Improving Pandemic Response: Employing Mathematical Modeling to Confront COVID-19

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Summary: Modeling has informed public health decision making and policy development throughout the COVID-19 response. CDC has launched the Infectious Disease Modeling and Analytics Initiative to continue to enhance the use of modeling during public health emergencies.

Abstract: Modeling complements surveillance data to inform COVID-19 public health decision making and policy development. This includes the use of modeling to improve situational awareness, to assess epidemiological characteristics, and to inform the evidence base for prevention strategies. To enhance modeling utility in future public health emergencies, the Centers for Disease Control and Prevention (CDC) launched the Infectious Disease Modeling and Analytics Initiative. The initiative objectives are to: (1) strengthen leadership in infectious disease modeling, epidemic forecasting, and advanced analytic work; (2) build and cultivate a community of skilled modeling and analytics practitioners and consumers across CDC; (3) strengthen and support internal and external applied modeling and analytic work; and, (4) working with partners, coordinate government-wide advanced data modeling and analytics for infectious diseases. These efforts are critical to help prepare CDC, the country, and the world to respond effectively to present and future infectious disease threats.

Keywords: modeling, COVID-19, pandemic, forecasting, public health

When urgent public health decisions are needed and data are limited, mathematical modeling offers opportunities to combine data from multiple sources, assess critical uncertainties and needs, and inform decisions. The Centers for Disease Control and Prevention (CDC) has used mathematical modeling to inform public health practice for emerging infectious diseases for many years, working in collaboration with partners in other government agencies, academia, and the private sector. During the 2009 H1N1 pandemic, CDC utilized mathematical modeling to estimate the transmissibly and clinical severity of the pandemic virus in order to inform strategies to help slow transmission [1-3]. During the 2014–16 Ebola virus disease epidemic in West Africa, CDC utilized modeling to estimate the potential impacts of an epidemic with and without changes in interventions or human behavior and of a delayed public health response [4, 5]. In the 2016-2017 epidemic of Zika virus in the Americas, modeling provided critical early insights on the risk of microcephaly [6]. Outside of major public health emergency responses, CDC has utilized modeling to help inform human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) prevention approaches and to inform prevention of the spread of antimicrobial resistant organisms [7, 8]. CDC has also led collaborative work to advance operational epidemic forecasting, working with the academic and private sector modeling communities to improve the accuracy and usability of forecasts of seasonal influenza, dengue, the spatiotemporal distribution of *Aedes* mosquitoes, and West Nile virus—in addition to other infectious diseases [9].

In collaboration with academic, private sector, and U.S. government modeling partners, CDC rapidly built upon this modeling experience to support CDC's COVID-19 response efforts. Modeling has utilized epidemiological and laboratory data to inform public health decision making and policy development throughout the response. This includes the use of modeling to improve situational awareness, to synthesize and assess epidemiological characteristics that were important for understanding the use and impact of mitigation measures, and to inform the evidence base for mitigation strategies (Table 1). Here, we discuss specific examples from the CDC COVID-19 response to highlight the contribution and utility of modeling to the CDC and its federal, state, and local public health partners.

One of the critical components of public health planning is assessing current patterns and anticipating future trends in the COVID-19 pandemic to inform risk assessment, resource allocation, and healthcare preparedness. Building on previous forecasting work for influenza and vector-borne diseases, CDC partnered with the University of Massachusetts Amherst to create the COVID-19 Forecast Hub in April 2020 [10, 11]. The Hub, a forecast data repository, brings together forecasts from multiple external groups that predicted weekly numbers of new and total COVID-19 deaths (national and state/territory-level); daily numbers of new COVID-19 hospitalizations (national and state/territory-level); and weekly numbers of new COVID-19 cases (national, state-/territory-, and county-level). These forecasts provide estimates of prediction uncertainty, which allows policy makers to assess the most likely and plausible best- and worst-case scenarios. This approach, conducted on an unprecedented scale in public health for COVID-19, encourages the open participation and evaluation of forecasting approaches that utilized different types of data, methods, and assumptions about the future impacts of interventions. The Hub enables open access to all of these forecasts in a standardized format to support comparison and assessment of forecasts for both research and applied purposes [10].

In addition to enabling comparison of multiple individual forecasts, this approach allows for the combination of the individual forecasts into location-specific ensemble (or aggregate) forecasts [10, 12]. The use of ensembles during previous infectious disease outbreaks has been shown to improve forecast accuracy and reliability [13, 14], and the ensemble was found to consistently be the most accurate forecast among 23 models that regularly submitted weekly incident COVID-19 mortality forecasts at the state and national level [15]. The ensemble was used to inform key communication points for public health officials, policy makers, and the general public on the potential short-term impact of the pandemic. For example, based on forecasts received November 23, 2020, when approximately 10,000 weekly new deaths were reported, the ensembles for new deaths predicted that the number of newly reported COVID-19 deaths in the U.S. would likely increase over the next month; the ensembles estimated that 10,600 to 21,400 new deaths would likely be reported the week ending December 19, 2020. Subsequently, approximately 18,000 new deaths were reported that week [16]. In addition to providing situational awareness in real-time, the repository of forecasts collected by this initiative provides a rich dataset to help inform future forecast development, including comparing the accuracy of different modeling or forecast combination approaches and assessing forecast accuracy over differing time horizons and during phases of epidemic growth or decline [10].

The emergence of the SARS-CoV-2 variant B.1.1.7 in the United Kingdom drove an early assessment of its potential impact on the future trajectory of the pandemic in the United States beyond the horizon of short-term forecasts [17]. This study demonstrated that B.1.1.7 had the potential to exhibit rapid growth in early 2021 and become the predominant SARS-CoV-2 variant in March 2021 and that enhanced genomic surveillance combined with continued implementation of effective public health measures (including vaccination and physical distancing) would be essential to limit the impact of B.1.1.7. At the time of the study, B.1.1.7 represented about 1% of U.S. infections during the 2-week period ending January 30, 2021, but this increased to 66.0% during the

2-week period ending April 24, 2021. This rapid expansion was consistent with the prediction that B.1.1.7 would become the predominant variant [18].

Assessing epidemiological characteristics of COVID-19 to inform the consideration of different control and mitigation strategies was another crucial need early in the COVID-19 response. Modeling contributed critical information to these efforts since early studies of new or emerging infectious diseases tend to be biased; only a subset of cases, typically the most severe, are initially identified [19]. In addition, many key epidemiological characteristics are difficult to directly quantify or assess during interventions because of challenges or ethical concerns in implementing appropriately controlled studies during an evolving pandemic. For example, the proportion of transmission from individuals who do not have symptoms at the time of transmission to a susceptible person cannot be estimated without rigorous, large-scale testing of symptomatic and asymptomatic individuals. Nonetheless, the impact of asymptomatic transmission on control efforts is of key importance for the public health response to COVID-19 and for determining the relative role of symptom monitoring and laboratory testing of persons with and without symptoms of COVID-19. To address this, the CDC Modeling Team developed a model that estimated that at least 50% of SARS-CoV-2 transmission likely occurred from persons who were asymptomatic at the time of transmission, despite the remaining uncertainty about underlying characteristics [20]. This meant that effective control of SARS-CoV-2 could not be accomplished solely by reducing transmission from people with symptoms.

The CDC Modeling Team also quantified the uncertainty in important characteristics of the natural history of COVID-19—including the infectious period, test-positivity relative to time of infection, transmission timing, and test sensitivity— to help inform the balance between strategies to improve quarantine adherence and those requiring maximal duration of quarantine while minimizing transmission risk [21, 22]. These analyses showed that reducing the quarantine period from 14 to 10 days would significantly improve adherence to quarantine—which would greatly reduce, but not eliminate, post-quarantine transmission risk. Also, testing at the end of quarantine could facilitate further reductions in the duration of quarantine (7 days). These analyses also indicated that contact tracing needed to occur within 5 days of exposure to an index case to achieve the greatest reductions in transmission and that there would be little benefit when close contacts were reached ≥6.5 days after exposure. These findings helped health departments prioritize case investigation based on the time interval from exposure to improve efficiency of contact tracing. This analysis rapidly provided insight at a time when public health resources were stretched thin and case follow-up investigations had to be prioritized since high proportions of untraced contacts and low rates of timely recruitment into contact tracing substantially lowered the effectiveness of contact tracing as a mitigation strategy [22].

Evaluations of larger-scale intervention strategies, including community reopening policies, were also critically needed. The CDC Modeling Team collaborated with multiple academic groups to evaluate the potential impact of different reopening strategies in a simulated population [23]. The evaluated strategies included: (1) closure throughout the 6-month prediction period, (2) re-opening when cases decline below 5 percent of the peak daily caseload, (3) re-opening two weeks after peak daily caseload, and (4) immediate re-opening. This unique collaboration concluded that complete cessation of community spread of the disease was unlikely with any of these re-opening strategies and that either additional stay-at-home orders or other interventions (e.g., testing, contact tracing and isolation, wearing masks) would be needed to reduce transmission while allowing workplace re-opening. This finding provided strong, timely evidence that control of the COVID-19 pandemic would require a balance of selected closure policies with other mitigation strategies to limit health impacts.

To assess the tradeoffs between vaccination coverage and decreased adherence of non-pharmaceutical interventions (NPI) as vaccination coverage increased in the U.S., the CDC Modeling Team collaborated with the COVID-19 Scenario Modeling Hub to use a multiple-model approach to compare the potential course of COVID-19 over a 6-month period across four different modeling scenarios with higher and lower rates of COVID-19 vaccination and NPI adherence [24]. The modeling results indicated that even moderate reductions in NPI adherence could undermine vaccination-related gains during the subsequent 2–3 months and that decreased NPI adherence, in combination with increased transmissibility of some SARS-CoV-2 variants, was projected to lead to surges in hospitalizations and deaths. These findings reinforced the need for continued public health messaging to encourage vaccination and the effective use of NPIs to prevent future increases in COVID-19.

The use of interventions to prevent outbreaks in congregate-care settings were of particular importance because a disproportionate number of deaths occurred among residents of these facilities [24, 25]. Strategies specific to these settings were needed to guide prevention and control efforts. The CDC Modeling Team evaluated testing strategies for preventing SARS-CoV-2 transmission in nursing homes with and without the presence of known cases [25, 26]. These analyses found that testing in response to an outbreak could be an effective approach to preventing SARS-CoV-2 transmission in nursing homes. These analyses were later extended to evaluate the potential impact of testing and vaccination strategies focused on nursing homes residents and healthcare providers, indicating a continued need for SARS-CoV-2 prevention activities even after COVID-19 vaccination begins in these facilities[27]. Modeling also provided critical information to update healthcare infection prevention and control recommendations in response to COVID-19 vaccination in nursing homes (e.g., updating indoor visitation policies) [28, 29].

Vaccines are a critical tool to control the pandemic, but the U.S. supply was not always sufficient for universal vaccination and future patterns of disease transmission are uncertain. In addition, in the early months of vaccine development, there was substantial uncertainty about vaccine efficacy (especially prior to final results of clinical trials), whether efficacy for prevention of disease would translate into prevention of mild illness or asymptomatic infection and transmission from those without apparent illness, variation in efficacy by age, and timing of vaccine availability. The CDC Modeling Team worked in collaboration with the Advisory Committee on Immunization Practices (ACIP) to evaluate different strategies for the initial prioritization of vaccine courses to healthcare workers, residents of long-term care facilities, older adults, essential workers, and persons with high-risk medical conditions [30]. We systematically varied uncertain parameters to assess their impact in each scenario evaluated; vaccinating older adults first averted more deaths, and vaccinating younger adults first (essential workers or younger adults with high-risk conditions) averted more infections. However, the largest single driver of vaccine impact was the timing of vaccine introduction in relation to increases in COVID-19 incidence; the earlier the vaccine is available relative to increasing transmission, the greater the impact. These results and those of other modeling studies emphasized the need for continued adherence to prevention measures before and during the vaccination campaign to maximize the impact of vaccines, while demonstrating that increasing vaccination rates may allow for the phasing out of some prevention measures as coverage increases [31].

While evaluating the evidence to support updated interim recommendations for the use of the Janssen COVID-19 vaccine in the United States following a recommended pause in its use, ACIP reviewed a risk-benefit assessment of thrombosis with thrombocytopenia syndrome (TTS) events after vaccination [32]. This assessment included a benefit analysis from the CDC Modeling Team, which estimated that Janssen COVID-19 vaccine resumption among persons aged ≥18 years at 50% of the pre-pause administration rate could prevent 3,926−9,395 COVID-19–related hospital admissions, 928−2,236 ICU admissions, and 586−1,435 deaths (depending on assumed future COVID-19 transmission levels). Based on these and other data (including the rate and characteristics of TTS cases, recent epidemiology, and data regarding whether changes to ACIP recommendations would disproportionately affect certain populations), ACIP reaffirmed its interim recommendation for the use of the Janssen COVID-19 vaccine in all persons aged ≥18 years [32].

The increased use of modeling at CDC during the COVID-19 pandemic has had some challenges, including staffing and the ability to rapidly increase support for partnerships with the external modeling community. To address these limitations, CDC has launched the Infectious Disease Modeling and Analytics Initiative (IDMAI). The objectives of this initiative are to: (1) strengthen CDC's leadership in infectious disease modeling and analytic work, (2) build and cultivate a community of skilled modeling and analytics practitioners and consumers across CDC, (3) strengthen and support internal and external applied modeling and analytic work, and, (4) working with partners, plan the interagency, government-wide coordination of advanced data management and analytics. IDMAI will work to support all stakeholder groups including federal, state, and local public health experts, infectious disease modelers, data managers, and policy makers to ensure integration into emergency response, routine public health activities, and both infectious and non-infectious diseases. Early support will establish a network of academic and governmental investigators to develop or extend models and advanced analytical methods for predicting and assessing public health threats and their prevention, building upon both pre-COVID activities and the COVID-19 activities described here. These activities will ensure the nation can continue to face the diverse challenges associated with the prevention and control of infectious and non-infectious diseases, ranging from emerging and established infectious agents to other evolving public health challenges, such as opioid addiction or e-cigarette-associated lung injury.

Modeling has been integral to the COVID-19 response. CDC built upon previous experience and forecasting networks to develop situational awareness tools that can anticipate short-term trends in COVID-19 activity at the national, state, and county level. Modeling has helped characterize critical epidemiological characteristics and illustrate the impact of those characteristics on efforts to reduce the spread of SARS-CoV-2. Finally, it has provided an evidence base for mitigation strategies by helping understand the impact of different reopening strategies and compare the impact of different vaccine allocation strategies and changes in their use. With the launch of IDMAI, CDC will strengthen the use of modeling to combat COVID-19, future pandemic threats, and other public health challenges.

Notes:

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Table 1. Key COVID-19 topics and infectious disease modeling examples

Topic	Example	Description
Situational awareness	COVID-19 Forecast Hub	The Hub, a forecast data repository, brings together forecasts from multiple external groups and creates ensembles for the predicted weekly numbers of new and total COVID-19 deaths (national and state/territory-level); daily numbers of new COVID-19 hospitalizations (national and state/territory-level); and weekly numbers of new COVID-19 cases (national, state-/territory-, and county-level) [10, 11]
	Potential impact of SARS-CoV-2 variant B.1.1.7 in the United States	This study demonstrated that B.1.1.7 had the potential to exhibit rapid growth in early 2021 and become the predominant SARS-CoV-2 variant in March 2021 [17]
Synthesize and assess key epidemiological characteristics	Assessment of the proportion of transmission from individuals who do not have symptoms	This study estimated that at least 50% of SARS-CoV-2 transmission likely occurred from persons who were asymptomatic at the time of transmission [20]
	Assessment to inform the balance between quarantine length and minimizing transmission risk	These studies quantified the uncertainty in the infectious period, test-positivity relative to time of infection, transmission timing, and test sensitivity to help inform the balance between strategies to improve quarantine adherence and prioritize contact tracing [21, 22]
Inform mitigation strategies	Evaluation of community reopening policies	This study used a multi-model approach to evaluate the potential impact of different reopening strategies in a simulated population, finding that complete cessation of community spread was unlikely [23]
	Assess the tradeoffs between vaccination coverage and decreased adherence of non-pharmaceutical interventions (NPI)	This study used a multi-model approach to compare the potential course of COVID-19 over a 6-month period across four different rates of COVID-19 vaccination and NPI adherence and found that even moderate reductions in NPI adherence could undermine vaccination-related gains during the subsequent 2–3 months [24]
	Evaluation of strategies for preventing SARS-CoV-2 transmission in nursing homes	These studies found that testing in response to an outbreak could be an effective approach to preventing SARS-CoV-2 transmission in nursing homes and that SARS-CoV-2 prevention activities were needed, even after COVID-19 vaccination began in these facilities [25-29]

	Evaluation of different strategies for the initial prioritization of vaccine courses	This study evaluated different strategies for the initial prioritization of vaccine courses, finding that vaccinating older adults first averted more deaths while and vaccinating younger adults first averted more infections [30]
	Benefit analysis for resuming Janssen COVID-19 vaccination among persons aged ≥18 years	Janssen COVID-19 vaccine resumption among persons aged ≥18 years at 50% of the pre-pause administration rate could prevent 3,926−9,395 COVID-19–related hospital admissions, 928−2,236 ICU admissions, and 586−1,435 deaths [32]