

# On a Mathematical Model for HBV and HCV Co-infection

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**Abstract**— We present a mathematical model which describes the development of coinfection with HBV (Hepatitis B virus) and HCV (Hepatitis C virus), in a patient in a “congested” environment. We assume that, while susceptible patients become infected with HBV and/or HCV through physical contact (sexual, sharing needles, and so on), coinfection occurs simply because they live in close proximity to each other, a situation which is true in densely populated situations like penitentiaries, refugee camps, etc., and sometimes in overpopulated countries. A similar assumption about coinfection with HCV and HIV (human immunodeficiency virus) has also been made by other researchers. We shall, accordingly, assume that a certain percentage of people who are infected with HBV in a densely populated environment are also co-infected with HCV, and vice versa. We give several examples to illustrate the behavior of the model.

**Index Terms**—basic reproduction ratio, co-infection, congested environment, Hepatitis B virus, Hepatitis C virus, mathematical modeling

## I. INTRODUCTION

ONE hundred and seventy million people are infected with HCV (Hepatitis C virus) worldwide [1, 2]. In North America, more than five million people are estimated to be living with HCV [2, 3]. Approximately 30,000 new cases are diagnosed each year, and this situation is projected to get worse as the number of people infected with HCV from blood transfusions before 1990 come to be newly diagnosed [2]. This is because, before 1990, there was no screening of blood against HCV (HCV was discovered in 1989), so that millions of patients must have been infected through blood transfusions. These cases are now coming to light because the disease can stay asymptomatic for 20 years and more. Historically, the disease is speculated to have been brought into the United States from West Africa at the time of the slave trade [2]. Today, it kills more people than HIV (human immunodeficiency virus) every year in that country. In some countries in Africa, like in Egypt, the virus affects almost one in every five adults. If untreated, HCV results in generally fatal liver failure. If treated, the treatment is unsuccessful in over half of the patients. Like HIV, HCV can stay dormant for years while attacking the liver all this time. HCV mutates easily which makes for a large number of mutant viruses (and makes the development of a vaccine that much more difficult). There are six known genotypes (numbered 1 through 6) and more than 50 subtypes (e.g., 1a, 1b, 2a ...). These genotypes and their subtypes are present in different proportions in different countries. As an example, genotype

1 is the dominant type in the United States, while in India, genotype 3 seems to be more prevalent [4].

The history of HBV (Hepatitis B virus) goes back to the 1950' s when a Dr. Baruch Blumberg was taking samples from the blood of aborigines in Australia. Dr. Blumberg was interested in polymorphism and he wanted to see whether inherited traits could make different people more or less susceptible to infection by certain viruses. During these trials, he tested the blood of several hemophiliacs because these people were routinely exposed to different kinds of blood through blood transfusions, and the immune system of the recipient should produce antibodies against the antigens in the donors' blood. In 1963, Dr. Blumberg identified an antigen that detected the presence of Hepatitis in the blood samples. That virus was officially recognized as HBV in 1967 and a vaccine for the virus was discovered in 1969 [5]. Today, more than 240 million people are chronically infected with the virus [6], mainly because, in many countries, vaccination is not followed thoroughly enough. In Southeast Asian countries for example, approximately 5 - 10% of the population are carriers of HBV, while in North America and Europe, this figure is about 0.5 % because of better vaccination practices. In Canada, the incidence of reported HBV infection has dropped dramatically after 1995. It was estimated at 2.3/100,000 in 1998 [7]. Dr. Blumberg received a Nobel Prize for his work in 1876.

While HCV infection can be cured, and the virus can re-infect, chronic HBV generally ends up in hepatocellular carcinoma (liver cancer). Almost 90 percent of babies and about 5 - 10% of adults who contract HBV develop the chronic form of it and may need liver transplant [7]. However, the chance of the virus being reactivated after liver transplant is also quite high. Overall, we may say that a certain percentage of people who get infected with HCV or HBV and get cured, get sick again with the same infection.

In many developing countries, with very high population densities, co-infection with both HBV and HCV is fairly common [8, 9, 10, 11]. According to one writer, “HCV superinfection in patients with chronic HBV infection was the most common clinical feature of coinfection in Asia-Pacific countries” [10]. This is perhaps because of over population in these countries. In such situations, people live in close proximity and generally, are not well cared for. Medical facilities are minimal, and these facilities are generally availed of only when the patients are seriously sick, which in the context of this paper, means when they are co-infected. Also, people who are already infected with HBV or HCV, are

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likely to have similar "risky" behavior (risk factors for both HBV and HCV are the same), so that contacts are fairly common (social, sexual, sharing needles and other), which facilitates coinfection. Considering all this, one may assume that a certain fraction of people, living in "congested situations" and suffering from HBV are also suffering from HCV and vice versa. Such considerations (about congestion) are applicable in many situations like penitentiaries, refugee camps, slums in big cities (Dharavi in Mumbai?) and so on.

We present a mathematical model which describes the development of coinfection with HBV and HCV, in a patient in a congested environment. We assume that, while patients become infected with HBV and/or HCV through physical contact (sexual, sharing needles, and so on) coinfection occurs simply because they live in close proximity to each other, a situation which is true in densely populated situations like penitentiaries, refugee camps, etc. A similar assumption about coinfection with HCV and HIV has also been made by other researchers [12]. We shall, therefore, assume that a certain percentage of people who are infected with HBV in a densely populated environment are also co-infected with HCV, and vice versa. We give several examples to illustrate the behavior of the model. However, these examples are not specific to HBV/HCV coinfection but simply to illustrate how the model behaves under such conditions.

## II. THE MODEL

### A. Set Up

We write

$$F_1(x_1, x_2, x_3, x_4) = A_1 - A_2x_1 - A_3x_1x_2 - A_4x_1x_3 - A_5x_1x_4 \quad (1a)$$

$$F_2(x_1, x_2, x_3, x_4) = A_3x_1x_2 + \theta_1A_5x_1x_4 - A_6x_2 + A_{11}x_4 \quad (1b)$$

$$F_3(x_1, x_2, x_3, x_4) = A_4x_1x_3 + (1 - \theta_1)A_5x_1x_4 - A_7x_3 + A_{12}x_4 \quad (1c)$$

$$F_4(x_1, x_2, x_3, x_4) = A_8x_2 + A_9x_3 - A_{10}x_4 - A_{11}x_4 - A_{12}x_4 \quad (1d)$$

with  $x_1' = F_1, x_2' = F_2, x_3' = F_3$ , and  $x_4' = F_4$ .

All the parameters  $A_1, A_2, \dots$  etc. are supposed to be non-negative.

In these equations,  $x_1, x_2, x_3$  and  $x_4$  refer to the number of susceptible people, people infected with HBV, those infected with HCV, and those who are co-infected, respectively. Susceptible people become infected with HBV and/or HCV when they come into contact with similarly infected people according to the terms  $A_3x_1x_2$  and  $A_4x_1x_3$ . If a susceptible person ( $x_1$ ) comes into contact with a co-infected person ( $x_4$ ), then he/she becomes infected with either HBV or HCV (but not both) according to the terms  $\theta_1A_5x_1x_4$  and  $(1 - \theta_1)A_5x_1x_4$ , so that a certain percentage of people ( $0 < \theta_1 < 1$ ) become infected with HBV and others with HCV (but not both). Also, a certain percentage of people who are infected with HBV (or HCV) also get co-infected (according

to the terms  $A_8x_2$ , and  $A_9x_3$ ) because of congested environments, and also because the risk factors for both infections are the same. Some of these co-infected people ( $A_{11}x_4, A_{12}x_4$ ) get cured, mostly through medical intervention, of either HBV or HCV (but not both) and become candidates for reinfection by that virus. We ignore the very small number of co-infected people who get cured of both the infections, and rejoin the  $x_1$  class.

### B. Positivity of the Solution

It is clear that, in the beginning, when the disease strikes,  $x_1$  is close to its equilibrium value of  $A_1 / A_2$ ,  $x_2$  and  $x_3$  are close to one, and  $x_4$  is zero, so that we are starting in the non-negative space, namely in  $x_1 \geq 0, x_2 \geq 0, x_3 \geq 0$ , and  $x_4 \geq 0$ . Now we write  $x = \{x_1, x_2, x_3, x_4\}$ . Now notice that we can write our equations as  $x' = F(x) - V(x)$  where  $F(x)$  and  $V(x)$  are appropriate vector functions. The function  $F(x)$  stands for all the 'positive' terms and  $V(x)$  for all the 'negative' ones in (1a) to (1d), so that

$$V(x) = \{A_2x_1 + A_3x_1x_2 + A_4x_1x_3 + A_5x_1x_4, A_6x_2, A_7x_3, (A_{10} + A_{11} + A_{12})x_4\}$$

and  $F(x)$  represents all the remaining terms. Now if the "particle" " $x$ " starts in the non-negative space ( $x_1 \geq 0, x_2 \geq 0, x_3 \geq 0$ , and  $x_4 \geq 0$ ), and follows the path  $x' = F(x) - V(x)$ , then it cannot go into the negative space because of  $F(x)$  (because all these terms are positive and we started in the positive space). Also if  $x_i = 0$  ( $i = 1, 2, 3, 4$ ), then the corresponding component of  $V(x)$  is also zero, and  $V(x)$  is a polynomial, so that this particle cannot go into negative space because of  $V(x)$  either. Since the initial conditions placed the particle  $x = \{x_1, x_2, x_3, x_4\}$  in the non-negative space, it is bound to stay in that space.

This proves the invariance of the non-negative space for the solutions of our model. In light of this result, (and since the initial conditions in our investigations will always be in the non-negative space), if there are any solutions of our equations (numerical or otherwise) with negative components, we shall call them irrelevant (or unviable, or non-reachable) solutions. In what follows, we shall prove the important result that there is **at most one** viable solution of our equations other than the disease free one.

### C. Boundedness of the Solution

We have

$$(x_1 + x_2 + x_3 + x_4)' = A_1 - A_2x_1 - A_6x_2 + A_8x_2 - A_7x_3 + A_9x_3 - A_{10}x_4.$$

Since  $A_7 > A_9$  and  $A_6 > A_8$  ( $A_6x_2$  and  $A_7x_3$  represent the number of people who get co-infected, *plus* those who die), the right hand side is clearly negative for  $A_2x_1 + A_6x_2 - A_8x_2 + A_7x_3 - A_9x_3 + A_{10}x_4 > A_1$ . Also this quantity is clearly positive for  $A_2x_1 + A_6x_2 - A_8x_2 + A_7x_3 - A_9x_3 + A_{10}x_4 < A_1$ . It follows that a particle starting in  $\{x_1, x_2, x_3, x_4\} \geq \{0, 0, 0, 0\}$  will approach the (*bounded*) region  $A_2x_1 + A_6x_2 - A_8x_2 + A_7x_3 - A_9x_3 + A_{10}x_4 = A_1$  and stay there. All the equilibrium points of the system

$F_i[x_1, x_2, x_3, x_4] = 0, i = 1, 2, 3, 4$  must be located in this region. The point  $\{x_1, x_2, x_3, x_4\} = \{A_1/A_2, 0, 0, 0\}$  is an example (the reader may verify for other solutions in this paper).

#### D. Equilibrium Points

The equilibrium points of our system can best be found by eliminating  $x_1, x_2, x_3,$  and/or  $x_4$  successively from the equations. Eliminating  $x_2$  from  $F_1 = F_2 = F_3 = F_4 = 0$ , for example, we get  $L_2 = 0$ , where, apart from the root  $x_2 = 0, L_2 = 0$  is a second degree equation like  $Ax_2^2 + Bx_2 + C = 0$ , where the terms  $A, B,$  and  $C$  are too long to reproduce here. This equation has two roots. We shall call them  $x_{21}$  and  $x_{22}$ . Similarly for  $(x_{11}$  and  $x_{12}), (x_{31}$  and  $x_{32})$  and  $(x_{41}$  and  $x_{42})$ . We find

$$(x_{21}x_{22}) / (x_{41}x_{42}) = \{A_{11}(A_{10} + A_{11} + A_{12})A_4 + A_{11}A_5A_9 + A_5[A_{10}A_7 + (A_{11} + A_{12})(A_7 - A_9)]\theta_1\} / [(A_4A_6 - A_3A_7)A_8];$$

$$(x_{31} x_{32}) / (x_{41} x_{42}) = -\{1/[(A_4A_6 - A_3A_7)A_9]\} \{A_{10}A_{12}A_3 + A_{11}A_{12}A_3 + (A_{12})^2A_3 + A_{10}A_5A_6 + A_{11}A_5A_6 + A_{12}A_5A_6 - A_{11}A_5A_8 - A_5[A_{10}A_6 + (A_{11} + A_{12})(A_6 - A_8)]\theta_1\},$$

and

$$(x_{21} x_{22}) / (x_{31} x_{32}) = \{-A_{11}A_9[(A_{10} + A_{11} + A_{12})A_4 + A_5A_9] + A_5A_9[-(A_{10} + A_{11} + A_{12})A_7 + (A_{11} + A_{12})A_9]\theta_1\} / \{A_8[A_{10}A_{12}A_3 + A_{11}A_{12}A_3 + (A_{12})^2A_3 + A_{10}A_5A_6 + A_{11}A_5A_6 + A_{12}A_5A_6 - A_{11}A_5A_8 - A_5(A_{10}A_6 + [A_{11} + A_{12}]\{A_6 - A_8\})\theta_1]\}.$$

Under the assumptions that  $A_6 > A_8$  and  $A_7 > A_9$  (notice that  $A_6$  and  $A_7$  represent the number of people who get co-infected *plus* those who die), it is easily seen that the quantity  $(x_{21}x_{22}) / (x_{31}x_{32})$  is negative. This says that either  $x_{21}x_{22}$  is negative (which requires either  $x_{21}$  or  $x_{22}$  to be negative) or that  $x_{31}x_{32}$  is negative, while the other number is positive. In either case, we must discard one of the two solutions,  $(x_{11}, x_{21}, x_{31}, x_{41})$  if  $x_{21}$  is negative and  $(x_{12}, x_{22}, x_{32}, x_{42})$  if  $x_{22}$  is negative. Similarly for  $x_{31}x_{32}$ . We are now left with only one viable solution (other than the disease free one) of our equations.

#### E. Basic Reproduction Ratio

The basic reproduction ratio of such a dynamic is a measure that indicates whether the disease will grow or die out. This number has been termed "the most significant contribution of Mathematics to Epidemiology" [13]. If, when ALL the people are susceptible, i.e. in the beginning when the disease strikes, one infected person infects MORE THAN ONE person in his/her (infectious) lifetime, then obviously the disease will spread (because one becomes two, two becomes four and so on), while if one person infects LESS THAN ONE person, then the disease will die out (because now four becomes two, two becomes one and so on). An elementary example for illustration of this idea is the equation  $x' = ax - bx$ , where  $x = 0$  is the uninfected state. If in the beginning when  $x = \epsilon > 0$  (the disease strikes) then, if  $a > b$ , the  $x$  values go to infinity, while if  $a < b$ , the  $x$  values go to zero. Since  $x = 0$  is the point of equilibrium in this case, it follows that this point of equilibrium is stable if  $a / b < 1$  and

is unstable if  $a / b > 1$ . In the latter case, the disease spreads while in the former case, it dies out. The terms  $ax$  and  $bx$  may be called the **incoming** and **outgoing** terms (to  $x'$ ) respectively. The Basic Reproduction Ratio  $R$  in this case is  $a / b$ . The disease spreads if  $R > 1$  and dies out if  $R < 1$ . In the above analogy ( $x' = F(x) - V(x)$ ), we have  $F(x) = ax$  and  $V(x) = bx$ . If  $F'(x) / V'(x) > 1$ , the disease spreads, and the  $x$  values increase, i.e. the equilibrium value ( $x = 0$ ) is unstable, while if  $F'(x) / V'(x) < 1$ , the equilibrium value ( $x = 0$ ) is stable and the disease dies out. The quantity  $F'(x) / V'(x)$  is the BASIC REPRODUCTION RATIO ( $R_0$ ) of this dynamic. If the number of equations in the dynamic is more than one, this ratio is replaced by a (very similar looking) ratio. Now  $F(x)$  and  $V(x)$  become appropriate matrices (of incoming and outgoing terms respectively),  $x$  represents an appropriate vector,  $F'[x]$  and  $V'[x]$  are matrices with components  $F_i(x_j)$  and  $V_i(x_j)$ , and the basic reproduction number (which is a ratio) is the (largest) eigenvalue of the matrix,  $F'[x] / [V'[x]]$ , (or, more appropriate in this setting, of  $F'[x] * [V'[x]]^{-1}$ ). This ratio is calculated at the point where the state of the system is uninfected (see [14,15] for details).

It is not clear as to how we should calculate this number in the case of co-infection/re-infection. Generally, the way to calculate  $R_0$  is that "Once an individual is diagnosed, his/her contacts are traced and tested.  $R_0$  is then computed by averaging over the number of secondary cases of many diagnosed individuals" [16]. So, what is a secondary case? If the susceptible people are infected and then get co-infected with HBV and/or HCV, and get re-infected (or reactivated) after getting cured, how should we count as to how many infected people a susceptible person originally produces? What are  $F(x)$  and  $V(x)$  for this situation? Is there a unique  $R_0$  in this case? If this reinfection and/or coinfection did not occur, would it not affect the total number of infected people and consequently, the basic reproduction ratio? It has been shown in the context of a different ailment (TB) that reinfection does change the Basic Reproduction Ratio [17]. Our results in this paper indicate that if  $R_0$  is computed by "averaging over the number of secondary cases of many secondary individuals" which are co-infected or re-infected, then you are likely to "underestimate" the true value of  $R_0$  in the important case when the disease is endemic.

If  $\{x_2, x_3, x_4\} = \{0, 0, 0\}$  is the uninfected state, should we take all entries into this state as the incoming terms or only those that involve  $x_1$ ? We try to answer this question for our model below by considering various cases. In our examples, we take  $\{x_2, x_3, x_4\} = \{0, 0, 0\}$  as the uninfected state.

##### 1) Case One:

From (1b) – (1d), we take the incoming and outgoing terms as

$$F(x) = \{\{A_{3x_1}x_2 + \theta_1A_{5x_1}x_4\}, \{A_{4x_1}x_3 + (1-\theta_1)A_{5x_1}x_4\}, \{0\}\};$$

$$V(x) = \{\{A_{6x_2} - A_{11}x_4\}, \{A_{7x_3} - A_{12}x_4\}, \{A_{10}x_4 + A_{11}x_4 + A_{12}x_4 - A_{8x_2} - A_{9x_3}\}\}.$$

Then,

$$F'(x) = \{ \{A_{3x_1}, 0, \theta_1 A_{5x_1}\}, \{0, A_{4x_1}, (1-\theta_1)A_{5x_1}\}, \{0, 0, 0\} \};$$

$$V'(x) = \{ \{A_6, 0, -A_{11}\}, \{0, A_7, -A_{12}\}, \{-A_8, -A_9, A_{10} + A_{11} + A_{12}\} \}.$$

The basic reproduction ratio,  $R_0$ , is the spectral radius of  $F'(x) * [V'(x)]^{-1}$  [9]. However, this matrix has three eigenvalues, let us call them  $R_0$ ,  $R_{00}$ , and  $R_{000}$ . The largest of these eigenvalues is  $R_0$  where

$$R_0 = \{A_{10}A_4A_6x_1 + A_{11}A_4A_6x_1 + A_{12}A_4A_6x_1 + A_{10}A_3A_7x_1 + A_{11}A_3A_7x_1 + A_{12}A_3A_7x_1 - A_{11}A_4A_8x_1 - A_{12}A_3A_9x_1 + A_5A_6A_9x_1 + A_5A_7A_8x_1\theta_1 - A_5A_6A_9x_1\theta_1 + \sqrt{[-A_{10}A_4A_6x_1 - A_{11}A_4A_6x_1 - A_{12}A_4A_6x_1 - A_{10}A_3A_7x_1 - A_{11}A_3A_7x_1 - A_{12}A_3A_7x_1 + A_{11}A_4A_8x_1 + A_{12}A_3A_9x_1 - A_5A_6A_9x_1 - A_5A_7A_8x_1\theta_1 + A_5A_6A_9x_1\theta_1]^2 - 4*(A_{10}A_6A_7 + A_{11}A_6A_7 + A_{12}A_6A_7 - A_{11}A_7A_8 - A_{12}A_6A_9)(A_{10}A_3A_4x_1^2 + A_{11}A_3A_4x_1^2 + A_{12}A_3A_4x_1^2 + A_3A_5A_9x_1^2 + A_4A_5A_8x_1^2\theta_1 - A_3A_5A_9x_1^2\theta_1)}\} / [2*(A_{10}A_6A_7 + A_{11}A_6A_7 + A_{12}A_6A_7 - A_{11}A_7A_8 - A_{12}A_6A_9)].$$

**Note:** It should be noticed that if  $\{x_{11}, x_{21}, x_{31}, x_{41}\}$  is the (only) viable solution, then the basic reproduction ratio of our dynamic may also be written as  $A_1 / (A_2x_{11})$ . This is because, at the point of equilibrium, each newly infected person must exactly replace him/herself, i.e. produce one new infected person in his/her (infectious) lifetime, (this is what equilibrium should mean). The number of infected persons that one infected person produces (in his/her infectious lifetime) clearly depends upon the number of susceptible persons that the infected person interacts with. If an infected person interacts with 100 people and produces one infected person say, then if that person interacts with 200 people, s/he will produce two infected persons (on the average). So, if the susceptible number of persons is  $A_1 / A_2$  in the beginning and interaction with these people produces  $R$  infected people say, then the susceptible number of persons at the point of equilibrium (when one infected person produces exactly one infected person), must be  $1/R$  times the original number of persons. It follows that

$$x_{11} = A_1 / (A_2R) \text{ or } R = A_1 / (A_2x_{11}) \quad (2)$$

It is now clear that, if we have an independent expression for  $x_{11}$  in our model we can get another expression for  $R$  (we shall call this expression  $R_1$ ). Such an expression for  $x_{11}$  can be obtained by eliminating  $x_2, x_3$  and  $x_4$  from the equations in our model. The result of this elimination is  $[x_1 - (A_1 / A_2)] L_1 = 0$  where  $L_1$  is a second degree polynomial of the type  $Ax_1^2 + Bx_1 + C$ . The smaller of the two roots of  $L_1$  turns out to be  $x_{11}$  (corresponding to the larger value of  $R$ ), while the larger of these two roots corresponds to the other smaller eigenvalue. (The root  $x_1 = A_1 / A_2$  of the original equation corresponds to the infection free equilibrium value of  $x_1$ ). We get

$$x_{11} = \{A_{10}A_4A_6 + A_{11}A_4A_6 + A_{12}A_4A_6 + A_{10}A_3A_7 + A_{11}A_3A_7 + A_{12}A_3A_7 - A_{11}A_4A_8 - A_{12}A_3A_9 + A_5A_6A_9 + A_5A_7A_8\theta_1 - A_5A_6A_9\theta_1 - \sqrt{4*(A_{10}A_6A_7 + A_{11}A_6A_7 + A_{12}A_6A_7 - A_{11}A_7A_8 - A_{12}A_6A_9)(A_{10}A_3A_4 + A_{11}A_3A_4 + A_{12}A_3A_4 + A_3A_5A_9 + A_4A_5A_8\theta_1 - A_3A_5A_9\theta_1)} + (-A_{10}A_4A_6 - A_{11}A_4A_6 - A_{12}A_4A_6 - A_{10}A_3A_7 - A_{11}A_3A_7 - A_{12}A_3A_7 + A_{11}A_4A_8 +$$

$$A_{12}A_3A_9 - A_5A_6A_9 - A_5A_7A_8\theta_1 + A_5A_6A_9\theta_1)^2\} / [2*(A_{10}A_3A_4 + A_{11}A_3A_4 + A_{12}A_3A_4 + A_3A_5A_9 + A_4A_5A_8\theta_1 - A_3A_5A_9\theta_1)],$$

and then  $R_1 = A_1 / A_2x_{11}$ . As we pointed out above, the basic reproduction ratio is also the spectral radius of an appropriate matrix. Each eigenvalue of this matrix corresponds to an equilibrium value (stable or otherwise) of  $x_1$ . Since the spectral radius refers to the (numerically) largest eigenvalue of a matrix, the corresponding value of  $x_{11}$  should be the minimum of all such values. This explains the minus sign before the square root sign in the above expression.

a) Example 1

As an example, we show the values of  $R_0$  and  $R_1 = A_1 / A_2x_{11}$  for some values of the parameters. Notice that they are coincident (there is a continuous line under the dots in Fig. 1). We take  $A_1 = 1$ ;  $A_2 = A_1/15,000$ ;  $A_4 = 0.9A_3$ ;  $A_5 = 0.9A_3$ ;  $\theta_1 = 0.5$ ;  $\theta_2 = 1 - \theta_1$ ;  $A_6 = 1/2000$ ;  $A_7 = 0.5A_6$ ;  $A_9 = 0.0002$ ;  $A_8 = A_9$ ;  $A_{10} = 0.01$ ;  $A_{11} = 0.1A_{10}$ ;  $A_{12} = A_{11}$ ;  $x_1 = A_1/A_2$ ,

and calculate the values of these two quantities for some values of  $A_3$ :

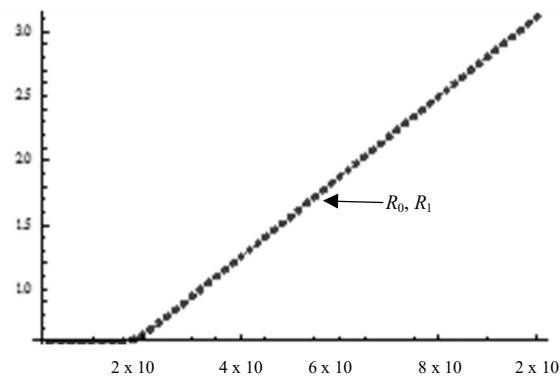


Fig. 1. Values of Basic Reproduction Ratio (as  $R_0$  and  $R_1$ ) against values of  $A_3$ , calculated two different ways (1) as  $A_1/A_2x_{11}$  and (2) as the largest eigenvalue of an appropriate matrix. Notice that they are coincident. (Notice the continuous line under the dots).

b) Example 2

As another example, we take  $A_1 = 1$ ;  $A_2 = A_1/10,000$ ;  $A_3 = 0.0000001$ ;  $A_4 = 0.5A_3$ ;  $A_5 = 0.5A_3$ ;  $\theta_1 = 0.9$ ;  $\theta_2 = 1 - \theta_1$ ;  $A_6 = 1/2000$ ;  $A_7 = A_6$ ;  $A_9 = 0.0002$ ;  $A_8 = A_9$ ;  $A_{10} = 0.001$ ;  $A_{11} = 0.3A_{10}$ ;  $A_{12} = A_{11}$ .

At  $x_1 = A_1/A_2$  we get

$$\{R_{00}, R_0\} = \{1.07713, 2.33463\},$$

where  $R_{00}$  is another eigenvalue of our matrix. The spectral radius turns out to be 2.33463 and we should get one (and only one) viable solution. Solving (1a) – (1d) in the software *Mathematica* we get:

$$\{x_1, x_2, x_3, x_4\} = \{10,000, 0, 0, 0\}, \{9283.92, -35.288, 203.776, 21.061\} \text{ or } \{4283.33, 1156.03, 189.069, 168.137\}.$$

The last one is the viable solution. Notice that although two

values of  $R$  are greater than one, there is only one viable solution as our analysis argues. Notice this value corresponds with the smaller of the two equilibrium values of  $x_1$ . Also notice that  $A_1 / A_2 * 4283.33 = 2.33463$ , and  $A_1 / A_2 * 9283.92 = 1.07713$ , which is the other value  $R$ .

Every eigenvalue of the matrix  $F'(x) * [V'(x)]^{-1}$  corresponds to an equilibrium value of  $x_1$  (stable or otherwise) in our solution, the largest eigenvalue corresponding to the only viable solution. Numerically graphing the solution using *Mathematica*, we see the distribution of HCV and HBV infected people in the population in Figs. 2 and 3. It should be noted that the number of HCV infected people is between approximately 3% and 20% of those who are HBV infected (approximate slopes of the two bounding straight lines in Fig. 2). The number of co-infected people ( $x_4$ ) amongst the HCV infected ones ( $x_3$ ) is given in Fig. 3. This number is close to 70% (slope of the straight line).

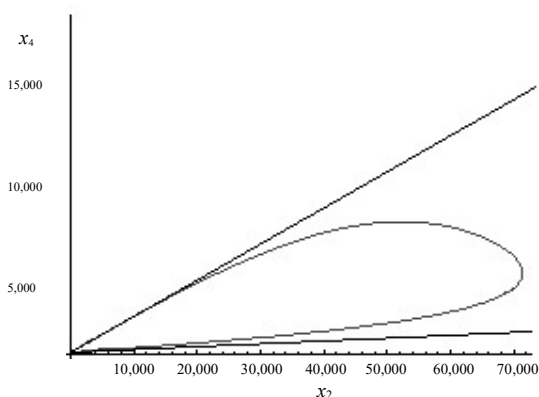


Fig. 2. Number of HBV infected people ( $x_2$ , along the horizontal axis) as against the co-infected ones ( $x_4$ ) in this example. This number of co-infected ones falls between approximately 3% and 20% of HBV infected ones (approximate slopes of the two bounding straight lines). In surveys, these rates vary from 9% to 30% [18]. The number of co-infected people rises in the beginning but soon recoils back, so that any time you take a sample, this ratio will be close to 10%.

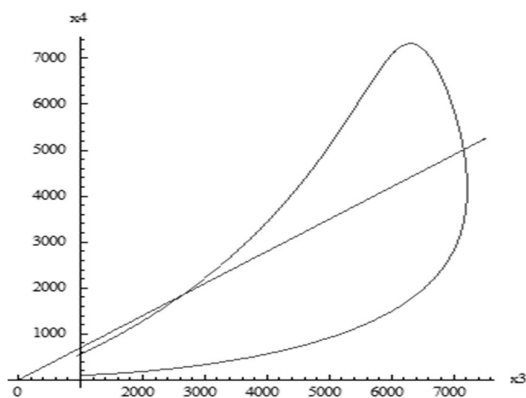


Fig. 3. Number of co-infected people ( $x_4$ ) amongst the HCV infected ones ( $x_3$ ) in this example. The number of HCV infected people rises in the beginning but soon recoils back, so that any time you take a sample, this ratio will be close to 70% (slope of the straight line).

**Note:** It may happen that  $x_{21}$  and  $x_{22}$  (or  $x_{31}$  and  $x_{32}$ ) are both negative, (for  $x_{21}x_{22}$  or  $x_{31}x_{32}$  to be positive). In this case both the solutions  $\{x_{11}, x_{21}, x_{31}, x_{41}\}$  and  $\{x_{12}, x_{22}, x_{32}, x_{42}\}$  must be discarded and we are left with NO viable solution. Similarly for  $x_{31}x_{32}$ . This should happen when the **basic reproduction**

**ratio** is less than one, as in the following example.

c) *Example 3*

We take  $A_1 = 1$ ;  $A_2 = A_1/1000$ ;  $A_3 = 0.0000001$ ;  $A_4 = 0.9A_3$ ;  $A_5 = 0.5A_3$ ;  $\theta_1 = 0.5$ ;  $\theta_2 = 1 - \theta_1$ ;  $A_6 = 1/2000$ ;  $A_7 = A_6$ ;  $A_9 = 0.0002$ ;  $A_8 = A_9$ ;  $A_{10} = 0.001$ ;  $A_{11} = 0.5A_{10}$ ;  $A_{12} = 0.5A_{11}$ .

Solving (1a)-1(d), we get:

$$\{x_1, x_2, x_3, x_4\} = \{5385.92, 19,896.9, -30,483.6, -1209.91\} \text{ or } \{1000, 0, 0, 0\} \text{ or } \{4030.24, 5178.52, -2135.87, -835.929\}.$$

Notice that there is no viable solution other than the disease-free one. Also, in this case at  $x_1 = A_1/A_2$  we get

$$\{R_{00}, R_0\} = A_1/A_2x_1 = \{0.185669, 0.248124\},$$

which says that both roots are less than one.

**Basic Reproduction Ratio Again:** We stated above that "If an infected person interacts with 100 susceptible people and produces one infected person say, then, if that person interacts with 200 susceptible people, s/he will produce two infected persons (on the average)." It is not clear whether such a linear relationship will be true if the infected people recover from their ailment and start getting infected again. In the case of ODE models in epidemiology, it is particularly difficult to calculate this number (the basic reproduction ratio) from the model [19]. In the case of the model mentioned above, namely  $x'(t) = ax - bx$ , if we write the same equation as  $x'(t) = (a + n)x - (b + n)x$ , for any number  $n > 0$ , would the new estimate of this ratio be  $(a + n) / (b + n)$ , which is different from  $a / b$ ? The obvious conclusion is that we cannot estimate this ratio from the mathematical model itself. However, notice that both these numbers  $a / b$  and  $(a + n) / (b + n)$  correctly predict the regime where the (infected) population will grow or will shrink, i.e. if  $a / b > 1$ ,  $a / b = 1$ , or  $a / b < 1$ , then so is  $(a + n) / (b + n)$  for any positive number  $n$ . A similar conclusion has been reached by other researchers in the field [19]. We shall now give a number of scenarios where an approximate ratio ( $R$ ) for our model is calculated differently each time.

2) *Case two*

In analogy with the above example about  $((a+n)/(b+n))$ , we shall take various forms of the incoming and outgoing functions  $F(x)$  and  $V(x)$  and calculate the corresponding  $R$ . In our model, we take  $\{x_2, x_3, x_4\} = \{0, 0, 0\}$  as the uninfected state and write, from (1b) – (1d):

$$F(x) = \{\{A_3x_1x_2 + \theta_1A_5x_1x_4 + A_{11}x_4\}, \{A_4x_1x_3 + (1-\theta_1)A_5x_1x_4 + A_{12}x_4\}, \{0\}\};$$

$$V(x) = \{\{A_6x_2\}, \{A_7x_3\}, \{A_{10}x_4 + A_{11}x_4 + A_{12}x_4 - A_8x_2 - A_9x_3\}\};$$

$$F'(x) = \{\{A_3x_1, 0, \theta_1A_5x_1 + A_{11}\}, \{0, A_4x_1, (1-\theta_1)A_5x_1 + A_{12}\}, \{0, 0, 0\}\};$$

$$V'(x) = \{\{A_6, 0, 0\}, \{0, A_7, 0\}, \{-A_8, -A_9, A_{10} + A_{11} + A_{12}\}\}.$$

This gives the eigenvalues of  $F'(x) * [V'(x)]^{-1}$ . (We suppress the long answer).

The basic reproduction ratio (which we write as  $R_2$ ) turns out to be

$$R_2 = \{A_{11}A_7A_8 + A_{12}A_6A_9 + A_{10}A_4A_6x_1 + A_{11}A_4A_6x_1 + A_{12}A_4A_6x_1 + A_{10}A_3A_7x_1 + A_{11}A_3A_7x_1 + A_{12}A_3A_7x_1 + A_5A_6A_9x_1 + A_5A_7A_8x_1\theta_1 - A_5A_6A_9x_1\theta_1 + \text{sqrt}[(-A_{11}A_7A_8 - A_{12}A_6A_9 - A_{10}A_4A_6x_1 - A_{11}A_4A_6x_1 - A_{12}A_4A_6x_1 - A_{10}A_3A_7x_1 - A_{11}A_3A_7x_1 - A_{12}A_3A_7x_1 - A_5A_6A_9x_1 - A_5A_7A_8x_1\theta_1 + A_5A_6A_9x_1\theta_1)^2 - 4*(A_{10}A_6A_7 + A_{11}A_6A_7 + A_{12}A_6A_7)(A_{11}A_4A_8x_1 + A_{12}A_3A_9x_1 + A_{10}A_3A_4x_1^2 + A_{11}A_3A_4x_1^2 + A_{12}A_3A_4x_1^2 + A_3A_5A_9x_1^2 + A_4A_5A_8x_1^2\theta_1 - A_3A_5A_9x_1^2\theta_1)]\} / [2*(A_{10}A_6A_7 + A_{11}A_6A_7 + A_{12}A_6A_7)].$$

3) Case Three

On the other hand, if we take (including the co-infected as newly infected)

$$F(x) = \{\{A_3x_1x_2 + \theta_1A_5x_1x_4\}, \{A_4x_1x_3 + (1-\theta_1)A_5x_1x_4\}, \{A_8x_2 + A_9x_3\}\};$$

$$V(x) = \{\{A_6x_2 - A_{11}x_4\}, \{A_7x_3 - A_{12}x_4\}, \{A_{10}x_4 + A_{11}x_4 + A_{12}x_4\}\};$$

$$F'(x) = \{\{A_3x_1, 0, \theta_1A_5x_1\}, \{0, A_4x_1, (1-\theta_1)A_5x_1\}, \{A_8, A_9, 0\}\};$$

$$V'(x) = \{\{A_6, 0, -A_{11}\}, \{0, A_7, -A_{12}\}, \{0, 0, A_{10}+A_{11}+A_{12}\}\},$$

we get

$$F'(x) * [V'(x)]^{-1} = \begin{pmatrix} \frac{A_3x_1}{A_6} & 0 & \frac{A_{11}A_3x_1 + A_5A_6x_1\theta_1}{(A_{10} + A_{11} + A_{12})A_6} \\ 0 & \frac{A_4x_1}{A_7} & \frac{A_{12}A_4x_1 + A_5A_7x_1(1-\theta_1)}{(A_{10} + A_{11} + A_{12})A_7} \\ \frac{A_8}{A_6} & \frac{A_9}{A_7} & \frac{A_{11}A_8A_7 + A_{12}A_9A_6}{(A_{10} + A_{11} + A_{12})A_6A_7} \end{pmatrix}$$

and  $R_3$  = the maximum absolute eigenvalue of the above matrix. (We suppress the long answer). In this case,  $R_3$  is the numerically largest eigenvalue of a cubic equation and cannot be specified any further.

4) Case Four

Again, we may write (including the cured ones as new candidates for infection)

$$F(x) = \{\{A_3x_1x_2 + \theta_1A_5x_1x_4 + A_{11}x_4\}, \{A_4x_1x_3 + (1-\theta_1)A_5x_1x_4 + A_{12}x_4\}, \{A_8x_2 + A_9x_3\}\};$$

$$V(x) = \{\{A_6x_2\}, \{A_7x_3\}, \{A_{10}x_4 + A_{11}x_4 + A_{12}x_4\}\};$$

$$F'(x) = \{\{A_3x_1, 0, \theta_1A_5x_1 + A_{11}\}, \{0, A_4x_1, (1-\theta_1)A_5x_1 + A_{12}\}, \{A_8, A_9, 0\}\};$$

$$V'(x) = \{\{A_6, 0, 0\}, \{0, A_7, 0\}, \{0, 0, A_{10}+A_{11}+A_{12}\}\}.$$

Then  $R_4$  is the spectral radius of  $F'(x) * [V'(x)]^{-1}$  where

$$F'(x) * [V'(x)]^{-1} = \begin{pmatrix} \frac{A_3x_1}{A_6} & 0 & \frac{A_{11} + A_5x_1\theta_1}{(A_{10} + A_{11} + A_{12})} \\ 0 & \frac{A_4x_1}{A_7} & \frac{A_{12} + A_5x_1(1-\theta_1)}{(A_{10} + A_{11} + A_{12})} \\ \frac{A_8}{A_6} & \frac{A_9}{A_7} & 0 \end{pmatrix}$$

Once again,  $R_4$  is the (numerically) largest eigenvalue of a cubic equation and cannot be specified any further. We omit the details.

III. CONCLUSION

Finally, the various values of  $R$  ( $R_0, R_1, R_2, R_3$  and  $R_4$ ) are compared in Figs. 4 and 5 for two particular cases, one for "small" values of coinfection and another one for not so small ones. For intermediate values of coinfection, we expect these values to fall between these two. Notice that they all intersect at  $R = 1$  so that they imply the endemicity or eradication of the disease for the same values of the parameters. In both these diagrams, the values of  $R_0$  coincide with those of  $R_1$ .

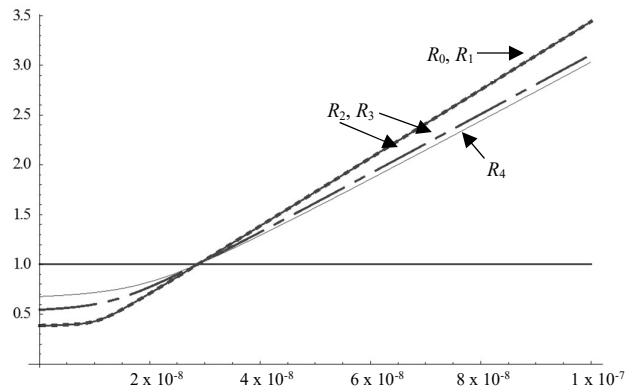


Fig. 4. Values of  $R_0, R_1, R_2, R_3,$  and  $R_4$  for different values of  $A_3$  ( $R_0$  and  $R_1$  at the top,  $R_2$  and  $R_3$  below that (notice the large and small dashes), and  $R_4$ , the lowest) for  $\{0.00000001 \leq A_3 \leq 0.0000001\}$  along with the horizontal line  $y = 1$ . Values of other parameters are  $A_1 = 1; A_2 = A_1 / 15,000; A_4 = 0.9A_3; A_5 = 0.9A_3; \theta_1 = 0.5; \theta_2 = 1 - \theta_1; A_6 = 1 / 2000; A_7 = 0.5A_6; A_9 = 0.0002; A_8 = A_9; A_{10} = 0.01; A_{11} = 0.1A_{10}; A_{12} = A_{11}; x_1 = A_1/A_2$ .

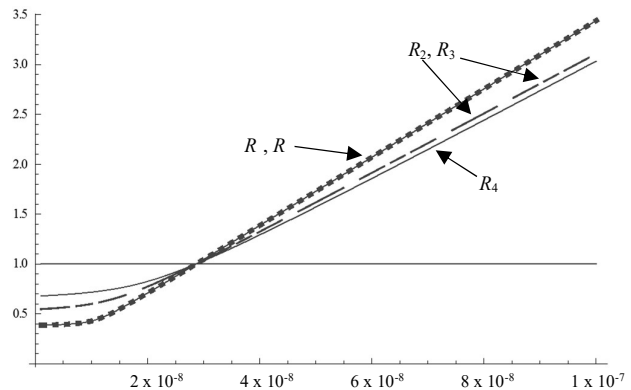


Fig. 5. Once again, values of  $R_0, R_1, R_2, R_3,$  and  $R_4$  for different values of  $A_3$  ( $R_0$  and  $R_1$  at the top,  $R_2$  and  $R_3$  below that (notice the large and small dashes), and  $R_4$ , the lowest) for  $\{0.00000001 \leq A_3 \leq 0.0000001\}$  along with the horizontal line  $y = 1$ . Other variables are  $A_1 = 1; A_2 = A_1 / 15,000; A_4 = 0.5A_3; A_5 = 0.5A_3; \theta_1 = 0.9; \theta_2 = 1 - \theta_1; A_6 = 1 / 2000; A_7 = 0.5A_6; A_9 = 0.0002; A_8 = A_9; A_{10} = 0.05; A_{11} = 0.5A_{10}; A_{12} = A_{11}; x_1 = A_1/A_2$ .

It is to be noticed that all these different expressions for  $R$  predict the instability of the equilibrium point  $\{x_2, x_3, x_4\} = \{0,0,0\}$  for the same value of  $A_3$  and that only the expression  $R_0$  satisfies condition (2). However, this is not of much use, since  $x_{11}$  is almost never known in an epidemic, and  $R_0$  is to be estimated using initial data. The article clarifies that only the contacts of initially infected susceptibles should be included in calculating the basic reproduction ratio. Our results also indicate that including the results of coinfection (as incoming terms) tends to lower the value of  $R$  if the disease is endemic. This corroborates our results in a previous paper [20]. It also corroborates the fact that  $R_0$  of H1N1 when it came back in 2009 was much less than the  $R_0$  of H1N1 when it first appeared in 1918, because the second time around, everybody was not susceptible to H1N1 [21]. Since the ratio of people who must be immunized to stop the spread of such a disease is  $(1-1/R)$ , this argues on the side of caution. Coinfection complicates treatment of both HCV and HBV infections. Considering that billions of people worldwide live in "congested" environment, the problem of coinfection is both widespread and urgent. The values of  $R$  in different cases considered here differ by about 5% in Fig. 4 and by about 10% in Fig.5, so that, in general, more people (about 5-10%) should be immunized in these circumstances to control the infection than a calculated  $R$  (reproduction ratio) warrants. As has been pointed out in the literature, if "HIV has an  $R_0$  of 3" and "SARS has an  $R_0$  of 5, unless they were calculated using the same method, we don't know if SARS is worse than HIV. All we know is that both will persist" [22].

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