

A model of regulatory burden in technology diffusion: the case of plant-derived vaccines

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ABSTRACT

Plant-derived vaccines may soon displace conventional vaccines. Assuming there are no major technological barriers undermining the feasibility of this innovative technology, it is worthwhile to generate quantitative models of regulatory burden of producing and diffusing plant-derived vaccines in industrialized and developing countries. A dynamic simulation model of technology diffusion, and the data to populate it, has been generated for studying regulatory barriers in the diffusion of plant derived vaccines. The role of regulatory burden is evaluated for a variety of scenarios in which plant-derived vaccines are produced and diffused. This model relates the innovative and conventional vaccine technologies and the effects of the impact of the uptake of the innovative technology on mortality and morbidity. This case study demonstrates how dynamic simulation models can be used to assess the long-term potential impact of novel technologies in terms of a variety of socio-economic indicators.

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INFECTIOUS DISEASE BURDEN

Immunization against infectious diseases (IDs) has been heralded as one of the most important weapons in the public health arsenal [22, 31] with the eradication of smallpox in 1979, and at present, the near elimination of polio [2, 21]. Vaccination programs are also touted as one of the best health care investments with regard to cost savings and cost effectiveness, when compared with other health interventions [6, 8, 16, 33]. Nevertheless, each year IDs exact a toll of more than 17 million deaths, 95 percent of which occur in developing countries [19]. Each year approximately 26 million newborns still have no protection from vaccine-preventable diseases like diphtheria, tetanus, measles and polio [15]. Every 24 hours, 40 000 children in developing countries die from vaccine-preventable diseases [6]. This paper investigates strategies for deploying a new technology, plant-derived vaccines (PDVs) as between two countries: the US and India.

HEPATITIS B PREVALANCE

Hepatitis B is a disease much more serious than many realize. The virus is more infectious than HIV, and is the second most common carcinogen after tobacco. Hep B is also highly prevalent, with approximately one-third of the world's population (around two billion people) showing serologic evidence of HepB infection [35]. An estimated 350 million are chronically infected, and HepB results in approximately 900 000 deaths a year [19]. Hepatitis B is the foremost cause of cancer deaths in males in sub-Saharan Africa and much of Asia as well as a significant cause of morbidity among women in these regions [12]. The outcomes of HepB infection are age-dependent and include acute or clinically visible hepatitis B, chronic HepB infection, cirrhosis and hepatocellular

carcinoma. Children infected with HepB seldom acquire acute HepB, but up to 90 percent develop into chronic carriers and hence future sources of Hep B infection causing acute and chronic infection [23]. Infants and young children have the highest risk of contracting HepB. Despite this, however, the vaccine which is 95 percent effective in preventing the development of chronic infection in childhood [39] covers just 50 percent of the world's annual birth cohort [23]

VACCINE SHORTAGE

In the late 1990s it became apparent that a world shortage existed for every category of Expanded Program on Immunization (EPI) vaccines with the greatest impact on developing countries. Until then, these vaccines were used in industrialized and developing countries, and thus UNICEF was able to buy vaccines at lower prices [33]. With the introduction of newer and sophisticated combination vaccines like Pediarix (combined diphtheria, tetanus toxoids, acellular pertussis absorbed, hepatitis B (recombinant) and inactivated poliovirus vaccines) [33], this situation changed resulting in an increasingly vulnerable supply of vaccine [18]. Between 1998 and 2001, 10 of 14 vaccine manufacturers opted to focus on high profit vaccines, cut back production or retreated from the vaccine market. Eight companies were key UNICEF suppliers of whom 6 were involved in major pharmaceutical mergers [3]. UNICEF now buys 65 percent of its traditional vaccines (with the exception of OPV) from two vaccine manufacturers [33].

Globalization has had a significant impact on vaccine development and availability. To supply developing nations with much needed vaccines, policymakers and immunization stakeholders are faced with the challenges of increasing funding, improving intellectual property rights protection, and creating regulatory harmonization [17, 25]. Manufacturers are not interested in rapidly increasing production because vaccines are not highly profitable, and the very nature of vaccine production results in scale-dependant manufacturing limitations. Furthermore, many developing countries' vaccine management is so poor that ineffective immunization campaigns worsen an already precarious situation. Vaccine integrity is always a problem in developing countries because of the reliability of the cold chain, stock management, diluents handling, and waste monitoring [38].

The fact is that, in light of growing health inequities aggravated by worsening wealth distribution, the need for vaccines in poor and developing countries has never been more pressing [13, 20]. The development of new, safe and affordable vaccines and new vaccine delivery technology for infectious diseases in developing countries is crucial for the survival of hundreds of millions of people, especially children [20, 10]. One of the outcomes of the World Summit for Children in 1990 was a call for the development of new vaccines and vaccine technologies. It was proposed that the ideal vaccine should have the following characteristics: be administered as a single dose, preferably oral, effective when given near birth, heat stable and comprise multiple antigens. Last, but not least, vaccines should be affordable. Many scientists worldwide took up the challenge set

out in the World Summit declaration including researchers interested in the concept of developing plant-derived vaccines.

Plant derived vaccines (PDV) are a novel method for producing and administering vaccines. Plants genetically modified (or transiently infected) to contain sub-unit vaccines can be grown, processed and administered orally in a method that departs significantly from cell-cultured vaccines that are costly to produce and administered by injection. PDVs are a proven research concept and are undergoing clinical trials [11]. The benefits of PDVs over traditional methods include lower production costs [28], potential for *in situ* production, and ease of distribution because they do not require the maintenance of a cold chain. PDV can be viewed as an ethical and socially responsible health care tool if they result in wider vaccination and overcome one of the most significant health care challenges: the reduction of infectious disease burden in developing countries [20]. To date, a Phase I clinical trial of a PDV for Hep B has demonstrated increased antigen-specific serum antibody titers [30]. The challenge now is to prove that PDVs are effective at establishing protective immunity in both animal and human clinical trials [24]. The research concept has been proven, promising products have been created, and all indications are that remaining scientific and technological challenges are surmountable.

A recent article by Milstein, Kaddar and Keiny [17] discusses the impact of globalization on vaccine development and availability, emphasizing the potential to harness the positive outcomes of globalization to benefit public health in the developing world.

Although vaccines are essential to health across the world, the immunization needs of people in developed countries differ from those of developing countries. Unfortunately, commercial vaccine development has been driven by industrialized countries alone. Currently, 90 percent of the effect of illness – measured in deaths and time lost – occurs in the developing world yet only 10 percent of research seeks to find ways to address the particular health situation in those countries (called the 90/10 health gap) [28]. The principal need of developing countries is to adapt existing technologies to their specific delivery needs. Better delivery mechanisms, such as PDVs, will target “global public health priorities, not just vaccines for the most financially attractive markets” [17: 1067]]

The vaccine market which previously relied upon multinational companies has seen a recent shift. The capacity and quality offered from emerging vaccine manufacturers in developing countries has improved and is now relied upon for much of the vaccine supply. Recognizing that infectious diseases are not constricted by national boundaries, international regulations and agreements have been established in order to standardize vaccine quality and harmonize the application and interpretation of the requirements for vaccine registration. Some attempts to promote joint research initiatives and improve global access to essential vaccines have been noticed such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [37]. International organizations such as the WHO’s Expert Committee on Biological Standardization (ECBS) and the Developing Countries Vaccine Regulators Network (DCVRN) have also been important in promoting immunization access through information dissemination and defining best practices.

REGULATORY BURDEN

Three Possible Scenarios for Diffusing PDV Technology to the Developing World

The United States is most likely the country that will produce PDVs, given that the technology is, to a major extent being developed there and many of the controlling interests are American [24]. Among all of the countries in the world that would benefit greatly from PDVs, India is a priority because of its large population and chronic infection rate. Further, its capacity for biotechnology means it is likely to become a producer of PDVs, not just a recipient of finished product. Taking just the United States and India into consideration, however, raises questions about how best to structure production and distribution between the two countries.

To address this, this paper considers three possible scenarios. In the first, the production of PDVs and control over their distribution is undertaken solely by a US-based actor. In a second scenario, the vaccine is produced in the the US but its distribution is under the control of an Indian enterprise. The third scenario involves both the production and distribution of the vaccine by an Indian organisation.

Summary of the Three Possible Scenarios for PDV Diffusion	
	Summary
Scenario 1	PDVs are produced in the United States and distributed in India by a US firm. Production must meet US regulatory standards regarding containment and confinement practices. Finished product must meet US drug and biologic regulations. These regulations ensure product safety and efficacy, but are

	expensive. India is open to foreign investment, but firms must undertake due diligence to ensure intellectual property rights protection. Import tariffs must be reviewed, and the distribution firm may be subject to review by the Reserve Bank of India.
Scenario 2	PDVs are produced in the United States by a US firm but distributed in India by an Indian firm. US environmental regulations and regulations for the finished product safety and quality apply. The US firm would likely negotiate a license with the Indian firm to distribute the final product, including licenses for intellectual property rights. In this scenario, the burden of foreign investment barriers is traded for licenses and importation tariffs. Like Scenario 1, the burden of US regulation in US, and high cost of production must be considered.
Scenario 3	Scenario 3 involves the production and distribution of the PDV in India by an Indian firm, requiring compliance with Indian environmental and manufacturing standards which may not be as stringent as in the US. Several Indian authorities have regulatory jurisdiction over the commercialization of biotechnology, making the regulatory pathway somewhat uncertain and slow. Biosafety is a concern, and appears in many regulations, including the Indian Patent Act. While the technology would be licensed, importation and tariff rules no longer apply.

These scenarios reflect the current state of affairs: the initiative to research and develop PDVs has been undertaken in an industrialized country and is therefore likely to continue to finished products being made available. It is reasonable to anticipate that the country in which the vaccine is first produced is not going to be the same country in which it has its greatest impact on health, particularly given current global health and wealth disparities. Moreover, the scenarios reflect the potential for production and distribution dynamics to change as developing country biotechnology capacity improves around the world.

Some basic assumptions underlie the elaboration of the three scenarios:

- Although it may be possible for further research and development efforts to be undertaken regarding PDV technologies within India (e.g. research on plants that are indigenous to India as PDV candidates) or the United States (e.g. substitution or improvement of production processes), the scenarios described here do not give consideration to future R&D efforts.
- The PDV transgenic plants will be grown within a contained facility, namely a greenhouse facility, even though transgenic plants could be field-grown. Contained growth lessens biohazard risks [26], and improves lot-to-lot consistency.
- The transgenic plants will be created through stable expression technologies, where the gene of interest is incorporated into the host plant genome.
- The growth facility and the production plant will be a part of the same manufacturing facility. Having both facilities connected will reduce the risk of escape of these plant materials into the environment as may occur during transportation.

- To provide vaccination protection to the Indian population, PDV products will need to be distributed to both urban and rural areas, some of which may be remote.

A temporal PDV product development plan is illustrated in Figure 1. In this ideal plan, process development, manufacturing/facility development, intellectual property rights development, clinical development and regulatory development happen simultaneously, minimizing the time delay between clinical development completion and public access PDVs.

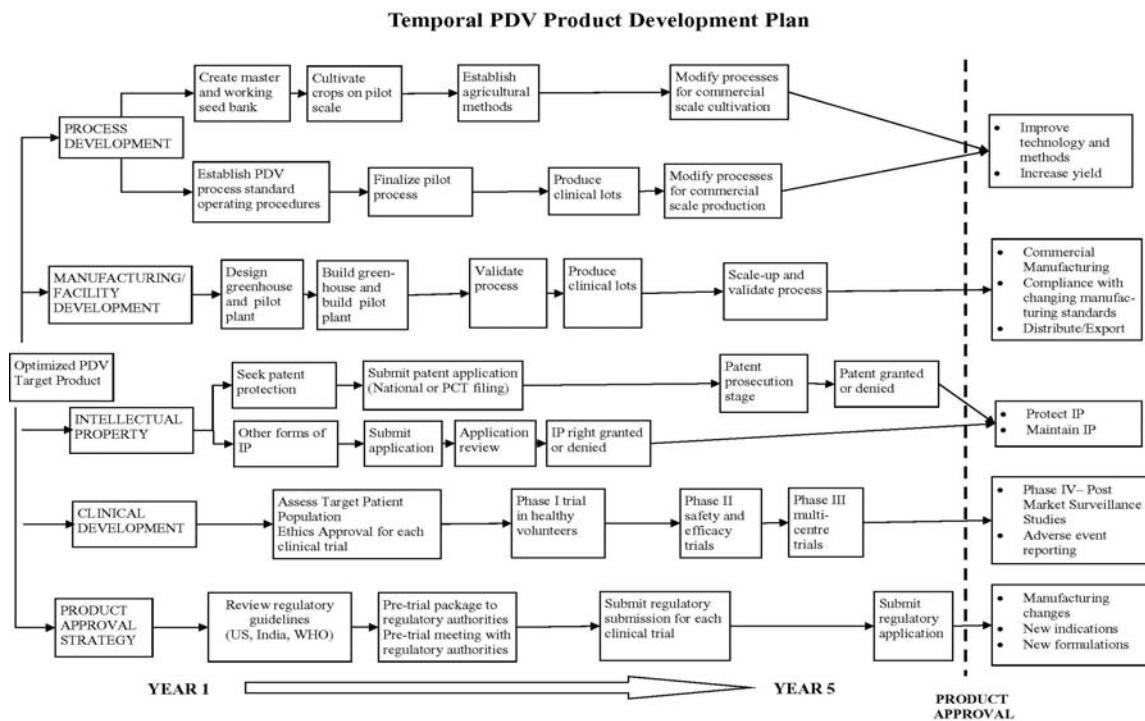


Figure 1.

The costs, time delays, and the degree of uncertainty, linked to the regulatory burden are due to six sources of regulations that must be considered as the product is being developed, manufactured and distributed:

1. Intellectual property
2. PDV transgenic seed approval
3. PDV product approval

4. Transgenic plant production
5. PDV manufacturing
6. PDV import/trade

The time delay of intellectual property (IP), seed approval, product approval, transgenic plant production, and PDV manufacturing regulation specifications slowdown the beginning of PDV production. These delay will affect when production can be initiated. Time delay linked to PDV import/trade regulation applies only if the PDV production takes place in a country different from the country in which it is used. PDV import/trade regulations do not hamper the start of production but will affect the number of doses available on the market. The costs associated with intellectual property, PDV transgenic seed and product approval apply only to the year in which PDV production is initiated. By contrast, transgenic plant production, PDV manufacturing, and import/trade regulations generate costs for each PDV product commercialized. Regulatory uncertainty also increases risks for increased costs.

METHODOLOGY

Influence Diagrams

Influence diagrams are a technique of visually representing systems of phenomena to gain insight into research questions by mapping, in a two dimensional format, different factors and relationships. Influence diagrams are an especially useful tool to integrate disciplinary knowledge as they create a shared model of a problem and serve to build a common language and knowledge base in order for a group of people from different disciplines to form the same, transdisciplinary understanding of how the system works. In addition, influence diagrams capture tacit knowledge about different relationships and how these interact with one another, including feedback loops. Collections of interacting

feedback loops represent complex systems and all decisions that affect a system are made within these loops and affect the loops. Once created, influence diagrams represent a hypothesis about how a given system works. They can therefore be used as the starting point for empirical investigation. Empirical data will include both current and historical econometric data as well as other quantitative and qualitative data (e.g. surveys). An advantage of using influence diagrams over other mapping methodologies is that they identify links and definitions precisely. Hence it is possible to design and empirically test different configurations of IP systems.

In the case of PDV, the model design and execution follows the steps outlined in Sterman [27]. First, the research problem was identified and its scope specified. Second, the PDV influence diagram was formulated out of the dynamic hypothesis to represent the structure of the hepatitis B virus propagation, PDV adoption, taking into account the substitution of existing technology, and population changes in India. Third, a fraction of the PDV ID was translated into a system dynamics (SD) level-rate model. A level-rate model is used to calculate the results from the quantitative simulation model. That model was calibrated using data collected from a variety of publicly available sources (see below). As discussed later, the availability of data limits the calibration of a more elaborate model. Fourth, the model was evaluated for its consistency. Due to the very nature of the prospective case under study, this modeling step was challenging to execute for historical consistency. This dimension of this model evaluation step was conducted for the historical population portion of the model because data was available for

comparison. Fifth, a number of scenarios looking at policy uncertainty were elaborated and the results from the model were analyzed.

The structure of the dynamic hypothesis showing the main feedback loops of the model is shown in Figure 2 with key time delays highlighted using double bars. The dynamic hypothesis contains twenty-one balancing feedback loops and three reinforcing feedback loops. There are three main sets of interrelationships represented within this structure. The population dynamics is disaggregated between the infant (0 to 4 years old) and the non-infant cohorts (five years old and over). An important dynamic is the virus propagation in both infant and non-infant populations. The inherent dynamics of PDV diffusion are modeled.

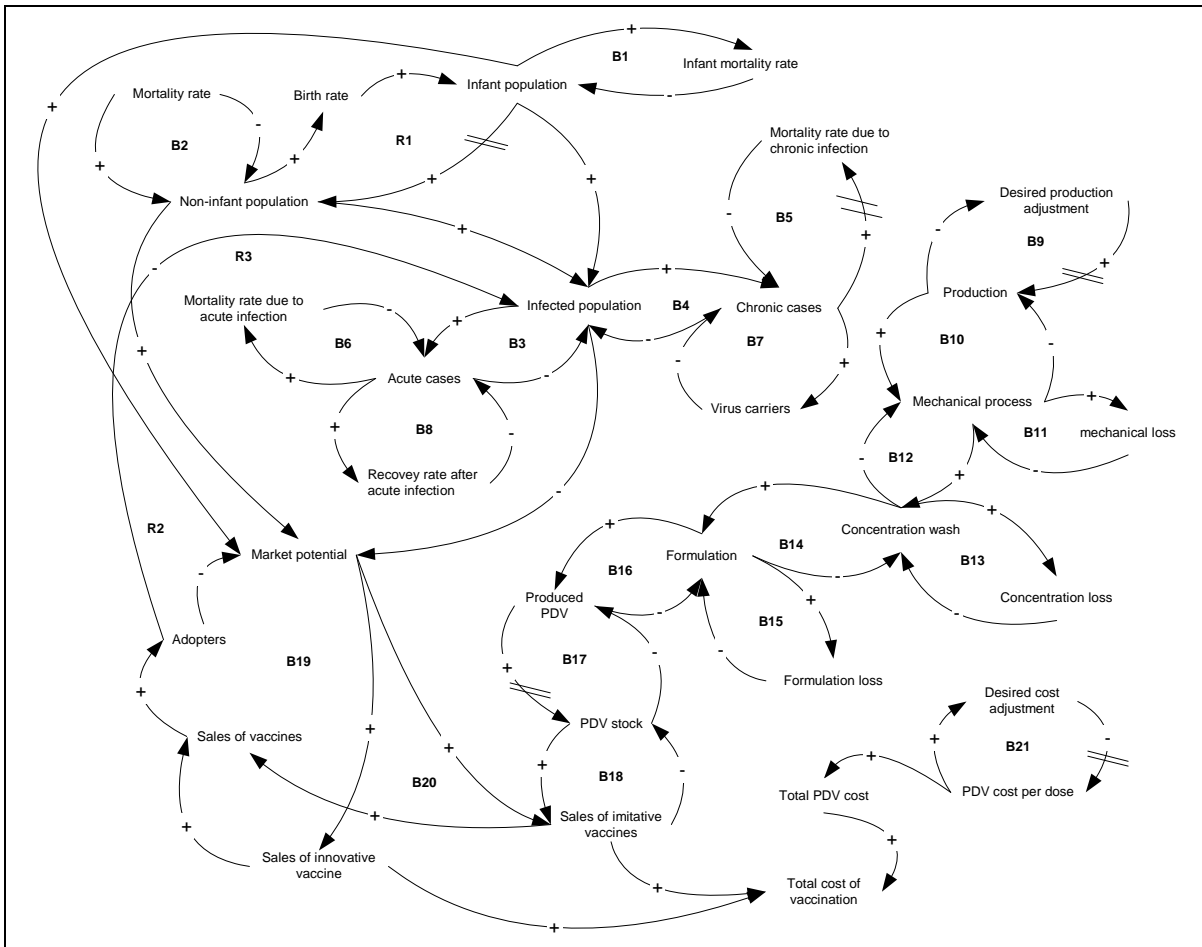


Figure 2. Influence diagram of the PDV level-rate model

PDV diffusion dynamics: Assumptions

The term “infant population” refers to the population between the age of 0 to 4 years old, and the non-infant population defines the population above age 5. The reinforcing feedback loop R1, represents the interaction between these two population cohorts, by the influence of the variable “birth rate”. The balancing feedback loops B1 and B2 are related to infant and non-infant mortality rates that affect their respective cohort population.

The virus propagation dynamics in the overall population is shown in the set of balancing feedback loops labeled B3 to B8. These relationships include the level of infection in the overall population, referred to as “infected population”, and the disaggregation of the population between acute and chronic cases. Although, not shown in Figure 2, these feedback loops also keep separate this dynamic for both infant and non-infant cohorts.

The PDV model diffusion takes into account relationships relative to production, sales, and production costs. The balancing loops B9 to B17 represent steps that must be executed prior to PDV commercialization, that is, steps from plant production in greenhouses to vaccine storage. More precisely, plant production refers to the number of hectares under production. It is likely that production output will need to be ramped up and thus initial production levels will be below output objectives. The model assumes that the hectares in production will increase over a number of years to reach the desired production objective, and this is represented in balancing loop B9. Following plant production, a biomass is extracted from this production. This biomass extraction is conducted in three steps (mechanical process, concentration wash, and the formulation) that lead to vaccine production. There is wastage generated at each step, and this process slows down the PDV production output. The dynamics inherent to this transformation process are captured by the balancing loops B10 to B16. In the model, the balancing feedback loop B17 captures the number of PDV doses available for diffusion. The diffusion of PDV doses depends upon the quantity produced and the time delays. This time delay becomes important in case the market for diffusion differs from the country in which it is produced.

Regarding the PDV sales variable, the dynamic represented in Figure 2 is analogous to production diffusion and technology substitution, although the issue is really one of access for the target population. The PDVs can be modeled as substitutes to conventional vaccines. Thus, within the model, the sales of innovative vaccines refer to the sales of conventional vaccines while the sale of imitative vaccines refer to PDV sales. The population targeted by the vaccination program cannot be assimilated to a market potential. Likewise, individuals that have used one or the other vaccine cannot really be thought of as technology “adopters” within that context. These mechanisms of double diffusion, illustrated by the balancing loops B18 to B20, are thus linked to the existing use for conventional vaccines and to the emerging use of PDVs and their production.

A remaining factor to consider in respect of PDV diffusion is per dose vaccination costs, which includes production and administration costs. The assumption is that unit cost diminishes over time but eventually stabilizes. The time delay required is about the same as the time it takes to adjust production (B9), and this phenomenon is represented by the balancing feedback loop B21. The total PDV cost is thus a function of the PDV cost per dose and of the number of doses required by a patient to complete a full immunization series, but also additional costs linked to regulatory burden.

The impact of the PDV diffusion on the propagation of the hepatitis B virus is important as the number of vaccinated persons (or number of individuals with access to the immunization) reduces the infected population (as seen in reinforcing feedback loops R2 and R3).

Diffusion of PDV: The Simulation Model

The influence diagram depicted in Figure 2 represents the main feedback loops of the simulation model. 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. This overall model can be split into five main sub-sectors. The “slicing” of the model into these five sub-sectors was conducted as follows:

1. Demographic evolution in India;
2. Virus propagation in infant and non-infant populations;
3. Market potential for PDV and vaccines diffusion in infant and non-infant populations;
4. PDV production, including time delays due to regulatory burden;
5. Estimation of vaccination program costs, including costs due to the regulatory burden.

Hence, the propagation of the hepatitis B virus in India, for both infant and non-infant cohorts, was modeled and quantified according to the demographic evolution over time of the infant and non-infant cohorts. More specifically, the model includes the hepatitis B virus’s chronic versus acute infections, related deaths and infection recoveries. The hepatitis B viral infection rates were estimated through the birth cohorts. The vaccination rate is thus dependent on the diffusion of PDV in India, measured by the potential access to the technology by “adopters”. The quantity of PDV available on the market in a given period is directly linked to the production and distribution processes related to vaccines. This process is directly subject to time delays and costs in accordance to the various regulations examined.

The parameters of the baseline, or business as usual (BAU) calibration of the level-rate model were set using data collected from publicly available sources. Due to the

hypothetical nature of the problem modeled, only part of the results could be evaluated for historical accuracy. As stated above, the lack of reliable data made the task of model calibration a challenge. Table 1 shows the input parameters used in the model and their sources. Some entries are estimates using whatever data were available. The reference year for the model evaluation is 1995. Relative to the demographic evolution of India, simulated results were comparable to available historical data. This evaluation was conducted using past and future population estimates available for the period 1995-2015 [34].

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 [35] that estimated the number of infected cases, the number of virus carriers, number of deaths from the disease, etc. These data were particularly useful for looking into the rates of new infant cohorts.

Table 1. Model parameters: BAU specification ($t_0=1995$)

Input parameters	Value	Source
Data on population in India		
Initial population (0 - 4 years old)	119,212,928	34
Initial population (greater than 5 years old)	812,138,072	34
Birth coefficient	from 0.03 to 0.02	<i>Estimated</i> from [34]
Infant death coefficient	from 0.02 to 0.01	<i>Estimated</i> from [34]
Non-infant death coefficient	0.008	<i>Estimated</i> from [29]
Delay cohort in years	5	
Data on hepatitis B infection in India		
Initial infection infants	14,000,000	<i>Estimated</i> from [36]
Infant infection rate	0.1	<i>Estimated</i> from [36]
Chronic infection rate for infant	0.35	[12, 36]

Acute infection rate for infant	0.01	[12]
Death rate from chronic infant infection	0.2	<i>Estimated</i> from [36]
Initial infected population	162,000,000	<i>Estimated</i> from [36]
Infection rate of at risk individuals	0.2	<i>Estimated</i> from [36]
Rate of chronic cases	0.05	[12, 36]
Rate of acute deadly infection	0.001	<i>Estimated</i> from [36]
Death rate from chronic infection	0.15	[12, 36]
Data on traditional vaccines		
Infant vaccination rate	0.01	<i>Estimated</i> for Southeast Asia – [32]
Non-infant vaccination rate	0	<i>Assumption</i>
Efficacy of vaccines (%)	0.95	[37, 12, 36]
Cost of conventional vaccines (US\$)	1.26	3 doses at US \$0.42 [5]

Data on PDV production and distribution

The model specification assumes that a PDV will be available for use starting in 2010. However, the diffusion initiation may be delayed until later that year due to uncertainty in regulatory delays relating to the introduction of PDVs. Three assumptions were made for the estimation of data relative to PDV production. First, it was supposed that in each year, all newborns in India could benefit from the technology and that they should be vaccinated. To meet this need, more than 80 million doses of PDV and 27 million vaccines need to be produced annually. Given that production will need to ramp up, initial production would begin at a lower level. Second, PDVs would be produced in greenhouses and not in open fields. Third, the plant used for the vaccine from biotechnology would be tobacco. The data relative to PDV production, introduced in Table 2, are based on these assumptions.

Table 2 – Model parameters: PDV production

Input parameters	Value	Source
Initial production in hectares	1.5	
Desired production in hectares	3.5	
Production per unit (kg per hectares)	200 000	<i>Estimated from [5]</i>
Mechanical reject rate	0.17	<i>Estimated from [5]</i> (total reject rate = 50 % of production)
Concentration reject rate	0.17	
Formulation reject rate	0.16	
Doses per kg	200	<i>Estimated from [5]</i>
Doses per PDV	3	[5]

The effective cost of one PDV dose was determined and includes both production and administration costs. The initial proposed cost for a PDV dose should experience a reduction over time and stabilize. The initial cost corresponds to the effective cost estimated for a single dose, while the reduced cost is estimated on the basis of the production of a lot of ten doses.

Finally, the last dimension to be quantified includes costs, time delays, and the degree of uncertainty, linked to the regulatory burden. Quantitative information for these parameters had to be specified in the model for each of the six regulations (IP, PDV transgenic seed approval, PDV product approval, transgenic plant production, PDV manufacturing and PDV import/trade) detailed in the previous section. The model assumed that the greater the level of regulatory uncertainty, the greater the time would be needed to produce PDVs. This assumption is reasonable since uncertainty leads the creation of new policy and institutional tools that will have been smoothed out in clear regulatory environments.

The effective cost of PDV production and regulatory burden (costs, time delays, and uncertainty) depend upon the country in which the PDV is produced, and where

distribution is controlled. Data were collected for each of the scenarios presented in Table 3:

1. Production and distribution of the PDV controlled in the United States;
2. Production of the PDV controlled in the United States, and distribution controlled in India;
3. Production and distribution of the PDV controlled in India.

Table 3 – Model parameters: PDV costs and regulatory burdens

Input parameter	Scenario 1	Scenario 2	Scenario 3
Initial effective cost per dose (US \$)	0.18	0.18	0.113
Desired effective cost per dose (US \$)	0.133	0.133	0.053
Cost of IP (US \$ at the beginning)	10000	10000	8000
Delay of IP (year)	2	2	4
Certainty of IP (scale 1-10)	0	0	0
Cost of seeds (US \$ at the beginning)	5150	5150	3090
Delay of seeds (year)	0	0	0
Certainty of seeds (scale 1-10)	2	2	0
Cost of product approval (US \$ at the beginning)	1000000	1000000	600000
Delay of product approval (year)	0.75	0.75	6
Certainty of product approval (scale 1-10)	1	1	2
Cost of cultivation (US \$ / PDV)	Incorporated into the effective cost of one PDV dose		
Delay of cultivation (year)	1	1	2
Certainty of cultivation (scale 1-10)	4	4	6
Cost of manufacturing (US \$ / PDV)	Incorporated into the effective cost of one PDV dose		
Delay of manufacturing (year)	0	0	1
Certainty of manufacturing (scale 1-10)	3	3	6
Cost of import trade (% of increase / PDV dose)	0.32	0.32	0
Delay of import trade (year)	2	0.5	0
Certainty of import trade (scale 1-10)	5	3	0

Simulation Results

The simulation model was designed and calibrated to test and compare alternative scenarios; in this section the results of these specifications are presented. More precisely, the scenarios are compared on the basis of the data presented in Table 3. Moreover, the

repercussions generated by these scenarios are presented with a reference to a business as usual (BAU) baseline. The BAU represents a situation without PDV introduction, that is, where only the conventional vaccine is available. In accordance with the data presented in Table 1, only 1 % of children are currently vaccinated. The commercialization year for the PDV was set at 2010, and the time delays required for adjustment in production, and in costs, were specified at three years. For the purpose of the calculations presented, the assumption is that the PDV is not available in quantities large enough to satisfy the access need, and there will remain a penetration rate of 1 % for the existing (non PDV) vaccine.

The three scenarios identified earlier have led to the specification of three sets of parameters. The results presented in this section compare scenario results for:

1. The swiftness of the PDV production process (Figure 3);
2. The number of new infected cases by hepatitis B virus per year (Figures 4 and 5);
3. The mortality associated with these new infected cases (Figures 6 and 7);
4. The total cost of vaccination (Figures 8 and 9).

The swiftness of the production process is provided by the number of hectares in annual production. These results are shown on Figure 3.

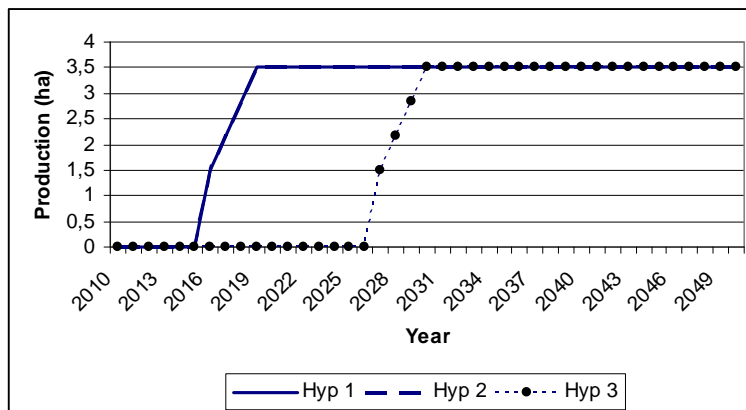


Figure 3– Swiftness of PDV production [7]

As mentioned above, the PDV is introduced for human use in 2010. Accordingly, there will be interference with the time delay associated with regulation, and burdens are imposed. The results shown on Figure 3 report that for scenarios 1 and 2, PDV production would begin in 2016, that is, after a time delay of six years, while for scenario 3, it would begin only in 2027, that is, after a time delay of 17 years. The extra time delay in India is due to differences in regulatory uncertainty and processes when compared with the US. Moreover, it is important to note that the results generated are coherent with the assumption that time delays are required to reach targeted production levels of 3.5 hectares. For each of the scenarios, the adjustment is realized over a three-year period. The target is reached in 2019 for scenarios 1 and 2 and in 2030 in the case of scenario 3.

Figures 4 and 5 present the repercussions of each scenario and of the BAU results on new infected cases of Hepatitis B in India per year. Figure 4 presents infant new infection levels for each birth cohort. The results in Figure 5 display new infection levels for non-infant cohorts, but for which infection will occur later in life.

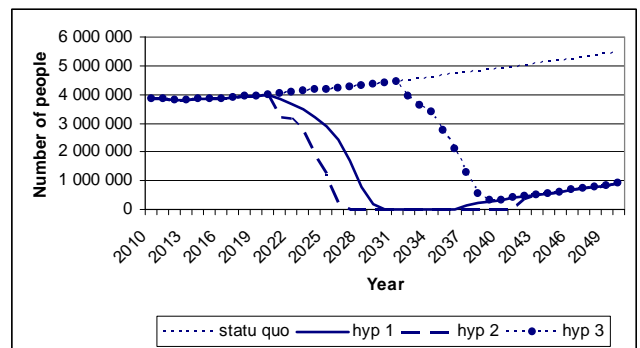
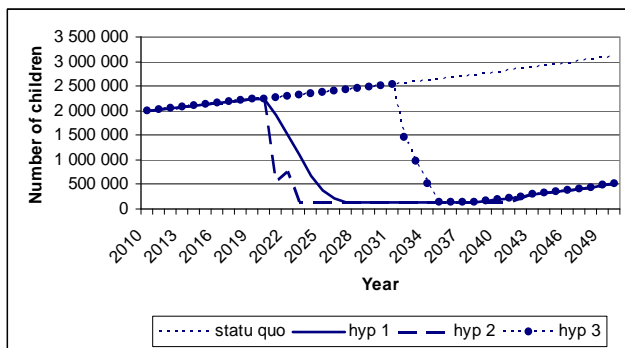


Figure 4 – Infant infection: New infections per year [7] **Figure 5 – Non-infant infection: New infections per year [7]**

The results presented show that the diffusion of PDVs, no matter the scenario, contributes to a reduction in cases of new infection per year. Indeed, by 2050, a reduction of nearly 84 percent in the total number of new infections could be achieved. The number of new infections declines soon after the introduction of PDVs. However, it can be observed that this figure never reaches zero. Two reasons explain this outcome. First, all vaccines, whether conventional or PDV, are not 100 percent reliable. More precisely, 95 percent of the individuals vaccinated could nevertheless develop an infection. Second, the targeted PDV production, set at 27 million vaccines, is not sufficient to cover all newborns until 2037, but a shortage is then expected, given the increase in the number of newborns.

Finally, the comparison of results for the three scenarios stress that the reduction in the number of infected cases is slightly more effective in scenario 2 than in scenario 1. This is due to the time delay and to the regulatory uncertainty of imports that are more significant in the case of scenario 1. The reduction witnessed in scenario 3 is much slower than for the other two scenarios. These results are coherent with the analysis conducted earlier regarding the swiftness of the production process for the PDV in India. The production of PDVs, if first conducted in India, could only begin 17 years after 2010, compared to 6 years for scenarios 1 and 2 where production first takes place in the United States.

Figures 6 and 7 present the repercussion of each scenario and of the BAU on the number of deaths due to the hepatitis B virus per year in India. Figure 6 shows infant deaths, while Figure 7 represents non-infant deaths.

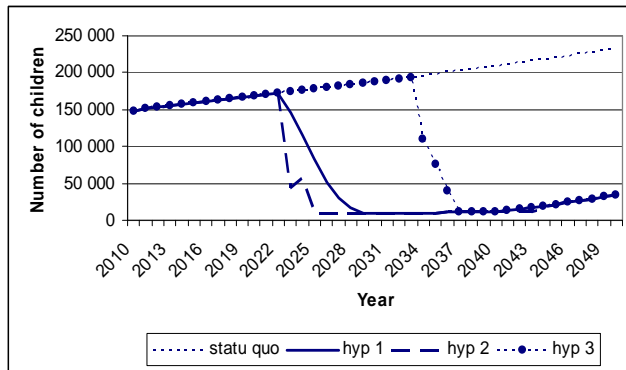


Figure 6 – Deaths caused by Hepatitis B: infant population [7]

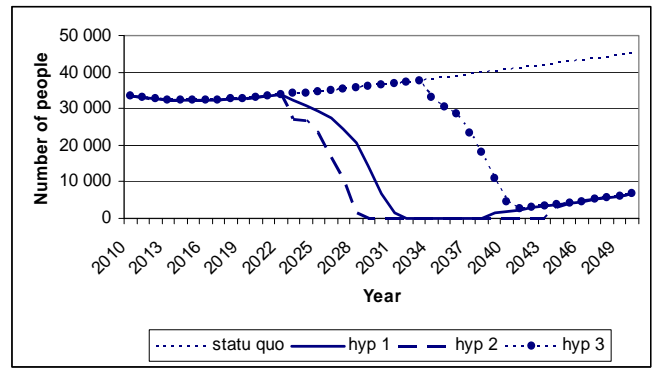


Figure 7 – Deaths caused by Hepatitis B: non-infant population [7]

Thus, in connection with the reduction in the number of infected cases emphasized earlier, the number of deaths due to the hepatitis B virus could decline rapidly if PDVs were commercialized. Indeed, starting in 2023, compared with the BAU baseline, a reduction by 29,883 and 137,921 deaths (in both infant and non-infant cohorts), respectively for scenario 1 and 2, is to be expected. Regarding the results of scenario 3, the reduction in deaths will be felt only by 2034, attaining in that year alone 89,972 avoided deaths. From 2010 to 2050, the model suggests that a total of 5.7 million deaths would be avoided for scenario 1, 6.1 million deaths for scenario 2, and 3.6 million deaths for scenario 3. The reasons for that difference are the same as the ones identified earlier, that is, the speed at which the PDV production process can be initiated.

Given the above analysis, scenario 3 presents the situation that represents the slowest diffusion of PDVs. The impact of this slower access to vaccines on the propagation of the hepatitis B virus is non negligible. While the differences in assumptions between scenarios 1 and 2 are only slight, their outcomes in terms of health remain significant, with scenario 2 having the greater impact.

Finally, the results have been examined for their effects on costs, and Figures 8 and 9 present these results.

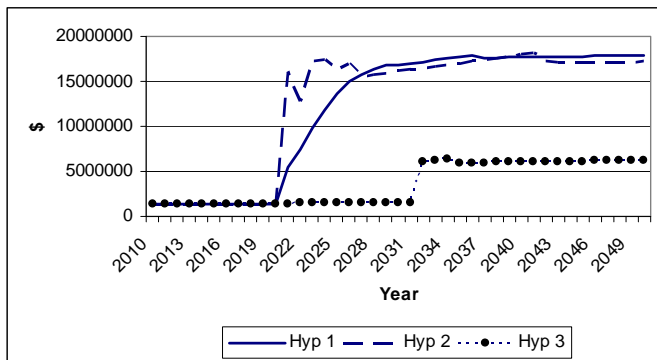


Figure 8 – Vaccination costs per year [7]

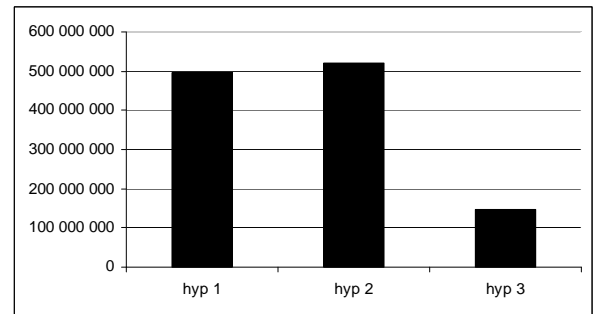


Figure 9 – Total vaccination costs (from 2010 to 2050) [7]

Prior to the production and distribution of PDVs, costs only relate to the sales of the conventional vaccine. The model approximates these costs at 1.5 million dollars (the assumption is that only one percent of infants are vaccinated in each year). From the time that PDVs are commercialized, this cost experiences increase, with the steepness of increase depending on the scenario under consideration. In 2050, the annual cost reaches 17.20 million dollars, 17.92 million dollars, and 6.24 million dollars, respectively for

scenarios 1, 2, and 3. Scenarios 1 and 2 show a slight difference between their respective annual costs. Similarly, with respect to the results in Figure 10, it appears that the total cost of the vaccination, that is, the cumulative costs from 2010 to 2050, differ according to the scenarios. For scenario 1, the total costs are 497.3 million dollars, for scenario 2, they are 519.2 million dollars, and for scenario 3 the total costs are 147.9 million dollars. Scenario 2 is the most expensive while scenario 3 is the least.

However, it is useful to recall that costs depend, among other things, on the number of PDV vaccines given annually, and that this number differed between scenarios. One therefore needs to establish a basis for comparing scenarios. For example, the basis of 27 million PDVs distributed (that is, the targeted production). Table 4 presents the estimated costs for each scenario based on a production of exactly 27 million distributed PDVs per year in the first year and after 3 years.

Table 4 – PDV cost comparison

Year	Scenario 1	Scenario 2	Scenario 3
Costs for the first year (\$US)	22 597 450	21 664 161	9 765 744
Costs after 3 years (\$US)	15 946 922	15 257 325	4 293 776

Hence, for the same number of PDVs produced and distributed, it appears that scenario 3 is much less expensive than either of the other scenarios. Scenario 1 represents the highest costs although scenario 2 is not far behind.

This comparative analysis suggests that scenario 2 is the one that generates the largest benefits with respect to the reduction in the number of infected cases and mortality

related to the hepatitis B virus. This can be explained by the fact that time delays are shorter for this scenario than for the others. In addition, the costs generated by this scenario, while higher, are fairly close to those of scenario 1. Regarding scenario 3, while costs are significantly lower, health benefits would take much longer to obtain. In other words, the results support the decision to produce PDV in the United States but that the control over the distribution be exercised in India.

Conclusion

This paper presented the results of a system dynamics model looking at the introduction of PDVs to combat hepatitis B infection. The focus was on the tractability of the method to investigate the repercussion over time of increasing a population's access to a new biotechnology. This problem was captured by taking into account production, economic and policy uncertainty specifications. These findings indicate that time delays due to regulatory barriers influence both the cost and the disease burden experienced by a population. Thus, technology transfer mechanisms under consideration for a new technology need to consider the composite impact of regulatory factors

Additional research should be conducted on other variables that could limit the effectiveness of vaccination programs, in addition to the availability of the technology. These variables include current vaccine management practices and cultural attitudes towards vaccination. Supplementary research is required to provide a model that places more emphasis on elements of adoption and of successful technology transfer, from the

standpoint of the adopters; especially, adopters of vaccines who are placed in a position of either having or not having access to the technology.

Despite the absence of all the desired data and the introduction of new variables, the present study provides a basis upon which to take a policy decision to invest in PDV production. Using such mechanisms as Advance Market Commitments [4], countries working alone or through organisations such as the World Health Organisation and philanthropic organisations could make significant headway into reducing the impact of hepatitis B on India and other countries.

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