an epidemic cancer model with chemotherapy in the form of a system of non-linear differential equations with three sub-populations. They presented the point of equilibrium and numerically determined the reproduction number of cancer cells. Pham [4] presented a model to estimate the US deaths toll related to COVID-19. Pham [7] recently discussed a time-dependent model considering

various factors related to COVID-19 including social distancing and reopening states in different communities. Pham [122] recently developed a virus-immune time-delay model of immune system, and later extended Pham's earlier work [122] by taking the factor of chemotherapy drug treatment into the model consideration [123].

In this section, we present a new mathematical time-delay model considering interactions between body's immune healthy cells, infected cells, and virus particles with the effect of vitamin D levels. We describe model assumptions based on recent studies in [121–123] and discuss a model formulation consisting of three time-dependent variables in terms of partial differential equations that represent the growth rate of immune cells, infected cells, and virus particles. We also discuss numerical results that illustrate the proposed model and present various cases to predict whether the infected cells or virus particles can be reached free state level or not as the time progresses.

Notation

The following notation are used in the model formulation:
a = infected cells death rate per unit time
s = constant growth rate of healthy cells
c = death rate of healthy cells unit time
g = healthy cells growth rate by taking probiotic supplement
x = the virus rate per unit time that enters the body
m = the rate that virus infects healthy cells
m_1 = the vitamin D rate that can enhance healthy cells
u = the rate that the healthy cells fail to fight infected cells
b = the rate that the healthy cells fight and destroy infected cells
n = the rate that the healthy cells manage to fight off the virus due to healthy immune system
k = the rate that infected cells produce virus
d = virus death rate per unit time
q = the half saturation constant that related to healthy cells
w = the half saturation constant that related to virus
$H(t)$ = the time-dependent function of number of healthy cells at time t
$I(t)$ = the time-dependent function of number of infected cells at time t
$V(t)$ = the time-dependent function number of virus in the body at time t

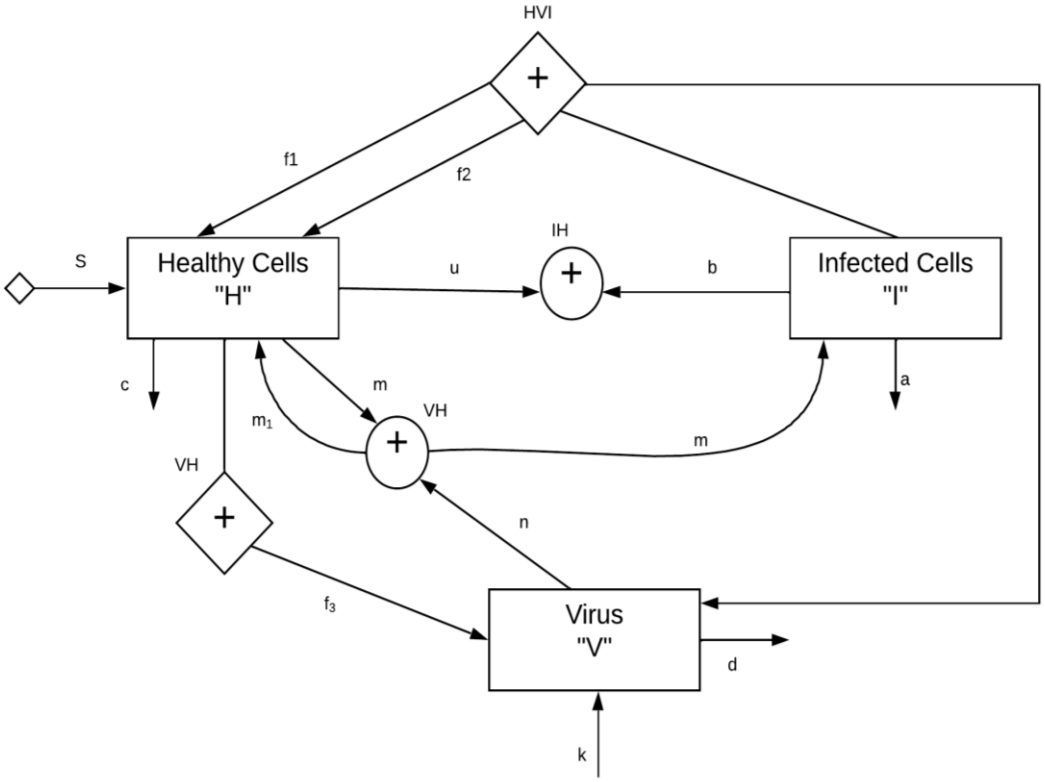
The following are the assumptions of our proposed model of time-delay interactions between body's immune healthy cells, infected cells, and virus particles with the effect of vitamin D deficiency:
1. The healthy cell has a constant growth rate, s.
2. The healthy cell has a natural death rate, c.
3. There is a reduced number of healthy cells due to the virus infects healthy cell at the rate m.
4. Vitamin D supplement can enhance healthy cells and improve body immunity that can fight off the virus at the rate m_1.
5. The healthy cells fail to fight infected cells with the rate u.
6. There is an increase of healthy cells with time-delay constant growth rate g by using probiotic supplement with a delay τ_1 time.

7. The healthy cells are able to fight infected cells at the rate *b* and also manages to fight off the virus at the rate *n* with a time delay τ_2.

8. The infected of virus particles and the healthy cells became the infected cells at the rate *m.*
9. The infected cell has a death rate per unit time *a*
10. *T*he healthy cells manage to fight off the infected cells at the rate *b.*
11. The infected cells produce the virus cells at the rate *k*
12. The virus particles have a death rate per unit time *d*
13. *T*he healthy cells manage to fight off the virus particles at the rate *n.*

14. The virus enters the body at the rate *x* per unit time with a time delay τ_3.

The proposed mathematical model includes three time-dependent variables: immune healthy cells H(t), infected cell I(t), and virus particles V(t). Virus particles invaded healthy cells with the rate m (i.e., *m*H(t) V(t)) and transform them into infected cells. Healthy cells, infected cells, and virus particles die at the rate *c*, *a*, and *d*, respectively.



$$f_1 = \frac{gH(t-\tau_1)I(t-\tau_1)V(t-\tau_1)}{q + I(t-\tau_1)V(t-\tau_1)}$$
$$f_2 = bnI(t-\tau_2)V(t-\tau_2)H(t-\tau_2)$$
$$f_3 = \frac{xV(t-\tau_3)H(t-\tau_3)}{W + H(t-\tau_3)}.$$

Figure 12. Mathematical process presentation of time-delay interactions between body's immune healthy cells, infected cells, and virus particles model.

The rate functions of the number of immune healthy cells H(t), infected cells I(t), and virus particles V(t) over time t of the proposed model can be formulatedbased on the assumptions (1-7), (8–10), and (11–14) respectively, as follows:

$$\frac{\partial H(t)}{\partial t} = s - cH - mHV + m_1 HV - uHI + \frac{gH(t-\tau_1)I(t-\tau_1)V(t-\tau_1)}{q + I(t-\tau_1)V(t-\tau_1)} + bnI(t-\tau_2)V(t-\tau_2)H(t-\tau_2) \quad (1)$$

$$\frac{\partial I(t)}{\partial t} = mHV - aI - bIH \quad (2)$$

$$\frac{\partial V(t)}{\partial t} = kI - dV - nVH + \frac{xV(t-\tau_3)H(t-\tau_3)}{W + H(t-\tau_3)}. \quad (3)$$

Figure 12 demonstrates the proposed mathematical presentation of the above equations. We develop an algorithm using R software to numerically obtain the results for H(t), I(t), and the number of virus particles V(t) as we will discuss with various cases in numerical examples in section 4.1.

4.1. Numerical examples

This section presents some numerical results based on the above delay system of differential equations using the numerical values based on some existing studies [121–123] as shown in Table 4 for the illustration of the model. Note that one can easily apply the proposed model to obtain the numerical results for any other sets of parameter values.

Table 4. Model parameter values.

s = 0.43/day	c=0.00212/day	m = 0.0004/day
u = 0.0002/day	g = 0.01/day	q = 0.20/day
b = 0.0001/day	n = 0.00005/day	a = 0.004/day
k = 0.0070/day	d = 0.004/day	x = 0.006/day
w = 0.90/day		

In this analysis, we assume that the initial number of virus particles, infected cells, and healthy cells are 30000, 35,000 and 75,000, respectively, for the algorithm and developed program can search to find the best solutions. It is worth to note that the results do not necessary depend on the assumptions of these initial numbers but analyst can provide any numbers as initial values for the purpose of numerically solving the system of differential equations. We now present various cases with some parameter values of the healthy cell growth rate as well as the rate that infected cells and virus particles where the first, second and third time-delay are 1, 2, and 2 days, respectively.

Case 1: s = 0.43, m = 0.0004/day, and m_1= 0

Here we do not consider the effect of the vitamin D, that is when m_1= 0 but will be taking into consideration of the probiotic that can be enhancing the healthy cells and therefore, to enhance the body immune systems.

Case 1a: Here we consider that g = 0.01/day

From Figure 13, we observe as expected the initial number of virus particles, infected cells, and healthy cells are 30000, 35,000 and 75,000, respectively. The infected cells begin to increase sharply until the 3rd day then starts to decrease until it slowly be stable after the 270th day at the level of around 11,500 (see Figure 13 in "blue"). The virus particles begin to decrease sharply until the 7th day but starts to increase until it slowly be stable at around 29,000 which is about the 260th day (see Figure 13 in "red"). The healthy cells (see Figure 13 in "green") decreases sharply at the beginning and it reaches the level of empty healthy cell at the level at about the 100th day.

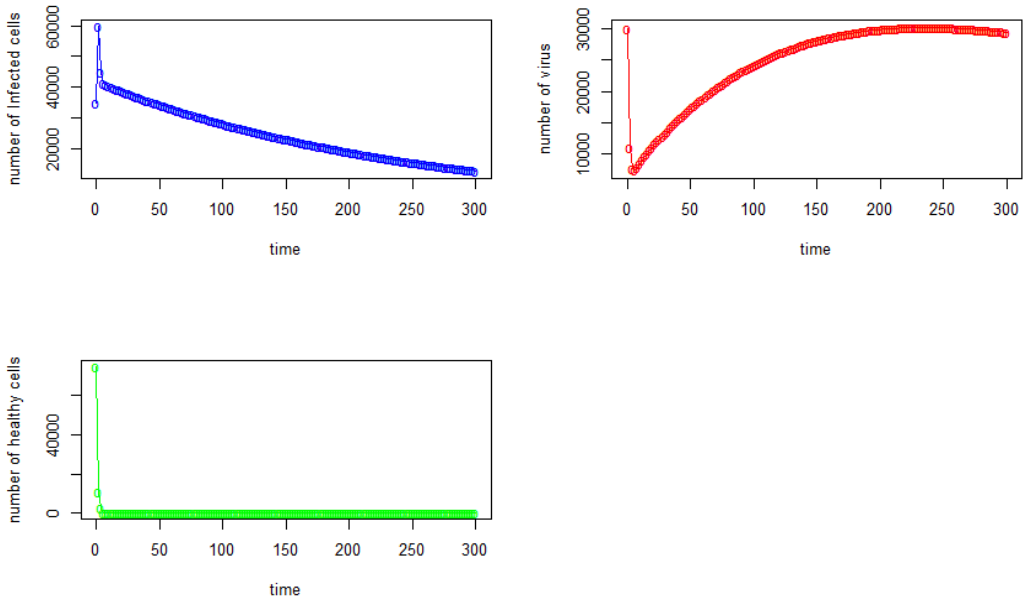


Figure 13. (Case 1a).

Case 1b: When g = 0.8/day

Similar to case 1a, we now increase the healthy cells growth rate by taking probiotic supplement from 0.01 to 0.8, we still do not see it much different from the previous case (case 1a) in terms of the infected cells, the healthy cell, and the virus particles as shown in Figure 14.

Case 1c: When g = 1.8/day

As seen in Figure 15, the healthy cells (see Figure 15 in "green") decreases sharply at the beginning until around the 10th day and starts to increase quickly that reaches the maximum number of healthy cells level at around the 35th day and then begins to decrease until they slowly stabilize at around the 275th day at the level of 180,000. Unlike the previous cases, although the infected cells slightly increase at the beginning, both the infected cells and virus particles decrease significantly to until they reach the infected cells (see Figure 15 in "blue") free state and virus particles (Figure 15 in "red") after around the 25th day as shown in Figure 15.

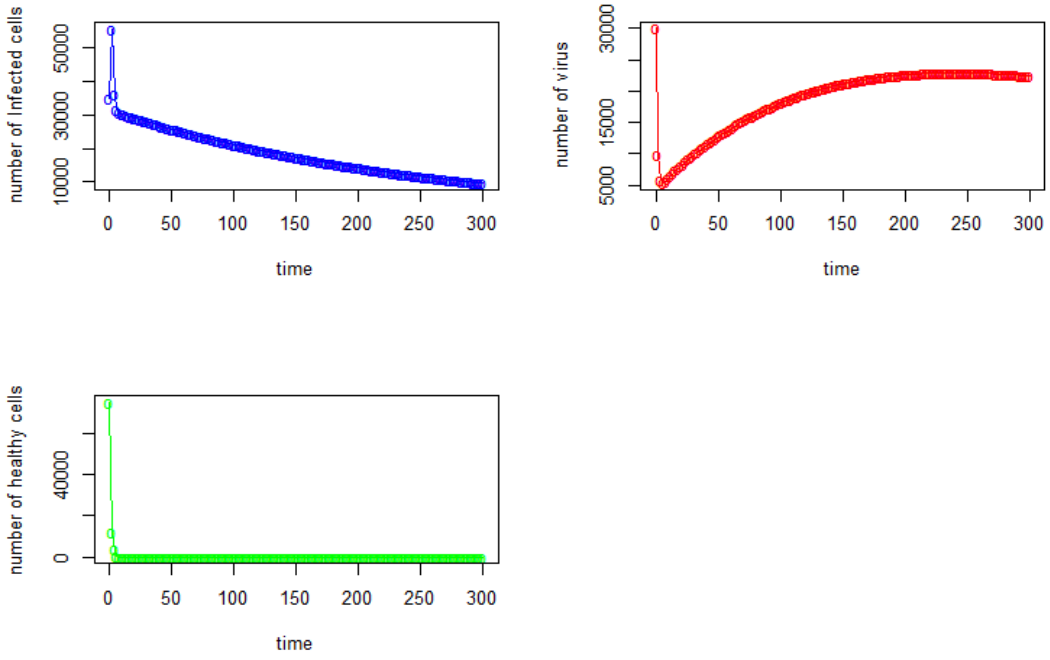


Figure 14. (Case 1b).

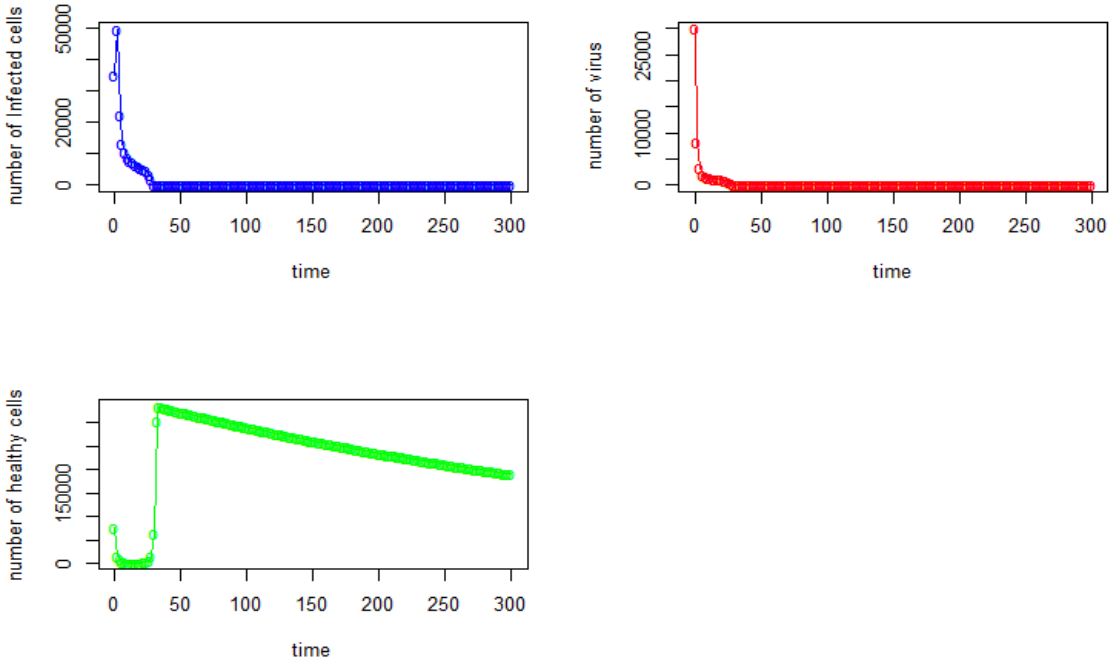


Figure 15. (Case 1c).

Case 2: s = 0.43, m = 0.0004/day, g = 1.8/day, and m_1= 0.00005

Here we assume that with a sufficient vitamin D level, it can enhance the number of healthy cells that can help to fight off the infected cells and virus particles. Since the healthy cells can be boosted due to the vitamin D sufficiency level. As can be seen from Figure 16 and the same results from Case 1c, the healthy cells (see Figure 16 in "green") decreases sharply at the beginning until

around the 5th day and starts to increase quickly that reaches the maximum number of healthy cells level at around the 50th day and then begins to decrease until they slowly stabilize at around the 300th day at the level of 205,000. Similar to Case 1c, both the infected cells and virus particles decrease significantly at the beginning to until they reach the infected cells (see Figure 16 in "blue") free state and virus particles (Figure4 in "red") free state after around the 15th day as shown in Figure 16.

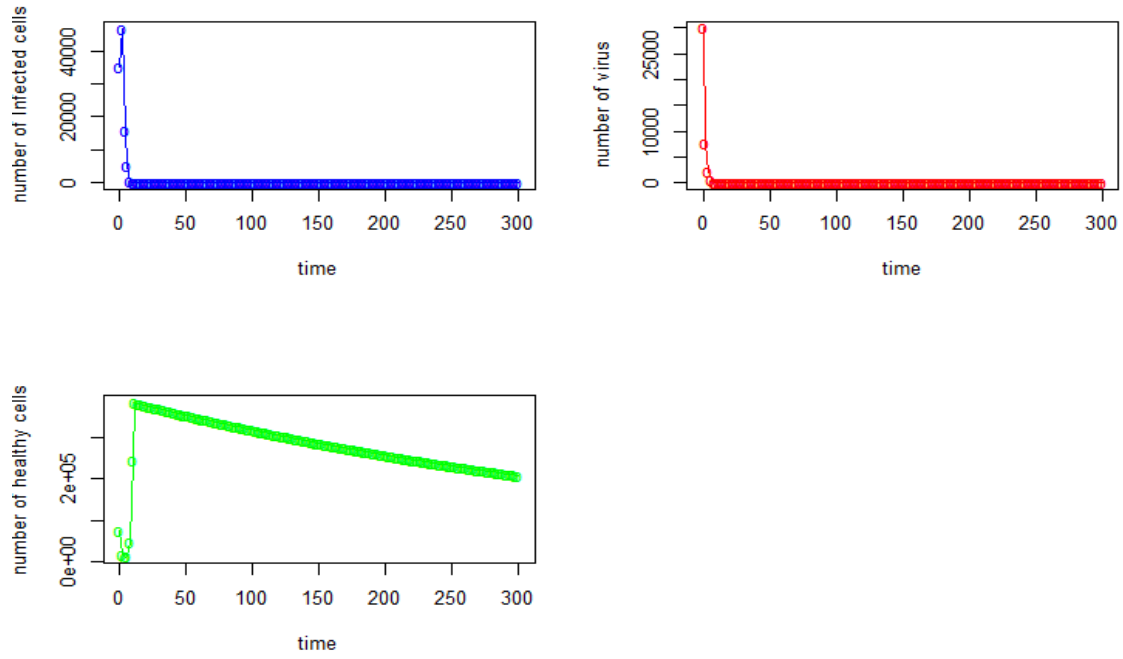


Figure 16. (Case 2).

Case 3: s = 0.43, m = 0.00035/day, g = 1.8/day, and m_1= 0.00002

Here we are interested in examining the effects of healthy cells, infected cells and virus particle subject to the rate that virus infects healthy cells and the vitamin D rate that can enhance healthy cells. We consider to slightly lower the rate that virus infects the healthy cells from m = 0.0004 reduced to 0.00035 but also lower the vitamin D sufficient level from m_1= 0.00005 (Case 2) also reduced to m_1= 0.00002.As shown in Figure 17 we observe that both the infected cells and virus particles decrease significantly at the beginning and quickly to reach the infected cells (see Figure 17 in "blue") free state and virus particles (Figure17 in "red") free state after around the 5th day as shown in Figure 17. The healthy cells (see Figure 17 in "green") although decreases sharply at the beginning until around the 5th day, it then starts to significantly increase that reaches the maximum number of healthy cells level at around the 30th day and then decreases until they slowly stabilize at around the 240th day at the level of 275,000.

Similarly, if we consider the third time-delay is as 3 days, instead of 2 days from Case 3, we observe that both the infected cells and virus particles decrease slightly at the beginning but quickly to reach the infected cells (see Figure 18 in "blue") free state and virus particles (Figure 18 in "red") free state after around the 7th day as shown in Figure 18. The healthy cells (see Figure 18 in "green") although decreases sharply at the beginning until around the 7th day, it then starts to significantly increase that reaches the maximum number of healthy cells level at around the 10th day and then decreases until they slowly stabilize at around the 300th day at the level of 488,000.

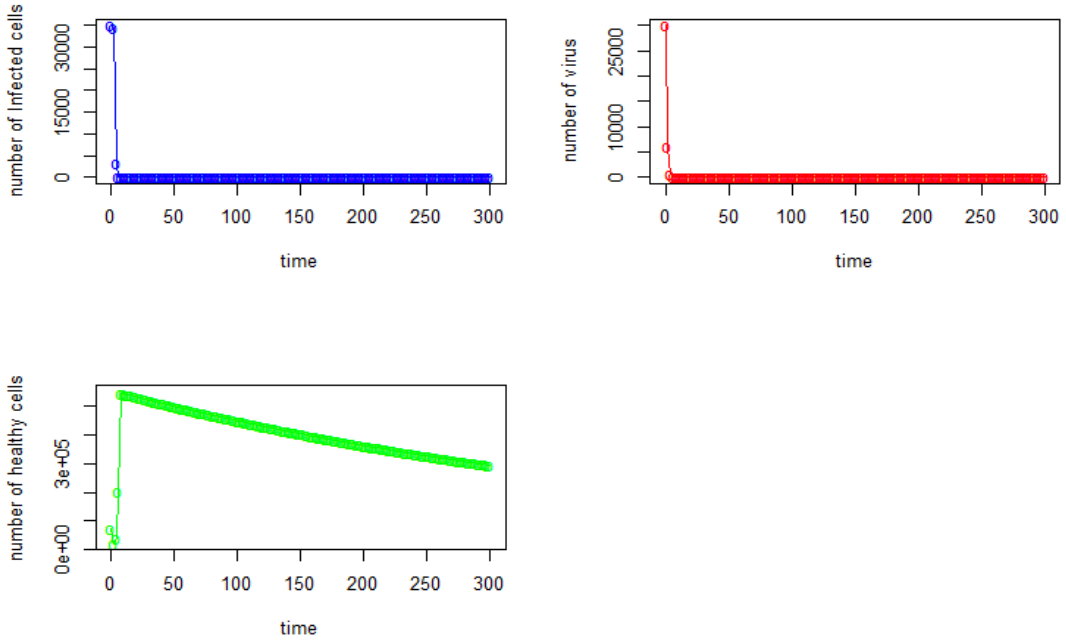


Figure 17 (Case 3). When the 1st time delay = 1 day, 2nd delay = 2; 3rd delay = 2 days.

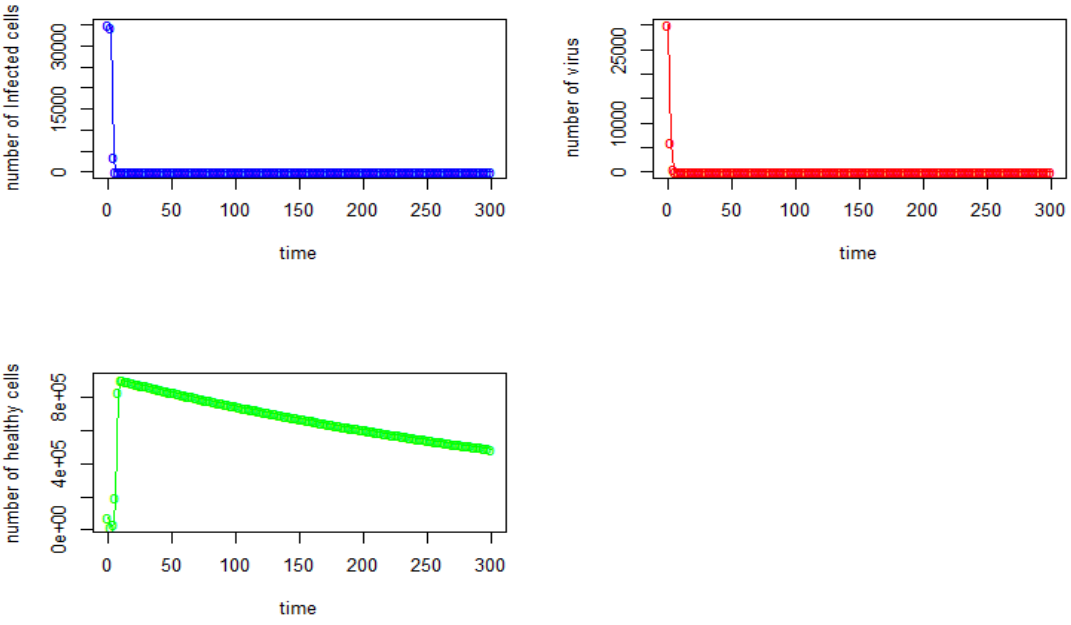


Figure 18 (Case 3). When the 1st time delay = 1 day, 2nd delay = 2; 3rd delay = 3 days.

When the proposed model does not consider the delays which means that the first, second and third delays are all 0, the infected cells begin to increase sharply until the 2nd day and starts to decrease until it slowly be stable after the 300th day at the level of around 18,000 (see Figure 19 in "blue"). The virus particles start to decrease until the 3rd day and quickly starts to increase until it slowly be stable at around 47,000 which is about the 290th day (see Figure 19 in "red"). In contrast to the delay case (see Figure 17), for the non-delay case, the healthy cells (see Figure 19 in "green") decreases sharply at the beginning and it reaches the level of empty healthy cell at the level at about

the 10th day. This numerical result shows an important finding that the analyst must carefully examining whether to consider the delay in the modeling or not.

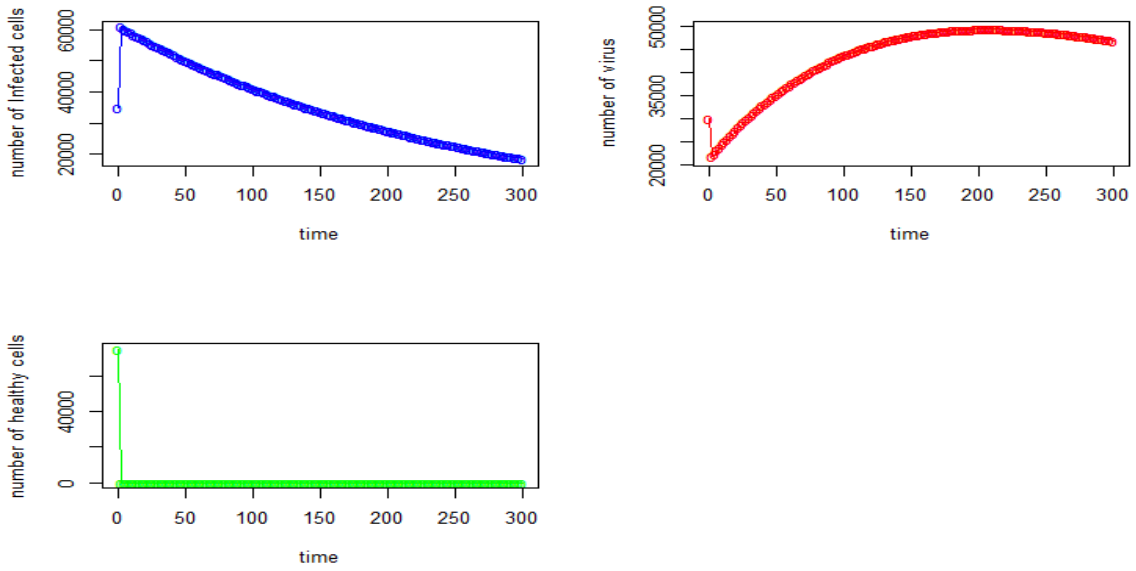


Figure 19 (Case 3). When there is no time delay (i.e. 1st delay = 2nd delay = 3rd delay = 0).

Case 4: Same as Case 3 (s = 0.43, m = 0.00035/day, g = 1.8/day, and m_1= 0.00002) but with various initial number of virus particles V(0), infected cells I(0), and healthy cells H(0) where the first, second and third time-delay are 1, 2, and 2 days, respectively.

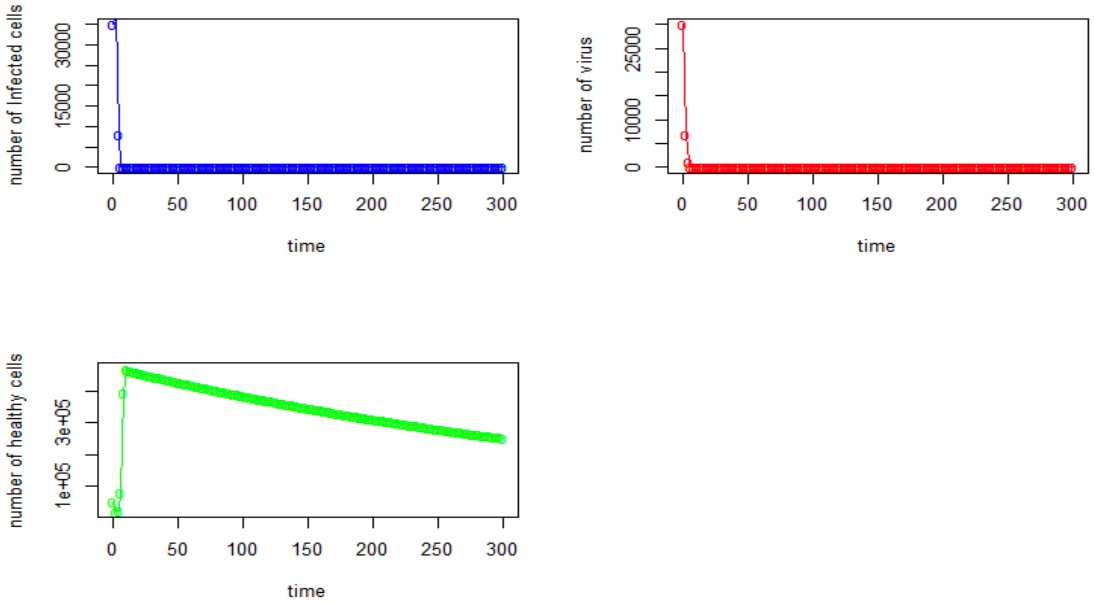


Figure 20. V(0) = 30,000; I(0) = 35,000; and H(0) = 50,000.

Case 4.1: V(0) = 30,000; I(0) = 35,000; and H(0) = 50,000.

From Figure 20 we observe that both the infected cells and virus particles significantly decrease at the beginning and quickly to reach the infected cells (Figure 20 in "blue") free state and virus particles (Figure 20 in "red") free state after around the 10th day. The healthy cells (see Figure 20 in "green") although decreases sharply at the beginning until around the 5th day, it then starts to significantly increase that reaches the maximum number of healthy cells level at around the 25th day and then decreases until they slowly stabilize at around the 300th day at the level of 250,000. Figure 21 shows about the same outcome.

Case 4.2: When V(0) = 30,000; I(0) = 35,000; and H(0) = 35,000.

We observe the same conclusion from Case 4.1 that the infected cells and virus particles significantly decrease at the beginning and quickly to reach the infected cells (Figure 21 in "blue") free state and virus particles (Figure 21 in "red") free state after around the 10th day. The healthy cells (see Figure 20 in "green") although decreases sharply at the beginning until around the 5th day, it then starts to significantly increase that reaches the maximum number of healthy cells level at around the 25th day and then decreases until they slowly stabilize at around the 300th day at the level of 250,000.

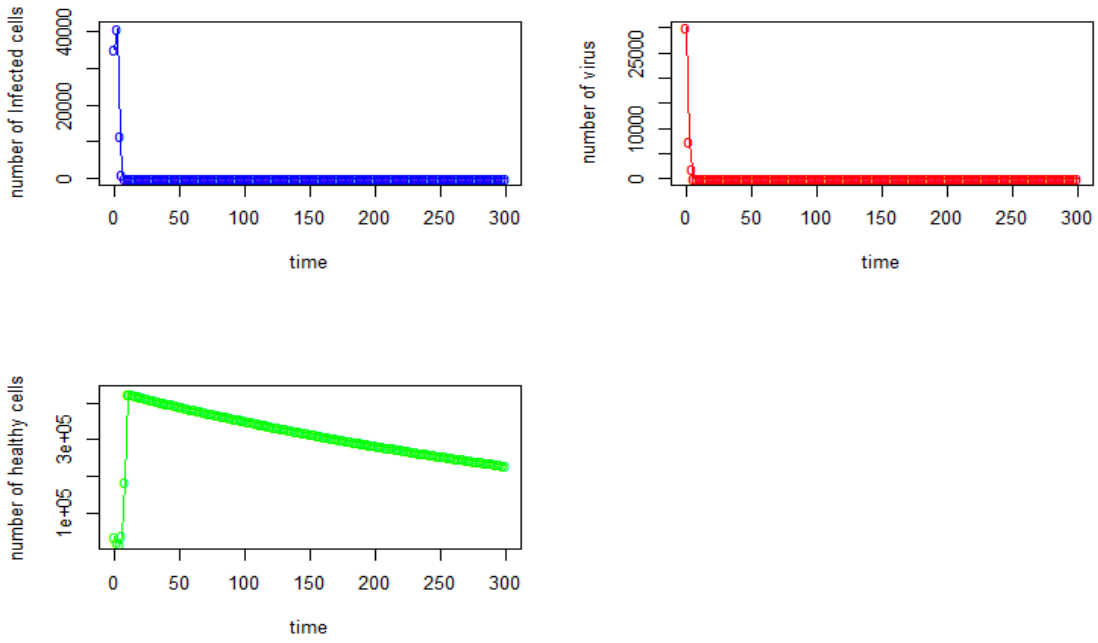


Figure 21. V(0) = 30,000; I(0) = 35,000; and H(0) = 35,000.

Case 4.3: When V(0) = 10,000; I(0) = 10,000; and H(0) = 10,000.

From Figure 22, we observe that the infected cells begin to increase sharply until the 8th day then starts to decrease until it slowly be stable after the 280th day at the level of around 6,500 (see Figure 22 in "blue"). The virus particles begin to decrease sharply until the 4th day but starts to increase until it slowly be stable at around 16,900 which is about the 270th day (see Figure 22 in

"red"). The healthy cells (see Figure 22 in "green") decreases sharply at the beginning and it reaches the level of empty healthy cell at the level at about the 100th day.

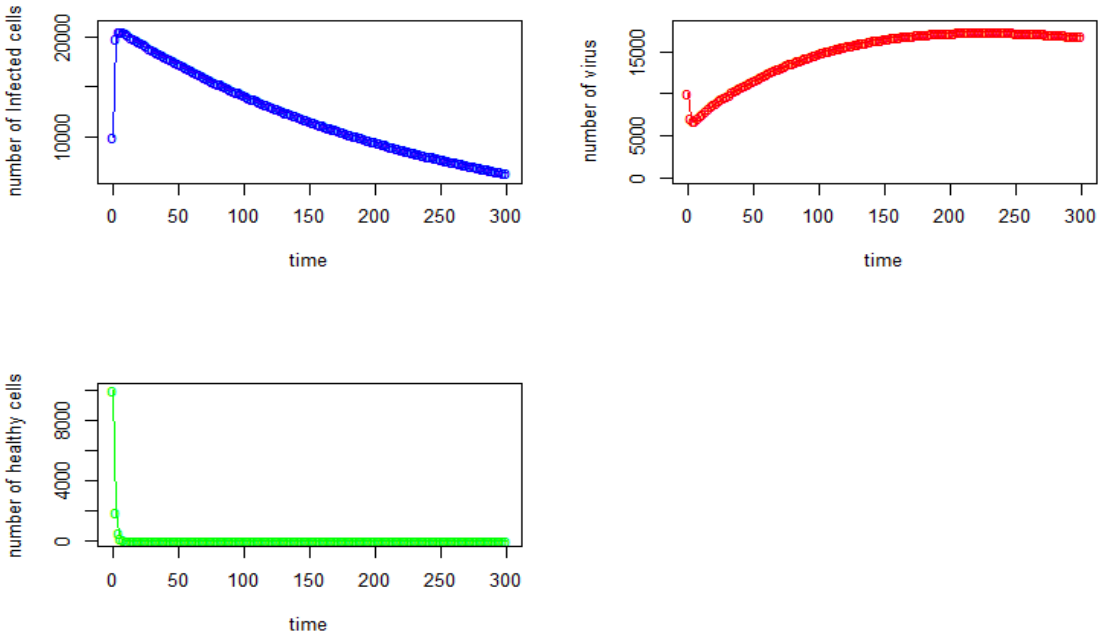


Figure 22. V(0) = 10,000; I(0) = 10,000; and H(0) = 10,000.

5. Conclusion

This paper studied the relationship between the vitamin D deficiency and COVID-19 infected cases and deaths toll among the countries in Europe and Asia continents. The results agreed with some recent studies that there seems to be a strong association between vitamin D deficiency, the COVID-19 deaths, and COVID-19 infected cases, and that the lower vitamin D levels were associated with higherCOVID-19 deaths. The proposed time-delay model of time-delay interactions between body's immune healthy cells, infected cells, and virus particles with the present of vitamin D sufficient levels and the probiotics supplement can be used to determine (1) the growth levels of the infected cells and virus particles, and (2) the prediction whether the infected cells and virus particles can be reached to free state status as time progresses. The modeling result also shows an important finding that the appropriate of time-delay duration that will take those cells (i.e., body's immune healthy cells, infected cells and virus particles) to effectively spread in the body is crucial in the model and that can make a significant difference of the modeling results. Some future research problems can be extended to (1) investigate the relationship between the vitamin D deficiency and the COVID-19 infected cases and death toll in the United States assuming those data are available, and (2) consider the growth rate of healthy cells as a function of ageing along with the vitamin supplements subject to time-delay aspects.

Conflict of interest

The author declares no conflicts of interest in this paper.

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