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The 2009 H1N1 influenza pandemic

A case study of how modeling can assist all stages of vaccine decision-making

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During the 2009 H1N1 influenza pandemic nearly every decision associated with new vaccine development and dissemination occurred from the Spring of 2009, when the novel virus first emerged, to the Fall of 2009, when the new vaccines started reaching the thighs, arms and noses of vaccinees. In many ways, 2009 served as a crash course on how mathematical and computational modeling can assist all aspects of vaccine decision-making. Modeling influenced pandemic vaccine decision-making, but not to its fullest potential. The 2009 H1N1 pandemic demonstrated that modeling can help answer questions about new vaccine development, distribution, and administration such as (1) is a vaccine needed, (2) what characteristics should the vaccine have, (3) how should the vaccine be distributed, (4) who should receive the vaccine and in what order and (5) when should vaccination be discontinued? There is no need to wait for another pandemic to enhance the role of modeling, as new vaccine candidates for a variety of infectious diseases are emerging every year. Greater communication between decision makers and modelers can expand the use of modeling in vaccine decision-making to the benefit of all vaccine stakeholders and health around the globe.

Key words: influenza, H1N1, vaccine, modeling, pandemic, vaccine development, vaccine distribution, vaccine administration

Abbreviations: MIDAS, Models of Infectious Disease Agent Study; ASPR, Assistant Secretary for Preparedness and Response; BARDA, Biomedical Advanced Research and Development Authority; DHS, Department of Homeland Security; CDC, US Centers for Disease Control and Prevention; ACIP, Advisory Committee on Immunization Practices; FDA, US Food and Drug Administration; WHO, World Health Organization; NIH, National Institute of Health

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Introduction

The 2009 H1N1 influenza pandemic fast-forwarded the new vaccine development, production, distribution and administration time-line from multiple years to less than half a year. Nearly every decision associated with new vaccine development and dissemination occurred from the Spring of 2009, when the novel virus first emerged, to the Fall of 2009, when the new vaccines started reaching the population (**Table 1**). Prior influenza pandemics (i.e., 1918, 1957 and 1968) over the past century did not have available the mathematical and computational modeling expertise and techniques that we have today. In many ways 2009 served as a crash course on how modeling can assist all aspects of vaccine decision-making.

The circumstances were ripe for the use of modeling: complex decisions with far-reaching implications, multiple stakeholders, time and practical constraints precluding traditional epidemiologic and clinical studies, and the world's eyes watching every step. Modeling has been a mainstay of decision-making in other industries (e.g., weather forecasting, stock and options pricing, transportation planning, manufacturing, natural resource exploration and aeronautical engineering) for years. In fact, vaccine decision-making may be ideally suited for modeling: retrospective data are often limited, prospective studies are difficult and in some cases impossible to perform, and decisions are complex with wide reverberations. Vaccine decisions cross a wide variety of disciplines and involve an array of people and resources.

The 2009 H1N1 pandemic also introduced much of the public to influenza modeling, as articles in newspapers and magazines described the ongoing influenza modeling activities. Modeling is the

Table 1. 2009–2010 H1N1 influenza pandemic timeline

H1N1 influenza timeline		H1N1 Vaccine timeline
	2009	
• CDC: respiratory samples from 3 children unsubtypable *influenza* A • First "swine" flu-attributable death occurs (Oaxaca, Mexico)	**April**	
• >10,000 cases reported worldwide • >98% of probable influenza cases testing positive for 2009 H1N1 • 2009 H1N1 virus isolated and identified as novel	**May**	• Vaccine development begins
• WHO declares pandemic (June 11)	**June**	• Planning for vaccine distribution and administration
	July	• Ongoing vaccine development, testing, production & planning for rollout
	August	• NIH initiates clinical trials to determine vaccine safety and immunogenicity • ACIP releases recommendations for vaccine prioritization
	September	• 4 vaccines against 2009 H1N1 influenza approved by FDA • Healthy adults and older children found to need 1 dose of vaccine to generate strong immune response; children under 9 need two doses
• Influenza activity peaks the second week of the month	**October**	• 3 million doses of nasal spray are the first vaccine ready for distribution • 14.1 million doses are available by the end of October
• CDC estimates H1N1 deaths among children and teens >500 • Flu activity begins to decline late in the month	**November**	• FDA approves a 5th vaccine against 2009 H1N1 influenza • FDA authorizes an additional vaccine for use among infants and children • 1 dose of vaccine is found to elicit a strong immune response among pregnant women • >61 million doses of vaccine available by the end of the month
• The number of states reporting widespread flu activity continues to decline	**December**	• >93 million doses of vaccine are available • Vaccination efforts expanded to the general public
	2010	
	January	
	February	• FDA and WHO recommend that 2009 H1N1 be included in the 2010–2011 seasonal influenza vaccine • ACIP recommends that all people >6 months of age receive yearly seasonal influenza vaccination • Early vaccine expiration dates approaching
	March	
• Increased number of cases and hospitalizations in the southeastern United States	**April**	• >80 million people vaccinated
	May	
• Southern Hemisphere reports of influenza A H3N2 and Northern Hemisphere reports of influenza B viral circulation exceed cases of 2009 H1N1	**June**	
	July	
• WHO cancels pandemic declaration (August 10)	**August**	

use of mathematical or computational equations to represent decisions, phenomena, and processes. Models can range from decision trees portraying the steps and options comprising a decision to large-scale agent-based models that simulate the people, locations and activities in a geographic region such as Allegheny County, the Washington, DC metropolitan region, the state of Pennsylvania, or the United States.[1-5]

Modeling did influence 2009 pandemic vaccine decision-making. During the pandemic, our modeling team from the University of Pittsburgh Models of Infectious Disease Agent Study (MIDAS) National Center of Excellence worked closely with the Office of the Assistant Secretary for Preparedness and Response (ASPR) at the US Department of Health and Human Services. This included being "embedded" in Biomedical Advanced Research and Development Authority (BARDA) offices for over two months. We also worked with the Department of Homeland Security (DHS) and Centers for Disease Control and Prevention (CDC) as well as public health officials in the State of Pennsylvania and the Allegheny County Health Department. Much of our work involved exploring different vaccination scenarios to assist decision-making.

Did modeling contribute to its fullest potential to vaccine decision-making during the H1N1 pandemic? The answer is a resounding no. Previous work on H5N1 avian influenza may have influenced opinions; some stakeholders, such as manufacturers, may have relied on internal models; and as mentioned above, some modelers worked directly with public health officials.[6-9] However, the majority of decisions that could have or even should have benefited from modeling did not. While decision makers in many industries would not think of proceeding without reviewing model results (imagine launching the space shuttle, tracking a hurricane, or making a major investment decision without a model), the public health and biomedical arenas have not yet embraced modeling with the same fervor. What follows is a chronicle of the types of vaccine decisions encountered during the 2009 H1N1 pandemic and how modeling helped or could have helped.

Questions Facing New Vaccines

Is a vaccine needed? When the novel H1N1 influenza virus emerged, one of the first decisions was whether developing a vaccine would even be needed or useful. For nearly any infectious disease, modeling can help forecast the value of a potential vaccine by estimating the morbidity, mortality, and economic burden of the disease and determining whether a vaccine could better mitigate the disease than other existing measures.[8,10] Outbreaks that are too small or too rapid may not benefit from a vaccine. Also, other pharmaceutical (e.g., antivirals) or non-pharmaceutical interventions (e.g., social distancing measures) may be alternatives.

It is unclear to what degree decision makers relied on previous H5N1 and concurrent H1N1 model results when giving the green-light to develop H1N1 vaccines. Regardless, model explorations supported development by demonstrating the value of an H1N1 vaccine over that of other potential strategies. For example, school closures alone may not have a noticeable impact unless maintained strictly for a long period of time (at least eight weeks). In fact, short-term (one or two week) school closures have the potential to worsen an epidemic by re-releasing susceptible schoolchildren back to schools in the middle of the epidemic.[3] Similarly, while antiviral medications could be helpful, models suggest that they would have done little to quell the epidemic as an isolated intervention.[11,12]

Lesson for future vaccine decision-making. Models can help investigators, policy makers, investors, and manufacturers decide whether to pursue developing a vaccine.

What characteristics should the vaccine have? Following the go-ahead to develop and manufacture a vaccine, questions about its target characteristics emerged. How efficacious does the vaccine need to be to quell the epidemic and to be worthwhile? How many doses should each individual receive? What price points would be reasonable? What side effect probabilities would be acceptable? Modeling can help forecast the impact of varying different vaccine candidate characteristics, set targets and thresholds for these characteristics, and in turn, guide development and prepare a vaccine candidate for the market.[1,13,14] Some stakeholders (e.g., manufacturers) may have used modeling to help establish target characteristics and facilitated price negotiations for the H1N1 vaccine, but most of this modeling was internal and did not enter public discussions.

Lesson for future vaccine decision-making. Constructing models early in development, when a vaccine's characteristics can still be altered, can enhance its chances of success. Such modeling could have helped some past vaccine candidates (e.g., FluMist vaccine against influenza and LYMErix vaccine against Lyme Disease) avoid obstacles that they encountered once they reached the market.[15]

How should the vaccine be distributed? Since a vaccine has to reach vaccinees to work, setting up an effective vaccine supply chain (the series of steps required to get a vaccine from the manufacturers to patients) is essential. The design and operation of a supply chain determines when the population is actually immunized. The timing of immunization can greatly impact an individual's and a population's risk of disease, especially during an epidemic.[16-18] Even a perfect vaccine can do little if it does not reach people.[15]

Because vaccine distribution can be quite complex, modeling may be one of the few methods available to predict the costs and effects of different strategies. Prospective studies can be costly and time consuming. There are too many variables to simply think through the problem or rely on gut instincts. Models essentially make decision-making transparent and place it "on the table" for others to see, comment, and adjust. Distribution companies such as McKesson, which helped handle the H1N1 vaccines, already utilize models extensively to plan their operations. Logistics experts for vaccine manufacturers often utilize models as well. However, other vaccine decision makers (e.g., public health officials and scientists) may not be using vaccine distribution

models as much as they should. The public health and biomedical literature certainly could use more vaccine distribution modeling studies.

Lesson for future vaccine decision-making. Not all vaccine decision makers are fully utilizing models to inform vaccine distribution decisions.

Who should receive the vaccine and in what order? The vaccine became available in limited quantities in October 2009, necessitating initial rationing. Public health officials had to select the initial target populations and the order in which people would receive the vaccine. Should immunization be "first come first served"? Alternatively, should children, older adults, health care workers, pregnant women, or other higher-risk individuals receive vaccine first?[4,19] Once an immunization order is established, how strictly should this be followed? In late August 2009, the Advisory Committee on Immunization Practices (ACIP) released its recommendations for the use of the 2009 H1N1 vaccine, based on reviewing the literature and expert opinion.[20] Subsequently, our work with ASPR included evaluating different vaccine prioritization strategies and determining the effects of varying compliance to each of these strategies.[5] Ultimately, model results favored early allocation to ACIP priority groups (versus other strategies). In the future, perhaps modeling could more actively assist expert panels, such as the ACIP, when formulating initial recommendations.

Lesson for future vaccine decision-making. Because vaccinating an entire population may not be possible or indicated, models can help identify and prioritize the vaccine's target populations.

When should vaccination be discontinued? As the pandemic approached its peak in October 2009 when vaccines first became available, the next question was whether continuing vaccination was worthwhile. Some questioned the utility of mass vaccinating a population that had already been widely exposed to natural infection. Would immunization have much effect when the pandemic seemed to have already run its course? Could there be a subsequent upsurge in the pandemic without vaccination?[21] Our explorations with ASPR supported continuing the immunization program by demonstrating how it could prevent a third pandemic wave (with the first two waves occurring in the Spring and Fall of 2009) from emerging in early 2010.[18]

Lesson for future vaccine decision-making. Once a vaccine is available, the epidemiology of an infectious disease may change. Models can help determine whether a vaccine and vaccination strategy need updating.

Expanding the Role of Modeling

As the 2009 H1N1 pandemic demonstrated, there are many opportunities for modeling to facilitate vaccine decision-making. Decision makers and modelers capitalized on some of these opportunities, but also missed many of them. So, how can the role of modeling in vaccine decision-making be expanded in the future, both in epidemic and non-epidemic settings? Decision makers and modelers could do following:

Decision makers: understand what models can and cannot do. Modelers: be better at communicating what models can and cannot do. The underuse or misuse of models often arises from a misunderstanding of the purpose of models. Models are simplifications, not replicas of real life; models can assist but should not make decisions. Modeling helps people better understand their own and others' decision-making processes by bringing them out into the open for everyone to view. Even the most brilliant and experienced minds cannot account for every factor in a complex decision the way that models can. Models are best at identifying important relationships, key factors in a decision, important questions and information that needs to be gathered. Anyone expecting models to give exact predictions, completely mimic real life, or represent every possible eventuality will be sorely disappointed.

Modelers: be as transparent as possible about models. Decision makers: give modelers the opportunity to fully explain their models. Models should not be "magic boxes" that spew out results. Without understanding a model's structure and parts, decision makers should neither implicitly trust nor disregard a model. Therefore, clear written and oral communication between decision makers and modelers is essential. Modelers must clearly state the advantages, disadvantages, assumptions and limitations of their models.

Decision makers: understand that all models are not the same and the value of multiple models addressing the same question. Modelers: encourage questions and competing models. Would you ever rely on a single retrospective or prospective study to make decisions? Should encountering a poorly constructed clinical study mean you should disregard all clinical studies? Similarly, no model is perfect—every model has its strengths and weaknesses. There is a wide range in model quality and comprehensiveness. Therefore, having different modelers and models tackle the same question can provide valuable insights. Comparing and revealing the differences among various models can be enlightening, similar to bringing multiple experts to the decision-making table.

Modelers: fully understand the important questions and the accompanying circumstances. Decision makers: tell modelers what questions are relevant. Models should reflect relevant decisions and incorporate important factors. Therefore, modelers should either be or work closely with subject matter experts. Otherwise, the model may be too conceptual or unrealistic and therefore be of limited value to decision makers.

Modelers: keep models as simple as possible. Decision makers: communicate which details matter and why. Models should only be as complex as needed. The purpose of modeling is to distill a decision down to its most important components and relationships. Adding unnecessary detail to a model only clouds the picture.

Decision makers: understand that all decisions can be modeled. Modelers: show how each decision can be modeled. When each of us makes a decision, we consciously or subconsciously model the decision in our heads. Even instinctual decisions are the result of rapidly operating internal mental models built from years of experience. If you can think it, you can model it.

Decision makers: help provide or find data for models. Modelers: clearly identify data needs. The 2009 pandemic modeling efforts revealed some important data gaps. No one knew the current status of the pandemic. At a given point in time, was the pandemic waxing or waning, near or far from its peak? How many people had been infected? What percentage of the infected individuals exhibited symptoms? Models were highly sensitive to this information. A vaccination program early in a pandemic would be much more effective than one late in the pandemic. This underscored the need for a national close-to-real time serologic surveillance program.

Decision makers and modelers: communicate and understand each other. Open communication is key. Modelers need to present their models and results in formats that are easily understandable and digestible by decision makers. During our H1N1 work with public health officials, we found that more traditional scientific graphs and charts were not always effective in communicating results. We had to speak the "language" of decision makers. Therefore, a substantial part of our efforts was devising better ways to convey our work (e.g., visualizations). At the same time, it is helpful for modelers to know what decision makers are thinking.

Conclusions

As the 2009 H1N1 pandemic demonstrated, modeling is a potentially powerful methodology that is currently underutilized (and in some cases mis-utilized) in vaccine decision-making. If used appropriately, modeling could benefit nearly every decision in new vaccine development, distribution and administration. There is certainly no need to wait for another pandemic to enhance the role of modeling, as new vaccine candidates for a variety of infectious diseases are emerging every year. Greater communication between decision makers and modelers can expand the use of modeling in vaccine decision-making to the benefit of all vaccine stakeholders and global health.

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