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A systems approach to vaccine decision making

Bruce Y. Lee *, Leslie E. Mueller, Carla G. Tilchin

Public Health Computational and Operations Research (PHICOR), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

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ABSTRACT

Vaccines reside in a complex multiscale system that includes biological, clinical, behavioral, social, operational, environmental, and economical relationships. Not accounting for these systems when making decisions about vaccines can result in changes that have little effect rather than solutions, lead to unsustainable solutions, miss indirect (e.g., secondary, tertiary, and beyond) effects, cause unintended consequences, and lead to wasted time, effort, and resources. Mathematical and computational modeling can help better understand and address complex systems by representing all or most of the components, relationships, and processes. Such models can serve as "virtual laboratories" to examine how a system operates and test the effects of different changes within the system. Here are ten lessons learned from using computational models to bring more of a systems approach to vaccine decision making: (i) traditional single measure approaches may overlook opportunities; (ii) there is complex interplay among many vaccine, population, and disease characteristics; (iii) accounting for perspective can identify synergies; (iv) the distribution system should not be overlooked; (v) target population choice can have secondary and tertiary effects; (vi) potentially overlooked characteristics can be important; (vii) characteristics of one vaccine can affect other vaccines; (viii) the broader impact of vaccines is complex; (ix) vaccine administration extends beyond the provider level; and (x) the value of vaccines is dynamic.

1. Introduction

Vaccines reside in a complex multiscale system that includes biological, clinical, behavioral, social, operational, environmental, and economical relationships (Fig. 1). Not accounting for these systems when making decisions about vaccines can result in "band-aids" rather than solutions, i.e., making changes that don't have a real or sustainable effect or making less than optimal changes but not solving the underlying issues. Even if a solution is provided, it may be unsustainable. Additionally, overlooking the systems may miss indirect (e.g., secondary, tertiary, and beyond) effects of a vaccine. In fact, without understanding the system, even well-meaning efforts can lead to unintended consequences. Finally, not understanding the relevant systems can lead to wasted time, effort, and resources when developing and implementing vaccines and vaccination programs.

A system consists of various interconnected components that interact with and affect one another, though they may appear independent. Many natural and human-made systems exist throughout the universe (e.g., ecosystems, air traffic control, meteorology), making few things truly independent and nearly everything part of a system. Altering a single aspect of a system tends to affect other parts of the interconnected system, often in complex ways. Therefore, unless all aspects of the system are taken into account, unexpected results may occur with changes.

A systems approach involves understanding, considering, and addressing the entire system when making any important decision, observation, or change. Some changes that may appear inconsequential may have lasting significant effects. The critical first step of a systems approach is to outline an overall picture of the entire system. However, understanding a complex system with many components may be difficult. Direct and immediate one-way cause-and-effect relationships may be easy to identify, while other effects (e.g., involving intermediaries, back-and-forth interactions, delays) may not be perceived at once.

Mathematical and computational modeling can help better understand and address complex systems by representing all or most of the components, relationships, and processes. Such models can serve as "virtual laboratories" to examine how a system operates and test the effects of different changes within the system in many settings [1–41]. An example of computational modeling is air traffic control systems. An air traffic control system takes data

* Corresponding author at: Department of International Health, Global Obesity Prevention Center (GOPC), International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health, 855 N. Wolfe St., Suite 600, Baltimore, MD 21205, United States.

E-mail address: brucelee@jhu.edu (B.Y. Lee).

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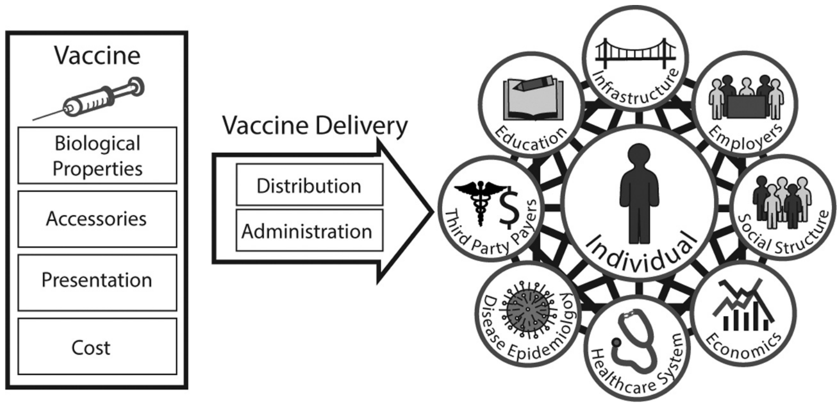

Fig. 1. Many lessons can be learned by using a systems approach to vaccine decision making.

and information from different sources (e.g., weather, environmental, runway capacity, and plane location data) and uses a computational simulation model to represent each component and process in the system, integrating everything and allowing air traffic controllers to view the system as a whole to make appropriate decisions. Without air traffic control computational systems, diagnosing system vulnerabilities, coordinating operations, developing solutions, and anticipating the impact of changes in the system or new technology would be considerably more difficult. The simulation model can anticipate consequences so that appropriate real life changes can be made (e.g., if airplanes need to alter their courses to avoid heavy traffic or storm systems). Similarly, taking a systems approach to vaccines can aid manufacturers, policymakers, and NGOs to make appropriate decisions for vaccines. Computational systems modeling for vaccines takes into account the interactions between economic modeling, biological and transmission modeling, clinical outcomes modeling, and logistics modeling. Here are ten examples of lessons learned from using computational models to take a more systems approach to vaccine decision making.

2. Ten lessons learned

2.1. Lesson 1: traditional single (or limited) measure approaches may overlook opportunities

Using a single or only a few measures to assess the burden of a disease or the impact of an intervention can lead to substantial over- or under-estimates. One example is Chagas disease, which has traditionally been considered a neglected tropical disease primarily affecting Latin America, which in turn may have kept development of a vaccine for Chagas disease lower on the global priority list. The challenge is that the clinical effects of Chagas disease do not even begin manifesting until over a decade after infection has occurred, meaning that traditional measures such as short term mortality and immediate direct medical costs will capture little of its impact [42–44]. Instead, accounting for the full spectrum of effects requires looking further into the future and incorporating future morbidity measures and productivity losses. Moreover, focusing only on Latin America overlooks other parts of the world that are affected such as North America and Europe. When using a computational model developed by the Public Health Computational and Operations Research (PHICOR) team that accounted for the downstream clinical sequalae such as congestive heart failure, future productivity losses, and other parts of the world, the annual global cost ($7.2 billion) of Chagas disease exceeds that of both cervical cancer and rotavirus [17,45].

With Chagas resulting in considerable costs throughout a patient's lifetime, it is not surprising that a vaccine to prevent *Trypanosoma cruzi* (which causes Chagas disease) infection would be highly cost-effective if the cost was less than or equal to $200 and even cost savings if the vaccine cost was $20, both with efficacy $\geqslant$ 75%, even if the infection risk was as low as 5%, based on computational modeling studies [18]. Therefore, not accounting for future morbidity and mortality and productivity losses may have severely underestimated the value of a *Trypanosoma cruzi* vaccine.

2.2. Lesson 2: complex interplay among many vaccine, population, and disease characteristics

The characteristics of a vaccine (e.g., biological and physical properties), target population, pathogen, and disease are all interwoven so that changing one can affect the others. For instance, a computational model developed by PHICOR shows how varying the cost, efficacy, and duration of protection for a potential norovirus vaccine interact with each other and affect the potential impact on different age groups [7]. A 75% efficacious vaccine would annually prevent 6,125 cases per 10,000 vaccines among children 0–4 years old. Decreasing efficacy to 25% would then reduce the number of cases prevented to only 2,036 cases (0–4 years old, 48 months protection) per 10,000 vaccines given. In an older age group (15–44 years old), the vaccine with 25% efficacy only prevented 100 cases per 10,000 vaccines administered with 12 months protection. Cost savings across all efficacies can also occur when administered to children under 5 years old provided that the vaccine cost is $\leqslant$$25 (Fig. 2). More expensive vaccines can also have cost savings, but need higher efficacy and longer periods of protection [7]. By taking into account these vaccine, population, and disease characteristics, human norovirus vaccine developers can be advised as to the necessary parameters for maximum population benefit.

2.3. Lesson 3: accounting for perspective can identify synergies

Different decision makers have different interests and therefore will respond to different measures and perspectives. For example, employers may be most interested in how a vaccine may affect their profits (revenues minus costs). Therefore, demonstrating that an influenza vaccine is cost-effective to society or third party payers may not convince employers to pay for or offer vaccination. However, showing how an influenza vaccine can save productivity losses with employees missing fewer days of work can be compelling. A computational model developed by PHICOR showed that employer sponsored influenza vaccination is inexpensive