Use of system dynamics and simulation in modeling and analysis of vaccine supply chain management

Arman Kussainov

Kazakh-British Tehnical University, Kazakhstan

Corresponding author's e-mail: arman.kusain@gmail.com

Received 1 March 2015, www.isma.lv

Abstract

Over the last century or more, immunization programs have contributed massively to public health advancement, significantly increased longevity and reduced child mortality rates, and to economic growth, development and prosperity across the board for most of the world. Consider, for instance, the success the global healthcare agencies and nations have had in eradicating small-pox, the "scourge of mankind" which had killed an estimated 300 million people in the 20th century alone, and in almost eradicating poliomyelitis (with only a few hundred cases reported in the last year in Pakistan, Afghanistan and Nigeria).

Keywords: vaccine, supply chain management, system dynamics, system modelling

1 Introduction

Despite the significant and indisputable economic benefits of immunization, vaccine supply chain management is not easy task. There are given the number of different actors involved (the governments of a host of countries, international health monitoring and disease-control organizations such as WHO, the US Centers for Disease Control, UNICEF or the United Nations Children's Fund, and GAVI or the Global Alliance for Vaccine and Immunization, public health planners, the pharmaceutical industry, clinics, hospitals and healthcare providers and the 3rd Party Logistics, or 3PL, providers). Also we have a slew of different factors or parameters relating to the clinical and regulatory environment (e.g., safety, efficacy, probability of success, and operational effectiveness), economic or commercial considerations (e.g., scalability, cost, and profit potential, which would depend on market shares and sales volumes, growth rates and gross or net margins) and the operational and strategic aspects of the vaccine supply chain or system.

Since the business of making vaccines became a commercial proposition, profitability has often been elusive, according to Lagerwij, et. al [1]. The economics are difficult: Costs of development and production, already high, are rising. Profit margins historically have been lower than those of other pharmaceutical products, in part because of the complexities of manufacturing and distributing vaccines as well as their stringent safety, testing, and quality requirements. And scaling-up of immunization programs along with the introduction of new vaccines have put a significant strain on decades-old logistics and delivery systems.

More importantly, the "winner-take-all" nature of the vaccine market dynamics translates into a rather limited number of suppliers for each product class, with high costs and associated risks representing major challenges to the "winners" in the vaccine market ("…compare the 38\% cost of goods sold (CoGS) with 21% for pharmaceuticals…The average vaccine takes 10.71 years to develop and has a 6% chance of making it to market…"). As a result, many major manufacturers, especially in the United States, have left the market, leaving 90% of the world's production and two-thirds of R&D to companies in Europe and elsewhere.

On the one hand, the vaccine value chain economics depend on the ease and accuracy with which vaccine sales can be projected or predicted, compared with other pharmaceuticals (pediatric vaccines being more readily forecastable based on annual birth counts, compared with hard to predict volume for vaccines targeted at limiting unpredictable outbreaks, e.g., H1N1 and other influenza viruses), since poor forecasting can result in delays or shortfalls in delivery, additional costs, and risks such as the loss of reputation, for instance.

On the other hand, a centralized, well-managed supply chain can get the right product to the right place at the right time, reducing waste, meeting market demand, and reducing operating costs. However, given how vital it is to ensure product stability and the limited capacities of many markets in this respect, a major obstacle to delivering vaccines to populations in the developing world is the temperature sensitivity of such products, necessitating the use of expensive but not very reliable cold chains for storage and distribution.

A number of recent developments have radically affected vaccine supply chain economics: i) live-attenuated vaccines (LAVs) are more effective as substitutes for inactivated versions, requiring a lower dosage and less exposure: once they are evaluated for safety and efficacy, LAVs may help reduce operational costs, carrying costs, and waste; (ii) a new wave of vaccines, e.g., DNA vaccines, stimulate a strong cellular response and are safer than LAVs, and are relatively easy and inexpensive to design, produce, and transport because they do not require temperature-controlled environments, as well as easier to administer, allowing vaccination teams to use less sophisticated and less expensive equipment. For instance, a study demonstrated that making a pentavalent vaccine thermostable increased its availability from 87% to 97%.

2 Vaccine Supply Chain Management

A supply chain describes the flows of merchandise and information from suppliers to customers. There are many components in a supply chain such as suppliers, manufacturers, distributors, retailers and customers. The simple supply chain can be represented by network with several stages that consists of multiple facilities. The main purpose of supply chain management is to maximize the overall value of the entire supply and distribution system. Products are manufactured and distributed in the right quantities, to the right locations at the right time, in order to satisfy demand at minimum cost. Vaccine is the biological product which is made from microorganisms to provide immunity and defend from diseases. Vaccine supply chain is built from five primary processes [2]:

- Inbound logistics: In this process we receive ad store raw materials.
- Operations: Here we transform raw materials received in previous process into vaccine dosages.
- Outbound logistics: These activities are associated with gathering, storing and distributing vaccines to physicians and pharmacies.
- Outbound logistics: These activities are associated with gathering, storing and distributing vaccines to physicians and pharmacies.
- Sales and marketing: These activities induce consumers to purchase vaccines and enable them to buy it.
- Services: These activities are associated with providing services to enhance or maintain the value of vaccines.

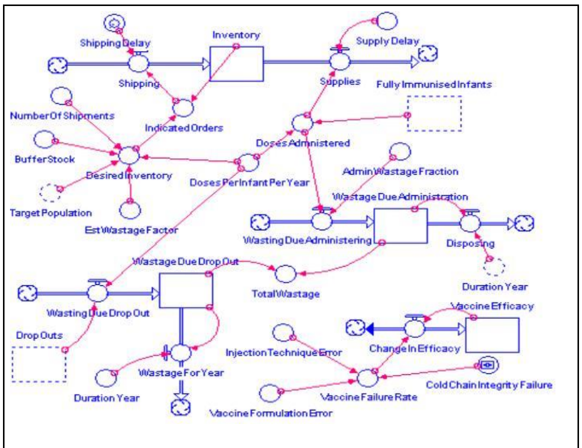

FIGURE 1 Vaccine Management Sector

Vaccine supply chain management is the key to the success of immunization programs. There is need to monitor the management of vaccines as well as have them replenished regularly in order to prevent over and under stocking which may lead to expiry of vaccines and low coverage respectively. We should represent our dynamics model in form with a minimum wastage. In Figure 1 we can see that vaccine wastage is the proportion of vaccine supplied but not administered to the recipients.

There are some issues that make supply chain model in vaccine harder. Because usually supply chain in any sphere examines procurement, production, transportation routes and types. But in vaccine management we should consider some additional issues:

- Temperature requirements during transportation and storage. We should use cold chain for some vaccines. Also most vaccines should be transported within specific temperature range.
- Vaccines have a limited shelf life. Some vaccines expire in 20-30 days.
- There may be significant fluctuations in the vaccine supply chain from international donations.
- Vaccine demand can be stable or may be campaigns for a particular vaccine immunization.

3 System Dynamics model of Pediatric Vaccine Supply Chain in Kazakhstan

The problem of managing the vaccine supply chain and determining the optimal stockpile exists in our country too. Distributing vaccine from manufacturers to the final recipients is composed of a series of procurement, storage, shipment and other related activities. One of the challenges is that vaccine demand and supply are variable. In Kazakhstan the demand for vaccines is changing exponentially because of the fluctuating growth in the birth rate. Additionally, vaccines are also used for the purpose of immediate response to disease outbreaks. Large quantities of vaccines are often stocked for mass vaccinations to prevent disease or to provide routine immunization of children. Vaccines are supplied by international organizations, and can come from multiple sources. It is difficult to coordinate orders from different suppliers. Furthermore, information provided to vaccine manufacturers can often be unreliable. The lack of good data leads to inaccurate demand forecasts, which is a critical impediment to proper planning. It is also important to recognize that vaccine supply considers both equity and efficiency. The goal is to provide vaccines uniformly to everyone in the system, while also ensuring that children can be immunized on time referred in the immunization schedule. To account for the trade-off between equity and efficiency, it is important to balance coverage within an optimal vaccine system design.

The main goal of the model is to simulate the behavior of vaccine supply where the optimal stockpile level for main distributor (Vaccine Main Stockpile) and dynamic of changing of it will be shown. The model simulates the simple vaccine supply chain in our country over time. There was made an assumption in the model that the main distributor center to all regions which is called as Vaccine Main Stockpile in the model is replenished just from one manufacturer called Vaccine Production.

3.1 THE LOGIC OF THE MODEL

System Dynamics (SD) is a computer-aided approach for analyzing and solving complex problems with a focus on policy analysis and design and also this approach uses a perspective based on information feedback and delays to understand the dynamic behavior of complex physical, biological, and social systems [3]. There are two software programs that were designed to facilitate the building and use of System Dynamics models: AnyLogic Simulating Software and Vensim. AnyLogic is a visual modeling tool that allows you to conceptualize, document, simulate, analyze, and optimize models of dynamic systems. It provides a simple and flexible way of building simulation models from causal loop or stock and flow diagrams.

We used system variables, arrows to make flow diagram. This diagram will represent structure of the system. In order to simplify, we consider the number of children that must be immunized divided into two groups by age counted in months, vaccine production and the number of doses injected taking from Vaccine Main Stockpile in supply chain. Moreover, we think that the number of children, vaccine production capacity and Vaccine Main Stockpile are core elements in supply chain of this model. From the angle of management, Children-Vaccine Production-Vaccine Main Stockpile in supply chain is complex and could be regarded as a system. In order to study the real system, we might build a simulation model. Firstly, we should determine the composing elements of the simulation system and the causal connections among them based on the real system. The elements associative directly with the system are children that must be immunized divided into two groups by age counted in months, vaccine production and the number of doses injected taking from Vaccine Main Stockpile. Starting from this point, we could determine all the composing elements through cause-effect analysis. According to the concept of system dynamics, we could divide the elements into levels, rates, auxiliaries and constants. Then, we could use the AnyLogic Simulation Software to build the flow diagram of the system (Figure 1). The main parameters of the model are listed below:

- main distributor stockpile level;
- number of doses for immunizing;
- immunization rate of the country;
- birth cohort;
- death rate;
- number of doses per fully immunized child;
- vaccine wastage rate;
- safety stock.

To make an order for vaccine supply at first we should anticipate the future demand of vaccine doses by analyzing birth and death rate which impact the birth cohort.

The number of doses n can be calculated by formula below:

$$n = i * b * d * \frac{1}{1-w} * (1 + r) \quad (1),$$

where i is immunization rate which is assumed to be about 75% in our country;
b is a birth cohort, there will be an assumption that average birth cohort is 360000 per month in the whole Kazakhstan;
d is the number of doses per fully immunized child which will be assumed as equal to 3 doses per child;
w denotes the wastage rate which is about 0.3 (30%);
r is reserve stock rate which should be about 0.25 (25%).

To determine the number of vaccine doses which will be required in the following years the same formula will be used. Just one exception is that we will not be taken into account the safety stock and all vaccines in the inventory:

$$n = i * b * d * \frac{1}{1-w} - s, \quad (2)$$

where s denotes the number of doses in the inventory.

Data required for anticipating the birth cohort should be derived from national committee of statistics or it's branches, but for this model I will make just assumption.

According to national or regional records of doses of vaccine the formula shown below is used to estimate the wastage (f):

$$f = \frac{(v+c)*d}{n}, \quad (3)$$

where v is the number of vials opened to use;
c is the number of closed vials which were destroyed because of failures in the cold chain;
d is the number of doses per vial;
n is the number of injected doses.

Thus, the wastage rate is calculating by the following expression:

$$w = 100 - \frac{100}{f}, \quad (4)$$

The factor of wastage where the stockpile size is taken into account can be calculated by the following formula:

$$f = \frac{(b+c-d)*e}{n}, \quad (5)$$

where b is the vials in stock which are suitable for using at the beginning of the year;
c is the number of vials issued from the inventory to be used for throughout the year;
d is the vials in stock which are suitable for using at the ending of the year;
e is the number of doses in one vial;
n is the number of injected doses.

The flow diagram represented in Figure 2 above includes 62 variables. There are 4 main stockpiles: Vaccine in bulk production, Vaccine bulk, Vaccine in filling pipeline and Vaccine final. Also there are 5 main rates like bulk production starts, bulk production, filling starts, filling, deployment, and 2 additional rates corresponding to the incurred costs like fixed costs and public health costs.

The model focuses on the primary objective of the pediatric vaccine stockpile to respond to normal demands over time. Appendix A provides the hypothetical values of constants used in the model for the stockpile supply chain model.

We focused on framing 1 described in the chapter 4 (optimization of the polio vaccine stockpile) to model the pediatric supply chain. Before starting to model we should understand which factors impact to the final vaccine stockpile level and vaccine production.

So firstly, the model relies on the plausible assumption that the penalty associated with each dose of unmet vaccine needs exceeds the costs of stockpiling a dose (costs flow is represented in the below of the Figure 2). If this assumption does not hold, then no economic justification exists for the stockpile, because the costs of the consequences do not exceed the stockpile costs. In addition, there is ignored expiry by assuming that we use vaccines for outbreak response soon after they enter the stock of final vaccine, which is possible if vaccine demand is deterministic and filling capacity is sufficiently high.

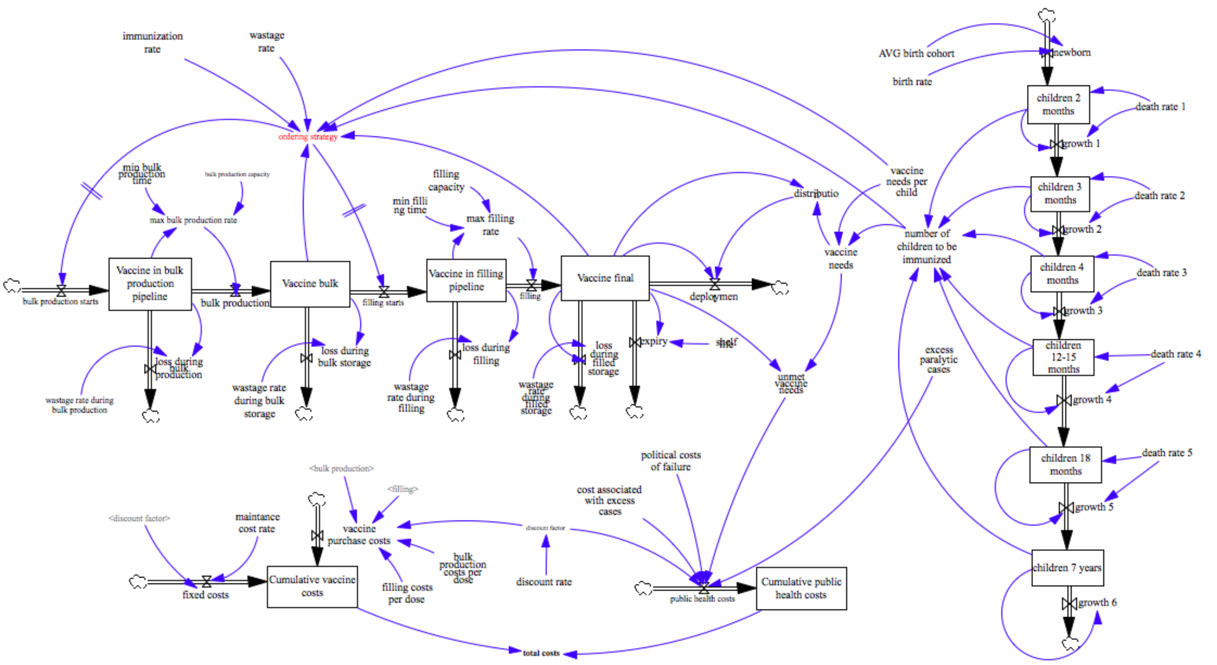

FIGURE 2 The flow diagram of the simulation model

Secondly, the next assumption of a fixed delay process for expiry, as in the model, is appropriate if disposal of expired vaccine lots occurs on the basis of expiry dates set at the time of filling, which is current practice. Alternatively, in the future random tests may possibly determine the disposal of lots or batches. In that case, a more appropriate model would disaggregate the stock by age, with the hazard of expiry increasing with age. In the model, we neglected expiry by assuming that we could receive newly filled vaccine only a short time before its required use, but this assumption does not hold if filling capacity is low relative to vaccine demand, filling and production costs increase over time, or vaccine demand is highly stochastic.

The ordering strategy here determines both bulk production starts and filling starts and may use information about current levels of vaccine bulk and vaccine final as well as the predictable expiry of vaccine final.

Vaccine supply chain also depends on the technical characteristics of the bulk production and filling processes which determine the appropriate model for the filling and bulk production delays. From the perspective of the stockpile owner, the production delay might look like a fixed delay, with no distribution around the time that doses arrive due to a single time of delivery. From the manufacturer’s perspective, however, a given order of bulk vaccine might potentially get produced over time, with production of some doses completing before others, which would suggest a first- or low-order delay. Filling involves a relatively fixed delay associated with testing batches of final product, but if many filling lines exist, each line might become available at a different point in time such that the delay could look more like a low-order delay. Given that the exact time that vaccine becomes available plays an important role in the event of potential shortage of vaccine, the choice of the delay in the model should reflect the physical reality of the process and the relevant perspective of the analysis.

The forecast of vaccine demand represents the key driver of decisions regarding the stockpile. In case of pediatric vaccine supply chain the vaccination i provided periodically according to the routine defined by healthcare centers fro children. Therefore forecasting future demand focuses on the birth rate and amount of stockpile remained. As this model is trying to minimize the stockpile level of vaccines to diminish wastage during providing enough vaccine for routine immunization anticipating a future demand is the main issue. The vaccine demand depends on both the stochastic risks and the stock of vaccine final, and in two different ways. If the vaccine demand exceeds the maximum output of filled vaccine, then this will likely create new demand due to the natural expansion of the birth cohort. This leads to a positive (reinforcing) feedback loop around vaccine demand, since the likelihood of unmet vaccine needs lead to more demand which leads to greater likelihood of unmet vaccine needs.

The next problem in vaccine supply chain which was not included to the formulation of the optimization model is the physical location of the stockpile. However, the trade-off between costs and risks of the stockpile may depend on the locations of the facilities.

Equations used to calculate the variables and levels from the simulation model are described below. The number of doses of vaccine which was distributed to the final stock d is derived from this formula where d_{max} is the maximum deployment rate:

$$d = MIN(d_{max}, d^*). \tag{6}$$

The number of deployed vaccine is derived from the formula below where V_f denotes Vaccine final, v denotes needs of vaccine per child, n is the number of children to be immunized. t_{depl} is the minimum time to deploy vaccine and t_{distr} is the minimum time for vaccine distribution. In the model assumed that both of these times are equal to 1 month just for simplicity.

$$\frac{dDV(t)}{dt} = MIN(\frac{V_f}{t_{depl}}, \frac{v*n}{t_{distr}}). \quad (7)$$

So the total vaccine need during fixed period of time can be calculated $v_n = v \times n$ (8)

Amount of final vaccine stockpile is equal to:

$$\frac{dV_f(t)}{dt} = f(t) - d(t) - \frac{V_f(t)}{t_s}, \quad (9)$$

where f is the amount of doses in the filling and t_s is shelf-life of vaccines which is assumed to be about 60 days.

Amount of vaccine in the vaccine bulk (b is bulk production):

$$\frac{dV_b(t)}{dt} = b(t) - f(t) \ (10).$$

Amount of vaccine doses in vaccine bulk production pipeline:

$$\frac{dV_b^p(t)}{dt} = bs(t) - b(t) \ (11),$$

where bs is bulk production starts flow in the flow diagram.

The graph of deployment level created by the model to analyze is represented in Figure 3. As we see it is not linear because of that birth rate and immunization rate are not constant which makes the model stochastic.

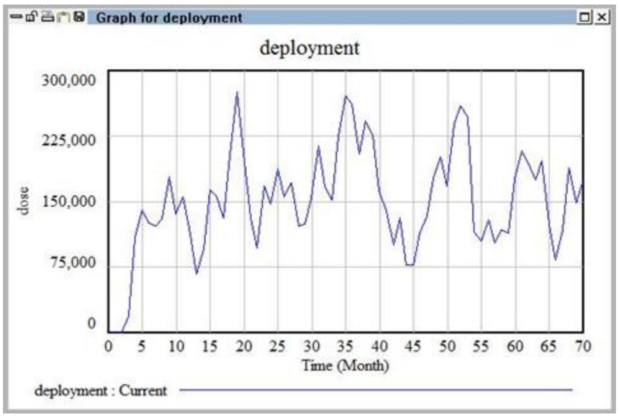

FIGURE 3 The deployment rate

3.2 THE RESULT OF MODELING

The whole supply chain should operate according to the birth cohort and keep sensitive to the change of normal demand for vaccine. Normal demand for vaccine depending on birth cohort is the origin of the production of vaccine and determining the optimal vaccine final stock. In supply chain, information of demands is transferred in form of orders. Orders are the results after processing different kinds of information and guesses and the data of orders often distort the real market information, thus leading to the phenomena of bullwhip effect. I think that number of newborns, average vaccine shipping rate which demands on vaccine production capacity and number of vaccines injected are core elements in pediatric vaccine supply chain.

Figure 1 represented above explicitly shows the accumulation of vaccine costs from bulk production, filling, and maintenance of the stockpile, the accumulation of public health costs due to excess cases and political costs associated with unmet vaccine needs, and all the inputs determining the flows (e.g., the different wastage rates that determine loss out-flows).

This model helps create a common platform for discussions among the various stakeholders and decision makers who must ultimately design and implement the stockpile. There is demonstrated with a simple example that optimization may lead to useful results in terms of the ordering strategy that minimizes the present value of public health and vaccine costs, although I emphasize that these hypothetical results depend on simplifying assumptions in the stockpile and model.

There is the need to address various issues in order to fully optimize the stockpile in the context of all its complexities described below:

- The technical details of the stockpile, such as capacity constraints and delays in the production and expiry processes, impact the dynamics within the supply chain and require careful consideration.
- The relationships between vaccine production risks and vaccine demand as well as between vaccine demand and financial constraints lead to additional feedback loops that merit further exploration.
- The perspective impacts the objectives and therefore the optimal policy for a stockpile.
- The vaccine demand is inherently stochastic, which implies some probability of unmet vaccine needs even for a very large stockpile.

4 Conclusions

Due to interruptions in the vaccine supply chain, vaccine shortage and low immunization coverage, some epidemics still occur in many countries in the world. If even some block of population won't be vaccinated against hazard viruses or the herd immunity will be insufficient in the epidemic case, the virus or epidemic will continue spreading among susceptible population till the pandemic cases. The great solution here is to immunize all children by recommended routine in every country. So in this case deciding the problems related with vaccine supply is actual nowadays to provide countries with enough number of doses.

There are have been used many variety of approaches in order to understand supply chain management problems in vaccine. But they have acknowledged shortages. Therefore to better understand vaccine supply chain problems and to generate insights that may increase the immunization coverage effectiveness, help to avoid vaccine stockpile shortages and diminish wastage, this project applied system dynamics modeling and field study research methods.

In this paper, we used System Dynamics and simulation to model and analyze the role of efficient and effective supply chain management in delivering the wide ranging benefits of immunization.

A set of important attributes that must be considered when deciding the number of doses for replenishing the pediatric vaccine stockpiles is analyzed by simulating the flow diagram model using system dynamics tool. A set of utility functions is also proposed, based on the knowledge of the vaccine supply chain.

References

[1] Antoinette, Sudeep S, Hintlian J, Chen K 2015 Robust Supply Chains Could Help Pave http://www.bioprocessintl.com/manufacturing/ vaccines/ special-report-path-vaccine-profitability/

[2] Jatvani A 2012 Transforming Vaccine Supply Chain with investments in IT http://www.infosys.com/ SAP/ thought-leadership /Documents /vaccines-supply-chain.pdf

[3] Shahanaghi K, Yazdian S.A 2009 Analyzing the effects of implementation of Total Productive Maintenance (TPM) in the manufacturing companies: a system dynamics approach *World Journal of Modelling and Simulation* 5(2) 120-129

Author

Arman Kussainov, 1991, Almaty, Kazakhstan.

Current position, grades: Master student in Kazakh-British Technical University, Almaty.
University studies: BSc in information systems Kazakh-British Technical University, Almaty, 2013.
Scientific interest: fuzzy logic, system dynamics, cloud computing.