Diffusion of an Innovative Biotechnology: The Case of Plant-Derived Vaccines using System Dynamics[†]

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Abstract

The possible diffusion of plant-derived vaccine (PDV) biotechnology in developing countries offers an interesting potential substitute to existing more expensive vaccine technology currently available on the market. This paper is concerned with the potential impact that the introduction of such a technology could have on the incidence of hepatitis B cases on India's population overtime. The objective of the paper is to look at the hypothetical issues of a PDV diffusion using a system dynamics (SD) model. Some illustrative results are presented to show the interaction between infection rates, mortality rates, and vaccination rates. In spite of promising features, such as much lower production costs, institutional hurdles to a widespread diffusion of the technology still need to be overcome.

Keywords: health care, technology diffusion, biotechnology, plant-derived vaccines.

[†] This research was conducted as part of the Canadian Program on Genomics and Global Health with the support of the Ontario Genomics Institute and Genome Canada, and was supported by the Social Sciences and Humanities Research Council of Canada (SSHRC) at the Centre for Intellectual Property Policy at McGill University.

Introduction

Plant-derived vaccines (PDVs) attract much interest from the research community. Based on transgenic plant technology, these vaccines, if approved commercially, could offer many advantages relative to existing vaccine technology. These advantages include substantially lower production costs, oral ingestion of the vaccine, much lighter production infrastructure than what is currently known in the world of immunization, to name but a few. Although not available yet commercially, research is making much progress in this direction. Indeed, commercialization could become reality in the not so distant future. At least four PDVs have successful met requirements for phase I clinical trials for illnesses such as measles, cholera, foot and mouth disease, and hepatitis B and C (see www.burnet.edu.au/researchandprograms/vaccine/plantderived). Given that the technology has reached such an advanced development stage, and has managed to maintain its potential; it is perhaps time to think about how this would work if it were introduced on the market. While it is not realistic to expect the commercialization of that technology in the near future given that many developments, regulatory, and institutional hurdles remain to be crossed, its prospects for commercialization are nevertheless interesting to examine in a prospective mode using a structured dynamic approach. In particular, this technology, if it were available commercially, could have the potential to fulfill important immunization needs in developing countries that cannot always afford to sustain these programs.

The model and the results presented in this paper are entirely hypothetical and prospective. While analogous to a case study research, the paper examines the problem of biotechnology diffusion for health care applied to the hypothetical commercialization of a PDV against hepatitis B in India. India was chosen as the setting to examine the technology diffusion problem of PDV for three main reasons. First, this country must manage a high rate of contamination of the hepatitis B virus, but it has only partially adopted immunization programs. Second, India could become a prime candidate for the introduction of this biotechnology as it has been making efforts to attract biotechnology R&D, and also knowing that new biotechnology products originate from the country (Mani 2004; Mehra, 2004). Third, India possesses an institutional and legal framework that supports the utilization of biotechnology products, and is a member of the WTO since 1995 (www.wto.org).

Therefore, it becomes inherently interesting to observe the potential health impacts related to the diffusion of plant derived vaccines on the population in developing countries. One of the key working hypotheses that underlie this work is that the system of technology diffusion is assumed complex due to the time and interrelationship dynamics amongst variables. This case research uses a system dynamics (SD) model which purpose is to examine the market introduction of a PDV vaccine in India against hepatitis B, as a substitute for the traditional vaccine technology. The literature in SD has a long tradition of looking at issues associated with new products adoption and diffusion (Maier, 1998; Milling, 2002), and even some related to the introduction of medical technology (Homer, 1987), and with health care policy (Hirsch, 2004; McDonnell, 2004).

The goal of the paper is to help individuals and groups interested in this hypothetical, but yet plausible future technology commercialization, examine these impacts and repercussions through time. As far as technology diffusion goes, this paper is concerned by three aspects of that

problem: 1) the demographic evolution of India, 2) the propagation of the virus in infant and non-infant cohorts, and 3) the market potential of that biotechnology product. Given the exploratory nature of this work, and the paucity of hard data to build a "definitive" model, little attention is paid to institutional issues associated with the introduction of the technology. This is not because these issues are not important, quite to the contrary. However, the current scope of the model can be used as a starting point to examine more narrowly the technology diffusion problem from an economic perspective, prior to enlarging it to broader legal and institutional considerations, which would be essential to fully examine the questions raised in this paper. Obviously, more multidisciplinary perspective would be required to look into these issues and augment the model (Gold et al., 2004).

The remainder of the paper is organized as follows. First, the next section includes some background information on hepatitis B and its incidence in India. Then, the following section includes a description of the research method. An influence diagram of the model is then presented and briefly described. The accompanying level-rate model is presented and commented. Some illustrative simulation results are presented and a conclusion follows.

Background and Rationale to the Problem

Hepatitis B is a disease that originates from a virus, transmitted though parenteral or percutaneous contacts, with infected blood or fluids, though sexual contact. The virus may trigger a chronic infection, cause liver cirrhosis or cancer, and possibly lead to death. However, in most cases, the infected individual may recover spontaneously. Chronically infected individuals, known as carriers of the virus, are more susceptible to contaminate other individuals during their lifetime (WHO, 2002c).

Every year, the chronic form of hepatitis B kills about one million people worldwide. Vaccines for hepatitis B are available since the 1980s. Since then, in agreement with the WHO, over a billion doses have been distributed in more than one hundred countries that have introduced it into vaccination plans (Valdees et al., 2003). In 1992, the WHO had set the objective to include the vaccine into all programs by 1997; by 2001 only 126 programs had included the vaccine. The failure to meet this objective may in part be due to the economic cost of vaccination programs against the virus. Note the important cost difference between the traditional vaccine and the PDV. According to the Biodesign institute at Arizona State University, a PDV dose would cost US$ 0.05, versus US$ 0.30 for the traditional vaccine. It is important to note that the traditional vaccine requires the administration of three doses, while the PDV could require more (www.azbio.org/centers/the-promise-of-plants.html).

Regarding hepatitis B in India, the chronic form of the disease touches somewhere between 2% to 10% of the population, and the total number of virus carriers would be roughly 50 million people (WHO, 2002b). According to UNICEF (2003), only 1% of children in Southeast Asia are vaccinated against hepatitis B. Given the incidence of chronic infections in India, and the low percentage of vaccinated children, it seems relevant to look at the behavior of that system in the case of a potential substitution of the traditional vaccine by a PDV.

Research Methods

The model design follows the steps outlined in Sterman (2000). First, the problem was defined along with the objective of the model. The fundamental idea underlying the model design is to observe the diffusion of the PDV into the market and its effects on the population given market assimilation of the technology. Second, an influence diagram (ID) was used to formulate the dynamic hypothesis that represents the structure of the dynamics of hepatitis B propagation, and the PDV adoption with respect to the substitution with existing technology in relation to the evolution of the population in India. Third, the dynamic hypothesis is converted into a SD level-rate model. That model was calibrated with data collected from publicly available information from many sources (see below). However, as will be discussed below, the availability of data remains an issue. The design of the model is also an opportunity to identify data needs. Fourth, the model was evaluated for its consistency. Due to the very nature of the prospective case under study, this modeling step was difficult to execute with respect to historical consistency. This dimension of this model evaluation step was conducted for the historical part of the model only for which data was available. Fifth, illustrative results were generated from the model.

The consultation of several data sources has proven most useful in providing the information and expertise necessary to build the model, and in particular to identify underlying feedback loops. A set of publications, data and information are publicly available from the following sources:

- United Nations Population Division (esa.un.org/unpp/);
- Indian Population Census (www.censusindia.net/);
- World Heath Organization, WHO (www.who.int/);
- United Nations Children's Fund, UNICEF (www.unicef.org);
- Children's Vaccine Program (childrensvaccine.org/html/v_hepb_id.htm);
- Biodesign Institute at Arizona State University (www.azbio.org/centers/the-promise-of-plants.html);
- Burnet Institute (www.burnet.edu.au/researchandprograms/vaccine/plantderived).

Diffusion of PDV: Dynamic Hypothesis and Level-Rate Model

The modeling of the PDV technology diffusion model is split into two parts. The next section contains the dynamic hypothesis, and subsequently, the level-rate model and its sub-sectors are introduced and briefly commented.

The Dynamic Hypothesis

The structure of the dynamic hypothesis with the main feedback loops is shown in figure 1. The dynamic hypothesis contains ten balancing feedback loops and three reinforcing loops. There are three main subsector dynamics represented by this dynamic hypothesis. First, the general population dynamics, disaggregated into a 0-4 years old cohort, henceforth referred to as the "infant cohort", and the remainder of the population of 5 years old and older, defines the "non-infant cohort". The feedback loops related to the population dynamics include the reinforcing

loop R1. The Balancing loops E1 and E2 are related to infant and non-infant mortality rates that affect their respective cohort population.

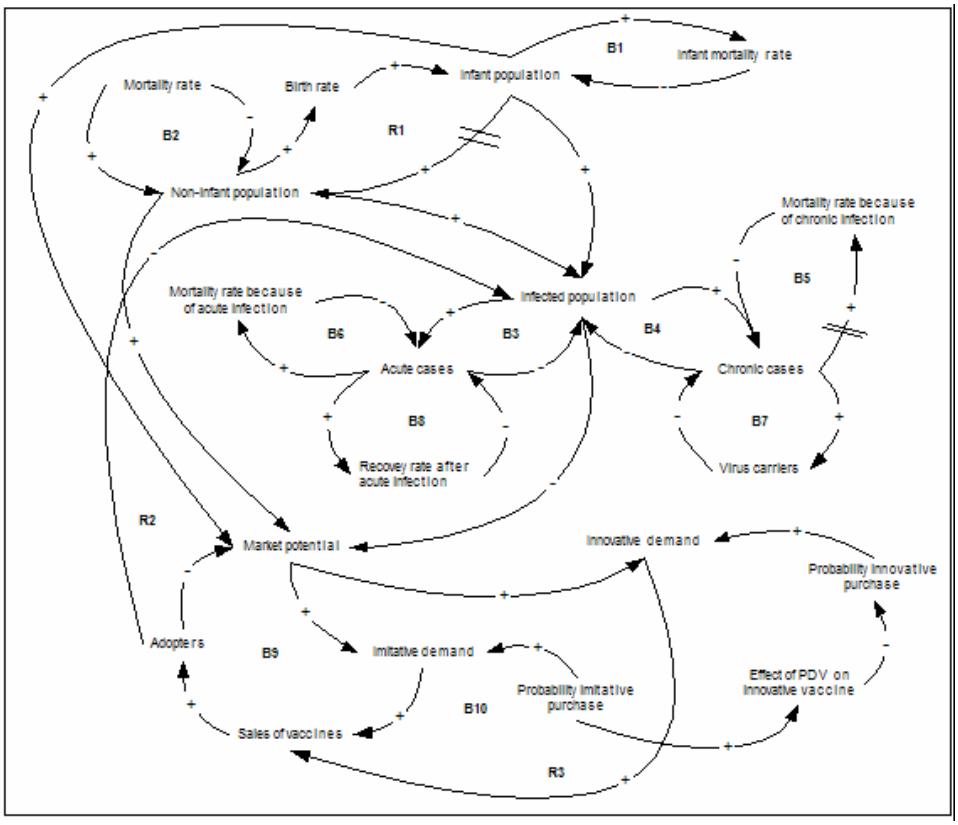

Figure 1 – Influence diagram of PDV diffusion

Second, the virus propagation dynamics in both infant and non infant cohorts are shown in the set of balancing feedback loops from B3 to B8. These dynamics include the level of infection in the population and the disaggregation of the population between acute and chronic cases. These feedback loops also keep separate this dynamic for both infant and non-infant cohorts. Third, the PDV diffusion is modeled with the balancing feedback loops B9 and B10. As can be seen, there is a demand for the technology which takes into account the sales of vaccines, adopters of the technology, the probability of innovative and imitative purchases. These substitution mechanisms between existing technologies are modeled following the work of Maier (1998). The impact of this third subsector (diffusion) on the propagation of the hepatitis B virus is important as the number of vaccinated persons (or number of adopters) reduces the infected population (as seen in reinforcing feedback loops R2 and R3).

This paper looks into the repercussions of the diffusion of plant derived vaccines on the transmission of the virus, and indirectly on the mortality caused by the virus. India faces an important number of infections and a low vaccination rate. This problem is common in most developing countries. In 1995, infant deaths were evaluated at 10.5 million, 99% of these occurring in developing countries. 63% of these infant deaths (6.7 millions), were attributable to single pathogens for which vaccines, available in developed countries, could have help prevent

(Jimenez, 2001). The high costs of a majority of vaccines make them only accessible in industrialized countries, therefore limiting their introduction in developing countries (Mahoney et al., 2000). Without sufficient effort to promote immunization programs in developing countries (low levels of adopters), we assume that the number of new cases of infection will follow an exponential curve. However, the low costs associated to PDV bring hope to these populations. We can presume that in an ideal context, where PDV availability is strong, its intake would strongly reduce the number of newly infected persons. The system would follow a "goal seeking" mode in which infected people would tend towards zero as infant and non-infant cohorts would eventually gain access to the vaccine. This model will focus on this particular behavior that illustrates the impact of PDV adoption on the number of infected cases.

The Level-Rate Model

The influence diagram shown in figure 1 defines the blueprint for the level-rate model introduced in this section. Given the nature of the problem examined, the model computes results on an annual basis. Note that all the feedback loops shown in the influence diagram are part of a large level-rate model presented in this section. For ease of presentation only, the overall level-rate model is split into its six main sub-sectors. The "slicing" of the model into these six sub-sectors was conducted as follows:

1. Demographic evolution in India (see figure 2);
2. Virus propagation – infant cohort (see figure 3);
3. Virus propagation – non-infant cohort (see figure 4);
4. Estimation of population at risk (see figure 5)
5. Market potential for PDV – infant cohort (see figure 6);
6. Market potential for PDV – non-infant cohort (see figure 7);

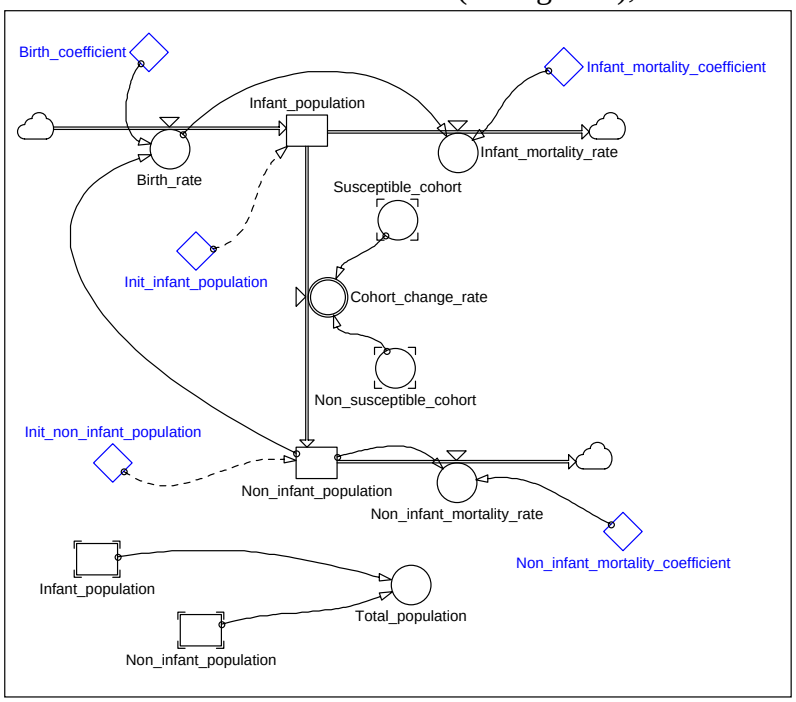

Figure 2 – Demographic evolution for both infant and non-infant cohorts in India

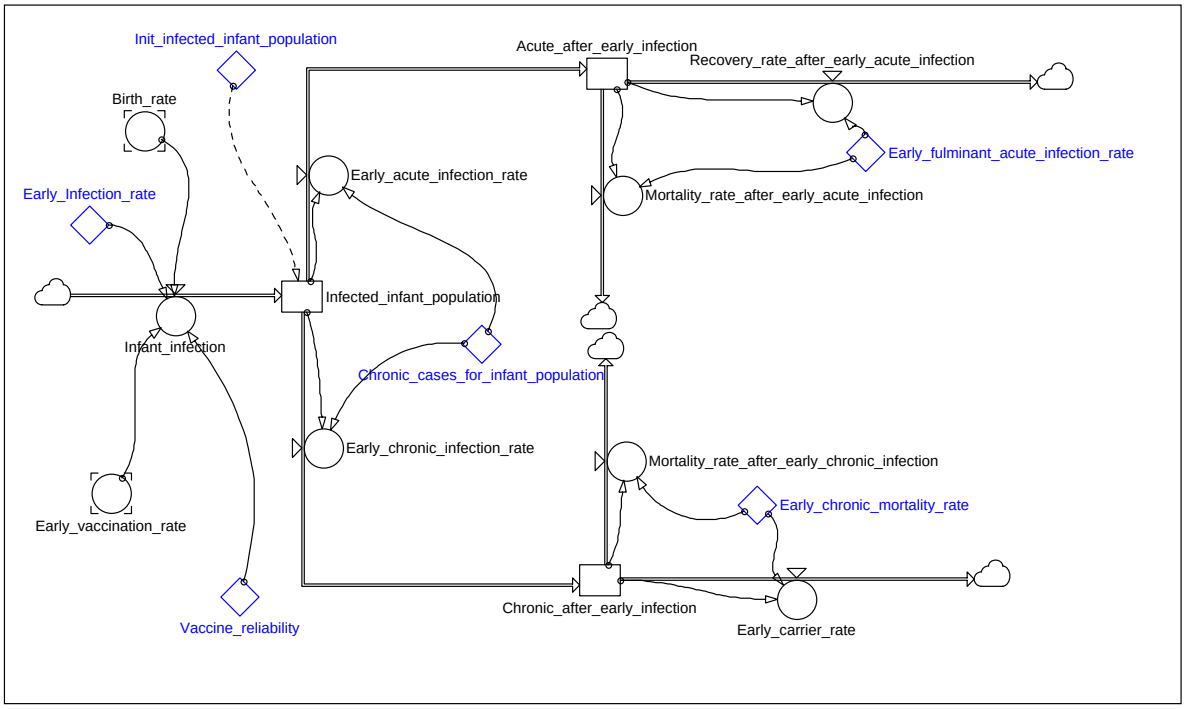

Figure 3 - Virus propagation – infant cohort

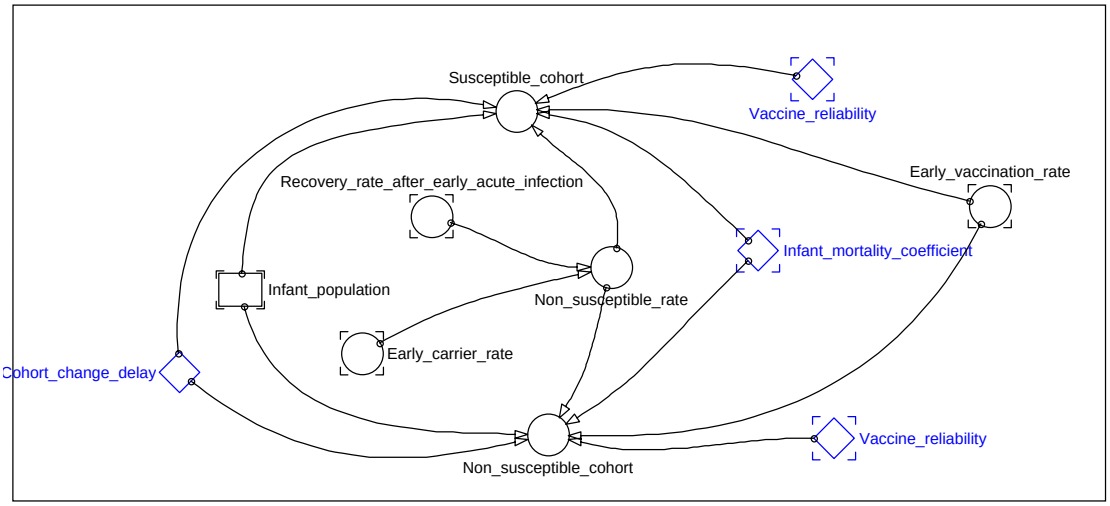

Figure 4 – Estimation of the population at risk for the non-infant cohort

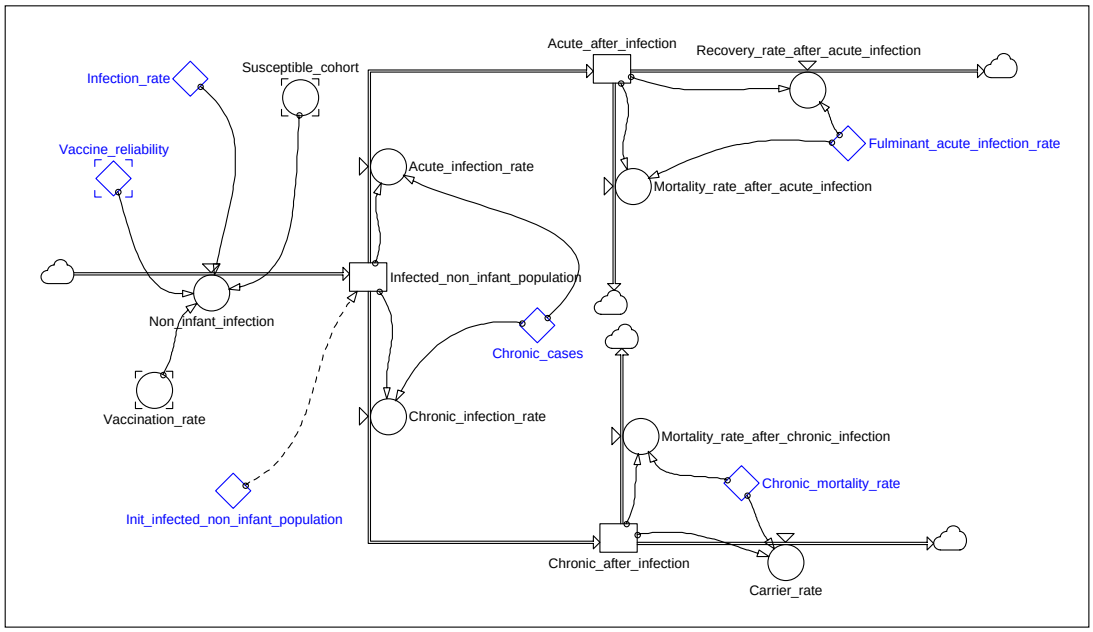

Figure 5 - Virus propagation – non-infant cohort

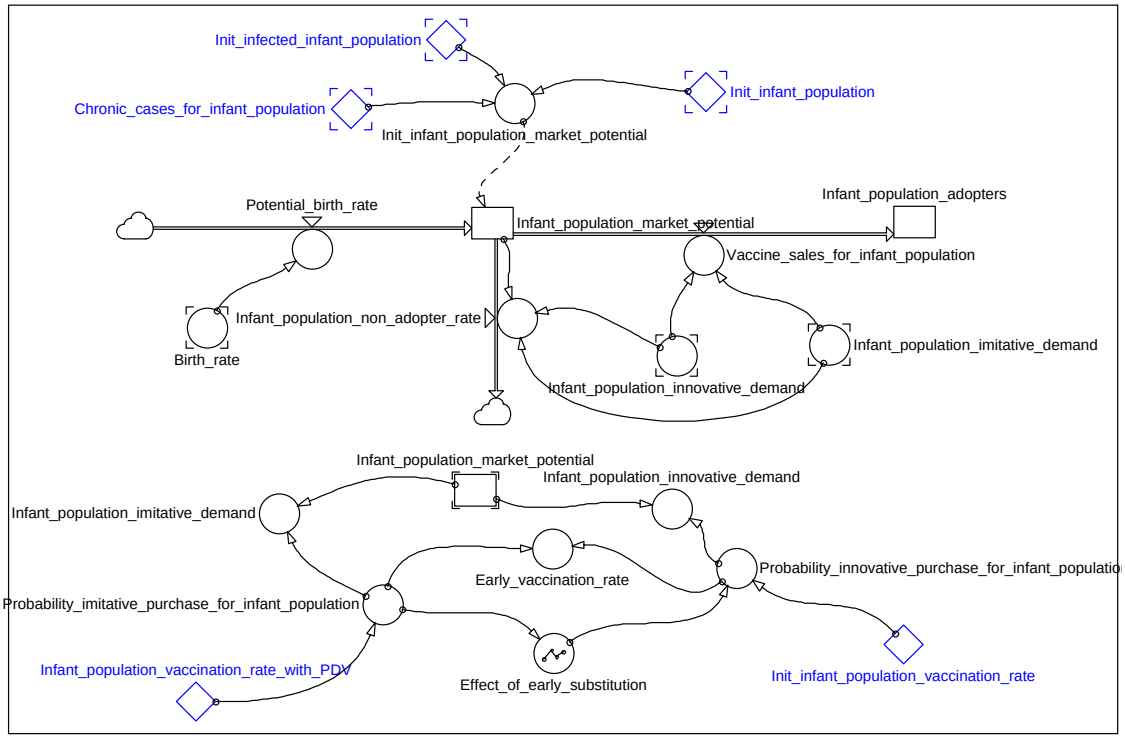

Figure 6 - Market potential for PDV – infant cohort

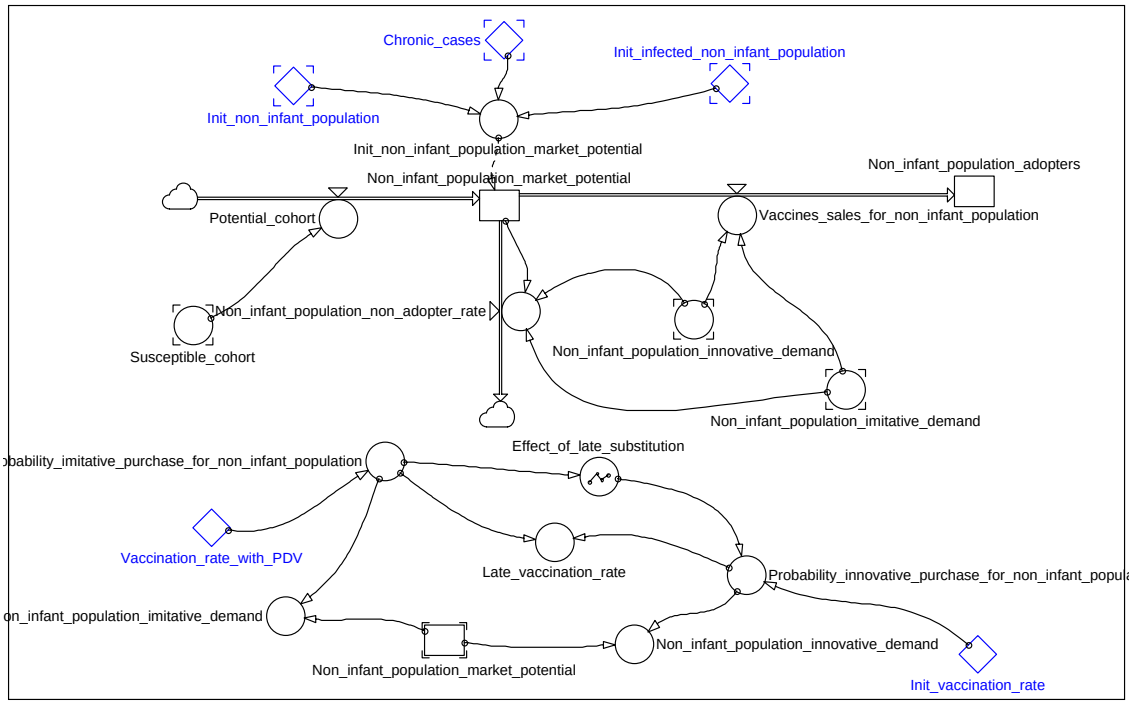

Figure 7- Market potential for PDV – non-infant cohort

Hence, the propagation of the virus in India, for both infant and non-infant cohorts, was modeled and quantified according to the demographic function. More specifically, different types of illnesses (hepatitis B: chronic versus acute infections), related deaths and infection recoveries were all included in the model. The vaccination rate is therefore dependent of the diffusion of the new vaccine in India, measured by the potential market and adopters. This model resembles Sterman's (2000) infectious disease model in many aspects, and specifically, the SIR (Susceptible, Infected, Recovered) model that includes the infected population, the population at risk and the population that recovered from the disease. In Sterman's model, the level of infected people in the population increases as the rate of infection increases. In this present model, the infection rate is not function of the infected population. The hepatitis B infection rates are estimated through the birth cohorts. Hence, the unavailability of certain variables compelled the simplification of two sub-sectors related to virus propagation: virus propagation for the infant cohort (sub-sector 2), and virus propagation for the non-infant cohort (sub-sector 3).

Model Calibration

The parameters of the base case level-rate model were set using data collected from publicly available sources. However, many data and information are not directly available. Due to the hypothetical nature of the problem modeled, only part of the results could be evaluated for historical accuracy. Table 1 shows the input parameters used in the model and their sources. Some entries are based on estimates of what they may be, given extraneous information. The reference year for the model evaluation is 1995. Relative to the demographic evolution of India, the simulated results were quite comparable to the available historical data. This evaluation was

conducted using past and future population estimates available for the period 1995-2015 (United Nations, esa.un.org/unpp).

Relative to the fraction of the population infected with the hepatitis B virus, no specific time series was available. However, the model was calibrated using data from a study conducted by the World Health Organization (WHO, 2000a), that has estimated the number of infected cases, the number of virus carriers, number of deaths from the disease, etc. These data were quite handy in looking into the rates of new infant cohorts.

Table 1 – Model parameters: Base case specification (t_0=1995)

Input parameters	Value	Source
Data on population in India		
Initial population (0 - 4 years old)	119,212,928	esa.un.org/unpp/
Initial population (greater than 5 years old)	812,138,072	esa.un.org/unpp/
Birth coefficient	from 0.03 to 0.02	*Estimated* from esa.un.org/unpp/
Infant death coefficient	from 0.02 to 0.01	*Estimated* from esa.un.org/unpp/
Non-infant death coefficient	0.008	*Estimated* from esa.un.org/unpp/
Delay cohort in years	5	
Data on hepatitis B infection in India		
Initial infection infants	14,000,000	*Estimated* from WHO, 2002a
Infant infection rate	0.1	*Estimated* from WHO, 2002a
Chronic infection rate for infant	0.35	WHO, 2002a et 2002c
Acute infection rate for infant	0.01	WHO, 2002c
Death rate from chronic infant infection	0.2	*Estimated* from WHO, 2002a
Initial infected population	162,000,000	*Estimated* from WHO, 2002a
Infection rate of at risk individuals	0.2	*Estimated* from WHO, 2002a
Rate of chronic cases	0.05	WHO, 2002a and 2002c
Rate of acute deadly infection	0.001	*Estimated* from WHO, 2002a
Death rate from chronic infection	0.15	WHO, 2002a and 2002c
Data on vaccines		
Initial infant vaccination rate	0.01	*Estimated* for Southeast Asia - UNICEF, 2003
Initial non-infant vaccination rate	0	*Assumption*
Infant vaccination rate if substitution available with PDV	0	PDV non availability
Non-Infant vaccination rate with PDV	0	PDV non availability
Efficacy of vaccines	0.95	UNICEF, 2003 ; WHO, 2002a, WHO, 2002c
Cost of existing vaccines	0.9	Biodesign Insitute (3 doses at US0.30)
Cost of PDV	0.25	Biodesign Institute (US$0.05 per dose) *Assumption*: 5 doses required

Simulation Results

The results shown in this section compare the results of two scenarios with respect to immunization for hepatitis B. The scenarios assume that a PDV would be available on the market starting in 2005, but with different diffusion levels.

The tables 2 and 3 show specifications for both scenarios. In the case of scenario 1, the vaccination program targets the infant cohort only. The table shows the assimilation of the PDV is slow to reach its target, as there are capacity limits to its diffusion.

Table 2 – Use of PDV – Scenario 1

Period	% immunized infants
before 2005	0
2005	1
2006	5
2007	10
2008	20
2009	30
from 2010	50

For scenario 2, the case is much more optimistic. The PDV is more widely available and both infant and non-infant cohorts have access to the product in larger quantities.

Table 3– Use of PDV – Scenario 2

Period	% immunized infants	% immunized non-infants
before 2005	0	0
2005	5	0
2006	10	0
2007	40	5
From 2008	80	10

For the purpose of the calculations presented, the assumption is the PVD is not available in quantities large enough to satisfy the need, and there is still a penetration rate of 1% for the existing vaccine.

The figures 8 to 11 display the results associated with:

- Total infected and chronic cases (both infant and non-infant)
- Mortality related to the hepatitis B virus (both infant and non-infant)

As can be seen from the results, the two scenarios show how the situation that prevails could be changed if more individuals had access to immunization for hepatitis B.

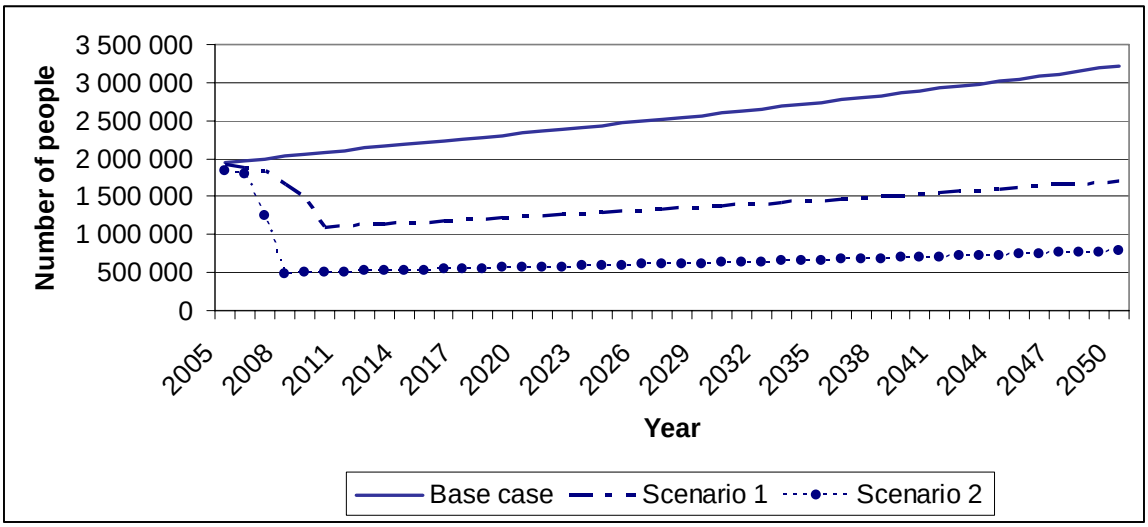

Figure 8 – Infant infection: Newly infected per year

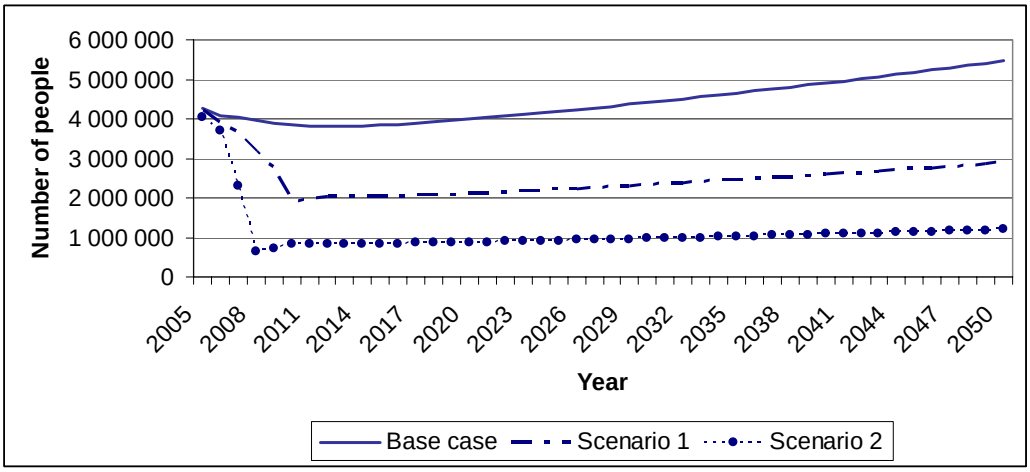

Figure 9 – Non-infant infection: Newly infected per year

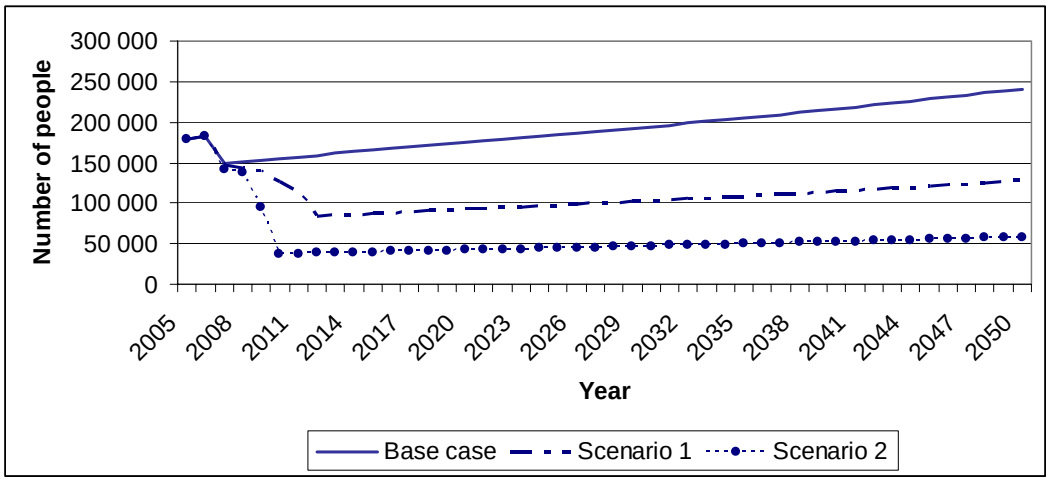

Figure 10 – Deaths caused by Hepatitis B: Infant cohort

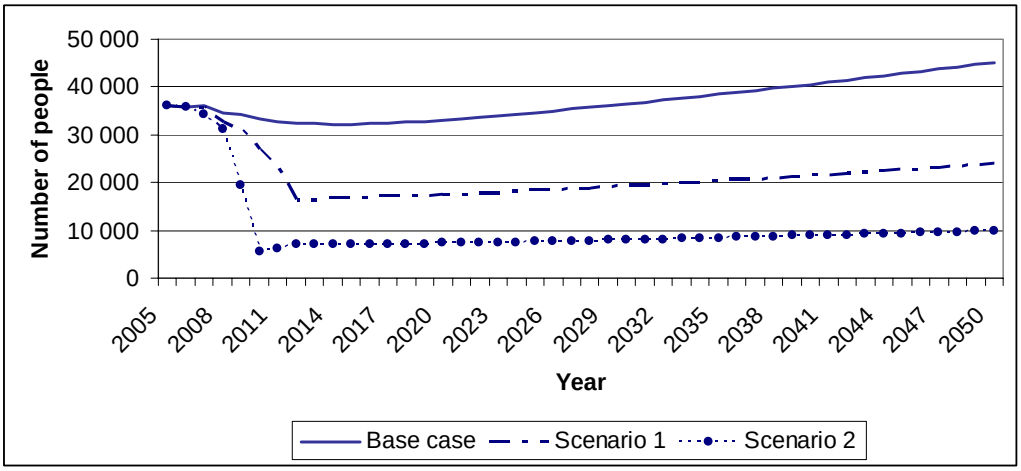

Figure 11 – Deaths caused by Hepatitis B: Non-infant cohort

The results (in figures 8 and 9) show that, by 2050, the first scenario would reduce the number of (total) infections by 47% compared to the status quo. On the other hand, the second scenario reveals better results with a 75% reduction in infant infection due to the disease, and a 78% reduction for non-infants.

For the results related to the number of deaths caused by the virus (figures 10 and 11), the implementation of vaccination programs as specified in scenarios 1 and 2, with the adoption of plant-derived vaccines, also depicts important decreases. By 2007, 1°807 deaths (including 1°424 deaths caused by infant infections) would be prevented in scenario 1. This number rises to 9°023 prevented deaths for scenario 2 (including 7°718 for the infant cohort). Finally, for the 2007-2050 period, approximately 4 300 000 and 7 150 000 deaths, for scenarios 1 and 2 respectively, would be prevented by the diffusion of the PDV.

Conclusions

This paper focuses on the introduction and diffusion of Plant Derive Vaccines, an innovative biotechnology that could change access to immunization programs by making them more affordable to the world population. While the commercialization is not imminent, there is substantial progress being realized towards that commercialization. The paper was concerned with the presentation of the use of SD to help understand some of the issues involved in the adoption and diffusion of this new promising technology. The scope of the model is mostly oriented toward the physical dimension of technology diffusion. However, to complete this analysis, more work will be required to cover cost-related aspects such as the financial impact of immunization programs for the different types of vaccines. It will also be important to analyze the legal and institutional aspects key to the commercial success of the PDV.

References

Biodesign Institute at Arizona State University. *The promise of plant-derived pharmaceuticals*. Available at: www.azbio.org/centers/the-promise-of-plants.html.

Children's Vaccine Program. Available at: childrensvaccine.org/html/v_hepb_id.htm.

Gold, E.R., Adams, W.A., Castle, D., Cleret de Langavant, G, Cloutier, L.M., Daar, A.S., Glass, A., Smith, P.J., Bernier, L. 2004. Probing benefits: Biotechnology innovation and the patent system. *Public Affairs Quarterly* 18: 299-344.

Hirsch, G.B. 2004. Modeling the consequences of major incidents for health care systems. *22nd International Conference of the System Dynamics Society*. Oxford, England.

Homer, J. 1987. A diffusion model with application to evolving medical technologies. Technological Forecasting and Social Change 31: 197-218.

Indian Population Census. Available at: www.censusindia.net/.

Jimenez, J. 2001. Vaccines – a wonderful tool for equity in health. *Vaccine* 19: 2201-2205.

Kapusta, J., Modelska, A., Figlerowicz, M., Pniewski, T., Letellier, M., Lisowa, O., Yusibov, V., Koprowski, H., Plucienniczak, A., Legocki, A.B. 1999. A plant-derived edible vaccine against hepatitis B virus. *FASEB J.* 13 : 1796-1799.

Mahoney, T.M., Ramachandran, S., Xu, Z-Y. 2000. The introduction of new vaccines into developing countries II. Vaccine financing. *Vaccine* 18 : 2625-2635.

Mahoney, T.M., Maynard, J.E. 1999. The introduction of new vaccines into developing countries. *Vaccine* 17 : 646-652.

Maier, F.H. 1998. New product diffusion models in innovation management – a system dynamics perspective. *System Dynamics Review* 14 : 285-308.

Mani, S. 2004. Institutional support for investment in domestic technologies: An analysis of the role of government in India. *Technological Forecasting and Social Change* 71 : 855-863.

McDonnell, G. 2004. Using System Dynamics to analyse Health System Performance within the WHO Framework. *International Conference of the System Dynamics Society*.

Mehra, K. 2001. Indian system of innovation in biotechnology – a case study of cardamom. *Technovation* 21 : 15-23.

Milling, P.M. 2002. Understanding and managing innovation processes. *System Dynamics Review* 18 : 73-86.

National Institute for Health Care Management Foundation. 2003. *Accelerating Quality Improvement in Health Care: Strategies to Speed the Diffusion of Evidence-Based Innovations.*

Prakash, C.S. 1996. Edible vaccines and antibody producing plants. *Biotechnology and Development Monitor* 27 : 10-13.

Quintana-Garcia, C., Benavides-Velasco, C.A. 2003. Cooperation, competition, and innovative capability: a panel data of European dedicated biotechnology firms. *Technovation*

Robbins-Roth, C. 2000. *Le Business des Biotechnologies : Révolution Biotech, Business Models, Investissements et Profits.* Paris, France : Dunod.

Royston, G., Dost, A., Townshend, J., Turner, H. 1999. Using system dynamics to help develop and implement policies and programmes in health care in England. *System Dynamics Review* 15 : 293-313.

Sterman, J.D. 2000. *Business Dynamics: Systems Thinking and Modeling for a Complex World*. New York, NY : Irwin-McGraw-Hill.

UNICEF. 2003. Statistical tables. Available at: www.unicef.org.

United Nations Population Division. Available at: esa.un.org/unpp/.

Valdees, R., Reyes, B., Alvarez, T., Garcia, J., Montero, A.M., Figueroa, A., Gomez, L., Padilla, S., Geada, D., Abrahantes M.C., Dorta, L., Fernandez, D., Mendoza, O., Ramirez, N., Rodriguez, M., Pujol, M., Borroto, C., Brito, J. 2003. Hepatitis B surface antigen immunoputification using a plant-derived specific antibody produced in large scale. *Biochemical and Biophysical Research Communications* 310 : 742-747.

World Health Organization (WHO). 2002a. Prevention of hepatitis B in India, an overview. *Regional Office for South-East Asia*. *August*.

World Health Organization (WHO). 2002b. Proceeding of the third global vaccine research forum. *Geneva, 9-11 June*. Available at: www.who-int/vaccines-documents/.

World Health Organization (WHO). 2002c. Hepatitis B. *Department of Communicable Diseases Surveillance and Response.*

World Health Organization (WHO). 1997. Striving for Better Health in South-East Asia Selected Speeches by Dr Uton Muchtar Rafei Regional Director, WHO South-East Asia Region. Volume II: 1997 – 2000. *International Conference on Meditech Asia 1997: New Medical Dimensions in the Next Decade*, Bangkok, March 1997.