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Mathematical Modeling to Support Public Health Officials with Evaluating Immunization and Non-pharmaceutical Intervention Strategies During and Outside Periods of Outbreak Response

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DOCTORAL DISSERTATION

Title: Mathematical modeling to support public health officials with evaluating immunization and non-pharmaceutical intervention strategies during and outside periods of outbreak response

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The individual studies described in Chapters 2-4 and their associated appendices were published in peer reviewed online journals as follows. Anyone referencing the individual works should use the citations provided here.

Chapter 2:

Rainisch, G., Adhikari, B., Meltzer, M. I., & Langley, G. (2020). Estimating the impact of multiple immunization products on medically-attended respiratory syncytial virus (RSV) infections in infants. *Vaccine*, *38*(2), 251-257. https://doi.org/10.1016/j.vaccine.2019.10.023

Chapter 3:

Rainisch G, Undurraga EA, Chowell G. A dynamic modeling tool for estimating healthcare demand from the COVID19 epidemic and evaluating population-wide interventions. Int J Infect Dis. 2020 Jul;96:376-383. https://doi.org/10.1016/j.ijid.2020.05.043

Chapter 4:

Rainisch G, Jeon S, Pappas D, et al. Estimated COVID-19 Cases and Hospitalizations Averted by Case Investigation and Contact Tracing in the US. JAMA Netw Open. 2022;5(3):e224042. https://doi.org/10.1001/jamanetworkopen.2022.4042

ABSTRACT

A growing number of public health officials rely on mathematical modeling to aid in making decisions, especially during outbreak responses. Math models simulate health phenomenon with equations and are useful for forecasting a disease's progression in a population and evaluating the potential effects of interventions. We generated three models to aid practicing health officials with addressing real-world issues.

The first model estimates the impact of immunization strategies on RSV-associated lower respiratory tract infections (LRTIs) among infants <12 months. Users input RSV burden and seasonality and examine the influence of altering product efficacy and uptake assumptions. We used the model to evaluate anticipated immunization products among a US birth cohort. We estimated without immunization, 339,650 – 475,980 LRTIs are attended annually in outpatient clinics, 126,070 – 168,510 in emergency departments (EDs), and 24,760 – 42,900 in hospitals. A passive antibody candidate given to all infants prevented the most LRTIs: 48% of outpatient visits without immunization, 51% of ED visits, and 55% of hospitalizations.

Our second model creates projections of healthcare demand during the early phase of the COVID19 pandemic and evaluates the impacts of social-distancing interventions. Users input case counts, healthcare resources, and select intervention strategies. Using data from Chile, we illustrated the tool as the pandemic unfolded there in April 2020. Our scenarios indicated COVID19 patients could overwhelm hospitals by June 2020, peaking in July or August at more than 6 times the current supply of beds and ventilators. A lockdown strategy or combination of case isolation, home-quarantine, social distancing individuals >70 years, and telework interventions could keep treatment demand below capacity.

Our third model estimated the impact of COVID19 case investigation and contact tracing

programs (CICT) in the US. By inputting CICT program data from 23 jurisdictions into our

model we estimated CICT averted between 1.1 to 1.4 million cases over 60 days during the

pandemic's first winter peak. Our upper estimate assumes all interviewed cases and monitored

contacts complied with isolation and quarantine guidelines, while the lower estimate assumes

fractions of interviewed cases and contacts did so. These results suggest CICT programs played a

critical role in curtailing the pandemic.

Dedication

To my late father, Reuben Rainisch, who valued education and hard work above most other things. Teddy Roosevelt once said, 'Far and away the best prize that life has to offer is a chance to work hard at work worth doing'. My father earned this prize one hundred times over. I can imagine your smile and pride as I hand you this dissertation.

To Scott Santibanez and the late Toby Merlin, leaders of public health, who planted the idea that I was worthy of a PhD and then found a way to support that pursuit when I believed them.

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List of Abbreviations

CDC – US Centers for Disease Control and Prevention

CFR – Case Fatality Rate

CHD - Congenital heart disease

CI – 95% Confidence Interval

CICT – Case Investigation and Contact Tracing

CLDP - Chronic Lung Disease of Prematurity

ED – Emergency Department

ELC - Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases program

ICU – Intensive Care Unit

IFR – Infection Fatality Rate

MA-LRTI – Medically-attended Lower Respiratory Tract Infection

NPIs – Non-pharmaceutical Interventions

OoS – Out-of-Season birth

SEIR - Susceptible-Latent-Infectious-Recovered Compartmental Model

RSV – Respiratory Syncytial Virus

RSV I²M - RSV Immunization Impact Model

R – Reproduction Number

RM - Región Metropolitana

WiS – Within-Season birth

CHAPTER 1 – Introduction and Statement of Purpose

Public Health Officials routinely face the need to make decisions without all the desired information for doing so. For example, determining the populations that should receive newly licensed vaccine or its regimen scheduling often rely on the results from a few clinical trials which have limited generalizability to the larger population. And during the early phases of an infectious disease outbreak, officials may need to intervene before having a complete understanding of the outbreak's characteristics, for fear that substantial and preventable morbidity and mortality may occur. A growing number of public health officials are relying on mathematical modeling to assist with decision-making in the absence of desired information.

Mathematical models are descriptions of phenomenon using equations. They are imperfect abstractions of the real world that are useful for simulating how phenomenon may play out in future or studying phenomenon which can't be tested due to the expense or ethical and logistical reasons. Models permit public health officials the opportunity to manipulate aspects of a disease or response (i.e., inputs) to see their effects on health outcomes (i.e., outputs). This is known as using a model to answer "what-if" questions: "What if we did this?", or "What if this happens?". In the above examples, public health officials may use modeling to examine the effects of deploying immunizations or non-pharmaceutical intervention strategies in different ways. The results from modeling provide quantifiable results showing strategies' absolute and relative values (compared to each other). They can also use modeling to appreciate the influence of unknown or unmeasurable quantities on these estimates. Furthermore, modeling can simulate what would have happened in the absence of public health interventions, permitting evaluation of their impact on health outcomes after they've been implemented.

This dissertation's aim was to generate mathematical models that can be used by practicing

public health officials to address real-world, unfolding public health issues, and to illustrate the

models' value by using them to generate results that can inform decision-making. I pursue this

aim through three modeling studies (Chapters 2-5): 1) an examination of the impact of directly or

indirectly immunizing infants in the US against respiratory syncytial virus (RSV) infection with

anticipated[1] immunization products, 2) forecasting the healthcare demands during the early

phases of the COVID-19 pandemic and evaluating the effects of social-distancing mitigation

strategies on the forecasted trajectories, and 3) estimating the number of COVID-19 cases and

hospitalizations averted by case investigation and contact tracing (CICT) programs across the US

during the pandemic's first winter peak.

With these three models I also aim to demonstrate the value of models which embrace design

elements that make them specifically suited for use by public health practitioners in an applied

setting. While each model deals with a separate practical public health issue, all contain common

design elements that distinguish them from models used in research or for extending theoretical

knowledge of disease transmission. First, all of the models are implemented in spreadsheets

(specifically, Microsoft Excel) versus being coded in a software (e.g., R, SAS, MATLAB).

Spreadsheets are familiar to our intended audience, eliminating the need for users to buy or learn

how to use a software before they can use the model. The familiarity with spreadsheets may also

engender comfort with using the model and trust in our calculation's transparency and logic,

which our intended audience will likely find easier to follow than coded programming. This is

due to most public health officials having little formal training in modeling methods (statistical

or mathematical), and, as such, unfamiliarity often generates suspicion and caution. A second

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[1] at the time of project conception and completion of analyses

design element common to all three models is an emphasis on balancing complexity and utility: we chose the simplest useful model for answering the very specific questions that each was designed for. While no model can perfectly reflect the reality of disease dynamics in a population, models attempting to do so would necessarily require too many parameters and relationships between them to have any practical value. We chose model frameworks and made simplifying assumptions that deliberately reduced the number of required inputs and the complexity of calculations, while still maintaining disease dynamics and features of the public health response officials would deem necessary. For example, we only required users input data we expected them to be familiar with and could reasonably obtain or estimate. And all calculations dealing with tracking case-patient counts over time were executed in discrete steps (e.g., compounded per day), permitting our use of simpler algebraic math versus the need for calculus-based equations. In our efforts to simplify our models, we also chose to make them deterministic versus stochastic. That is, the inputs and parameters in our models are fixed by the user instead of allowing for stochasticity (i.e., randomness or chance) to vary them with each model run. As such, our models produce the same result each time a given set of inputs are used, permitting health officials to more readily grasp the influence each input has on their outcome of interest. But employing "simpler" deterministic models does not mean our models do not account for uncertainties inherent in modeling. On the contrary, dealing with uncertainty is a distinguishing design element of our models: In all model interfaces we emphasize for the user what is known and its source, what is unknown, and how the model deals with this absence of information. Sometimes the unknown information is estimated, in other instances we assume values based on peer-reviewed literature, and/or we allow users to use multiple values (i.e., a range) simultaneously to define unknown parameters, so that the results of the model are output as a range.

In my efforts to develop models for these studies that espouse these design elements, I faced the same methodological choices and considerations all modelers do: what type of model to use, what features of the disease, population, and response do I want to include, how do I ensure my model is "good" enough for the intended user or audience, and how do I evaluate these choices? In Chapter 5, I offer some lessons learned from examining these considerations and summarize the overall contributions and implications of these studies to their field of research.

CHAPTER 2 – Study 1: Estimating the Impact of Anticipated Immunization Products on Medically-attended Respiratory Syncytial Virus (RSV) in Infants in the US

INTRODUCTION

Globally, respiratory syncytial virus (RSV) is a leading cause of severe respiratory tract infections among young children. In 2015, there were an estimated 33.1 million acute lower respiratory tract infections, 3.2 million hospital admissions and 59,600 in-hospital deaths attributed to RSV infections (RSVi) among children <5 years of age worldwide. About 45% of RSV-associated hospitalizations and deaths occurred among children <6 months of age [1]. Each year in the United States, ~1.5 million outpatient visits, ~500,000 emergency department (ED) visits, ~58,000 hospitalizations and ~150 deaths are associated with RSVi among children under 5 years of age [2, 3]. Rates of medically-attended RSVi (MA-RSVi) in the United States are highest amongst infants <6 months of age [4, 5]. In the US and other temperate climates, RSV season generally lasts six months between fall and spring with a peak during the winter [6]. In countries with tropical or subtropical climates, the season may be longer and less predictable [7]. Palivizumab, currently[1] the only licensed product to prevent RSVi, is recommended for use in children with certain "high risk" conditions [8]. It is given in monthly intramuscular injections during RSV season. There are over 40 vaccine and antibody products in development for prevention of RSVi [9]. Two products in late stages of clinical development target young infants: 1) a monoclonal antibody designed to provide direct protection (completed phase 2b clinical trial) [10]; and 2) a maternal vaccine designed to provide indirect protection through passive placental transfer of antibodies (completed phase 3 clinical trial) [11]. Both of these products aim to protect against medically-attended lower respiratory tract infections (MA-LRTI) due to RSV. Additional maternal vaccines and antibody products are in the clinical development pipeline [9].

Previous studies have evaluated the potential impacts of immunization on MA-RSVi in a variety of countries [12-13]. These analyses have focused on the hospital setting and impacts from single, theoretical vaccine products. Only one (Cromer et al.) simultaneously compared multiple products in the later stages of clinical development and across several healthcare settings [13]. Cromer et al. estimated the direct effects of various pediatric and maternal immunization candidate products and strategies using a cohort model in England. While Cromer et al.'s model more closely matches trial endpoints for products potentially close to licensure, its assumptions may not be generalizable to populations that have different rates of disease and seasonality. It also assumed the entire population eligible for an immunization product received it (i.e., 100% uptake), which likely overestimates the public response. The evolving state of product development highlights the need for flexible and accessible modeling tools, which can be readily updated to reflect advancements in our knowledge of product characteristics, and which can be applied to jurisdictions with varied RSV epidemiology.

We therefore developed a modeling tool, called the RSV Immunization Impact Model (RSV I^2M), for use by practicing public health officials and policy-makers in their jurisdictions, to estimate the direct effects of immunization candidates targeting young infants, on MA-RSV-associated LRTIs. RSV I^2M evaluates the potential impact of these products on outpatient clinic visits, ED visits, and hospitalizations based on user-adjustable RSVi rates and seasonality, in conjunction with assumptions about product uptake and efficacy. Model outputs (visits with and without immunization for LRTI due to RSV) can assist policy-makers in the United States and other countries with developing economic analyses and recommendations for RSV immunization. We also apply the model to a US birth cohort to estimate the potential impact of these products on MA-LRTI due to RSV in the United States.

METHODS

Tool Overview

RSV I^{2}M is a spreadsheet-based tool that uses a Decision Tree model (Appendix 1) to estimate the potential impact of three immunization strategies on MA-RSV-associated LRTIs among an annual birth cohort through 12 months of age. The birth cohort is divided into "high-risk" and "low-risk" (all other) infants. High-risk infants include those with hemodynamically significant congenital heart disease (CHD), chronic lung disease of prematurity (CLDP), and infants born prematurely at <29 weeks gestational age based on recommendations for who should receive palivizumab prophylaxis [30]. The first strategy (Strategy I) generally follows current US-based recommendations that high-risk infants receive monthly injections of palivizumab during the RSV season (typically October to March) during their first year of life [30]. In the model, palivizumab is given starting at birth for those born during the season, and starting at the beginning of the next RSV season when births occur out-of-season (OoS) (Table 1). The second strategy (Strategy II) provides a new antibody product, hereafter referred to as the "Antibody Candidate" strategy, injected as a single dose with the same timing of palivizumab initiation, but targeting all infants rather than just those at high risk. The third strategy (Strategy III), the "Maternal Vaccine Candidate + Palivizumab" strategy, combines providing vaccine to mothers in their third trimester throughout the year (not just during the season) and palivizumab to high-risk births based on the palivizumab schedule described above.

Table 1. RSV Immunization Strategies

	Strategy I	Strategy II	Strategy III	
Immunization Products	Palivizumab (licensed)	Antibody Candidate	Maternal Vaccine Candidate	Palivizumab (licensed)
Eligibility	High-risk infants*	All infants	All pregnant women¶	High-risk infants*
When offered	Within-RSV season	Within-RSV season	Year-round	Within-RSV season
Administration Schedule	Monthly injections for 5 months	Single injection	Single injection	Monthly injections for 5 months
Age when immunization initiated	Within-season birth: at birth Out-of-season birth: age at season's start (1-6 months)	Within-season birth: at birth Out-of-season birth: age at season's start (1-6 months)	3rd trimester of mother's pregnancy	Within-season birth: at birth Out-of-season birth: age at season's start (1-6 months)

* High risk conditions include hemodynamically significant congenital heart disease (CHD), chronic lung disease of prematurity (CLD), and prematurity (<29 weeks gestation) without CHD or CLD
¶ Risk status of infant is not known at time of immunization

Estimates of MA-RSVi visits without any immunization are based upon user inputs regarding the size of their birth cohort, prevalence and risk of RSV hospitalizations among those with high-risk conditions, rates of RSV (combined for high- and low-risk infants) by month of age in the outpatient clinic, ED, and hospital settings, the proportion of MA-RSVi visits resulting in a LRTI diagnosis, and RSV seasonality (Table 2). To estimate the effects of immunization, users input immunization uptake, efficacy, and duration of protection for each product (Table 2). Uptake was defined as the proportion of the population expected to receive the products. Efficacy is defined as the percent protected assuming recipients receive the full immunization dose at the correct time. For the maternal vaccine, efficacy is reduced by assumptions about the proportion of antibodies that successfully transfer to the infant (based on the timing of the mother's vaccination and the infant's gestational age a birth; Table A2, Appendix 1). Users can download the model via the link in Appendix 1 and can readily update several input values as new data

become available and/or to reflect a jurisdiction's desired immunization policy considerations.

To illustrate the tool, we used it to estimate the effects of the aforementioned immunization

strategies on a US birth cohort.

Table 2. Inputs and Parameter Values for All RSV Immunization Impact Scenarios.

Parameter	Baseline Value	Range (used in sensitivity analyses)	User-adjustable	Source
Population and Epidemiological				
Annual live births	3,945,975		Yes	[31]
Births with conditions putting them at "high-RSV risk" [§]	0.98%		Yes	[32]
Percent of "high-risk" hospitalized before 12 months	9.31%		Yes	Calculated, Appendix 1 (A1)
Rates of Medically-Attended RSV (per 1000 births) [¶]			Yes	
Hospitalizations	8.4	(1.5 – 30.8)		See A1 for data
Emergency Department (ED) Visits	66.2	(16.8 – 132.7)		tables/sources
Outpatient Clinic Visits	230.9	(71.0 – 337.2)		
Proportion of MA-RSVi visits with an LRTI diagnosis, by 0-5 / 5-11 months of age categories^			Yes	CDC/unpublished
Hospitalizations	1.00 / 1.00			
ED Visits:	0.65 / 0.50			
Outpatient Clinic Visits	0.65 / 0.30			
Case fatality ratios[†]			Yes	[1]
0-5 months (%)	0.10			
5-11 months (%)	0.10			
RSV season	October to March		Yes	CDC/unpublished; A1
Immunization				
Uptake[#]				
Palivizumab	38.0%		Yes	[33, 34]
Antibody Candidate				
Low-risk	71%	(66 – 76)	Yes	Assumed, [35, 36]**
High-risk	80%		Yes	Assumed, [32][¶¶]
Maternal Vaccine Candidate	56%	(51 – 61)	Yes	Assumed, [37][‡‡]
Antibodies proportion successfully transferred to infants	91.9%		Yes	Calculated, A1
Efficacy (associated with full immunization dosage)				
Palivizumab	51%		Yes	[38] [§§]
Antibody Candidate	80%	(73 – 85)	Yes	Assumed, [39]^^
Maternal Vaccine Candidate	80%	(73 – 85)	Yes	Assumed, [39]^^
Duration of Protection				
Palivizumab	150 days		No	[40, 41]
Antibody Candidate	150 days	(120 – 180)	Yes	[10]
Maternal Vaccine Candidate	90 days	(60 – 120)	Yes	[11]

[¶] Illustrative average (unadjusted) population rates. Appendix 1 (A1) contains the actual age-based (monthly) rates used in all analyses.

[§] High risk conditions include hemodynamically significant Congenital Heart Disease (CHD), Chronic Lung Disease of Prematurity (CLD), and Prematurity (<29 weeks gestation) without CHD or CLD.

^ Based on the average of number of lab-confirmed RSV visits from a national surveillance system between 2002-2009 with any of the following diagnoses: croup, bronchiolitis, bronchitis, pneumonia or asthma.

[†] Based on estimates for "high income/industrialized" countries.

[#] Percent of eligible population targeted to receive an immunization product that actually obtains and completes the full regimen. For Palivizumab: One injection monthly for 5 months on time. For Antibody & Maternal Vaccine Candidates: One injection.

** Baseline value is based on similar uptakes for Hepatitis B vaccine in neonates [36] (applicable to births within the RSV season) and Influenza immunization coverage among 6 month to 4 year olds [35] (applicable to births occurring outside RSV season). Range is -/+ 5 of baseline in the absence of data.

[¶¶] Based on the percent of births that obtained the 1st palivizumab injection [32].

[‡‡] Baseline based on average TdaP (tetanus, diphtheria, pertussis) uptake among pregnant women during a 15-month study period from April 2013 - June 2014 [37]; and range is -/+ 5 of baseline. TdaP, like the maternal RSV vaccine, is given in the 3rd trimester of pregnancy.

[§§] This is the efficacy associated with our assumed uptake (i.e. compliance with all doses) [38].

^^ Based on average efficacy for term infants across all healthcare settings (hospitalizations, ED, and outpatient clinics) in a study examining the efficacy of motavizumab and our assumption of similarity between it and this study's antibody and maternal vaccine candidates [39].

Calculations, Visits without immunization

To calculate the number of MA-RSVi resulting in LRTI for each of the three healthcare settings, we multiplied the "all-risk" (high- and low-risk) MA-RSVi rate by the proportion of visits in each setting with an LRTI diagnosis and the size of monthly birth cohorts (assuming births occur evenly across the year) (Appendix 1). These results were then distributed to calendar months based on RSV seasonality by multiplying them by the percent of annual visits occurring in each month. For countries that currently use palivizumab, like the United States, we added to the monthly visit counts MA-LRTIs that would have occurred in the absence of palivizumab. For the hospital setting, these additional visits were determined by multiplying the rate of hospitalizations among high-risk infants by the size of the high-risk cohort, palivizumab uptake, and palivizumab efficacy. The hospitalization rates used in this calculation are a weighted average across the different high-risk groups (Appendix 1). For the outpatient clinic and ED settings, we assumed the ratio of rates between high- and low-risk infants is the same as the ratio of hospitalization rates for high and low risk infants, and that palivizumab would have the same efficacy for preventing cases in these settings (Appendix 1).

Calculations, Visits prevented with immunization

To obtain the annual number of visits prevented with immunization for a given strategy and setting, we summed the visits prevented across all months that the immunization remained protective, based on its duration of protection. We calculated the monthly visits prevented with each immunization strategy differently. For Strategy I, LRTI visits prevented by palivizumab equaled the calculated number of MA-RSV-associated LRTIs without immunization among high-risk infants, multiplied by palivizumab uptake and efficacy. For Strategies II and III, visits

prevented by the immunization candidates equaled the number of MA-RSV-associated LRTIs

without immunization among both high- and low-risk infants, multiplied by the candidate uptake

in each risk group and efficacy. The efficacies for both candidates assume recipients receive the

full immunization dose. To account for incomplete transfer of antibodies from mother to child

for a portion of births, we multiplied the maternal vaccine efficacy in Strategy III by a reduction

factor. This factor considers the delay in the mother's production of antibodies after vaccination

(dependent on the timing of vaccination relative to birth) and the fact that the amount of antibody

transfer is dependent on gestational age at birth (Appendix 1). In Strategy III, high-risk infants

are also eligible to receive palivizumab; therefore, we added the number of visits prevented by

palivizumab when calculating the total annual prevented visits for this strategy. Finally, we

calculated the visits that would occur despite having each immunization strategy in place: this

equaled visits without immunization minus visits prevented.

Calculations, Deaths with and without immunization

Since data are sparse on the number of RSV-associated deaths that occur outside the hospital

setting, we estimated deaths with and without immunization based on deaths among hospitalized

infants. We calculated deaths without immunization by multiplying user-provided hospitalized

case fatality ratios (hCFR) for infants 0-5 months of age and for those between 6-11 months of

age and the total annual estimate for hospitalizations due to RSV-associated LRTIs without

immunization for these age groups. Deaths prevented by immunization were calculated similarly

to medically-attended visits prevented, whereby deaths that occur without immunization were

multiplied by the uptake and efficacy for each product. Finally, deaths that would occur despite

having each immunization strategy in place equaled deaths without immunization minus deaths prevented through immunization.

Model Inputs and Sensitivity Analysis

To illustrate the model, we estimated the impact of implementing the three immunization strategies in the United States. Table 2 includes all model inputs, values used and sources (with additional detail in Appendix 1).

We conducted two sensitivity analyses of immunization candidates' impacts. In the first, we evaluated the influence of high and low estimates for individual parameters, while all other parameters were held constant. For this analysis we used the 95% CI bounds for MA-RSVi rates, five percentage point reductions and improvements in the baseline uptake for the antibody candidate (66-76%) and maternal vaccine candidate (51-61%), the 95% CI bounds for efficacy reported in clinical trial results for an antibody candidate (73–85%, which we assumed for the maternal vaccine candidate as well), and one month reductions and improvements in durations of the antibody candidate (120-180 days), and maternal vaccine candidate (60-120 days) (Table 2). In our second sensitivity analysis, we examined the impact of uptake of the immunization candidates on LRTI visits by accounting simultaneously for uncertainty in RSV rates, uptake, efficacy, and duration. We present the results for this analysis as the lowest and highest possible prevented visits associated with a percentage point decrease or increase in uptake, respectively. We generated the lowest estimate by combining the 2.5 percentile values for MA-RSVi rates, lowest efficacy and uptake, and shortest duration, for each product as inputs (Table 2). High estimates were achieved by combining the 97.5 percentile values for MA-RSVi rates, highest efficacy and uptake, and longest duration, for each product.

RESULTS

3.1. Visits without immunization

We estimate, in the absence of palivizumab use, RSV-associated LRTIs in the US among infants

up to 12 months of age, would result in 407,360 annual outpatient clinic visits (range, based on

RSV rates uncertainty: 339,650 – 475,980); 147,240 annual ED visits (range: 126,070 –

168,510), and annual 33,180 hospitalizations (range: 24,760 – 42,900).

3.2. Visits prevented with immunization

In our illustrative scenario, Strategy II (the "Antibody Candidate") prevented the most annual

LRTIs. (Figure 1) This strategy prevents an estimated 196,470 (48% of visits without

immunization) RSV-associated LRTIs attended in the outpatient clinic setting (range: 163,810–

229,650), 75,250 (51%) LRTIs attended in the ED (range: 64,430 -86,090), and 18,140 (55%)

LRTI hospitalizations (range: 13,770–23,160). Strategy III (the "Maternal Vaccine Candidate +

Palivizumab"), prevented an estimated 58,210 (14% of visits without immunization) RSV-

associated LRTIs attended in the outpatient clinic setting (range: 48,520 –67,970), 19,580 (13%)

LRTIs attended in the ED (range: 16,760 – 22,400), and 8,190 (25%) LRTI hospitalizations

(range: 6,390 – 10,150). We estimate that Strategy I, ("Current US Recommendations"),

prevents 8,460 (2% of visits without immunization) RSV-associated LRTIs attended in the

outpatient clinic setting (range: 7,050 – 9,880), 3,240 (2%) LRTIs attended in the ED (range:

2,770 - 3,710), and 780 (2%) LRTI hospitalizations (range: 760 – 800).

Figure 1. Estimated number of RSV-associated LRTI Visits Expected without Immunization and Prevented by Immunization in the US, by Healthcare Setting and Immunization Strategy
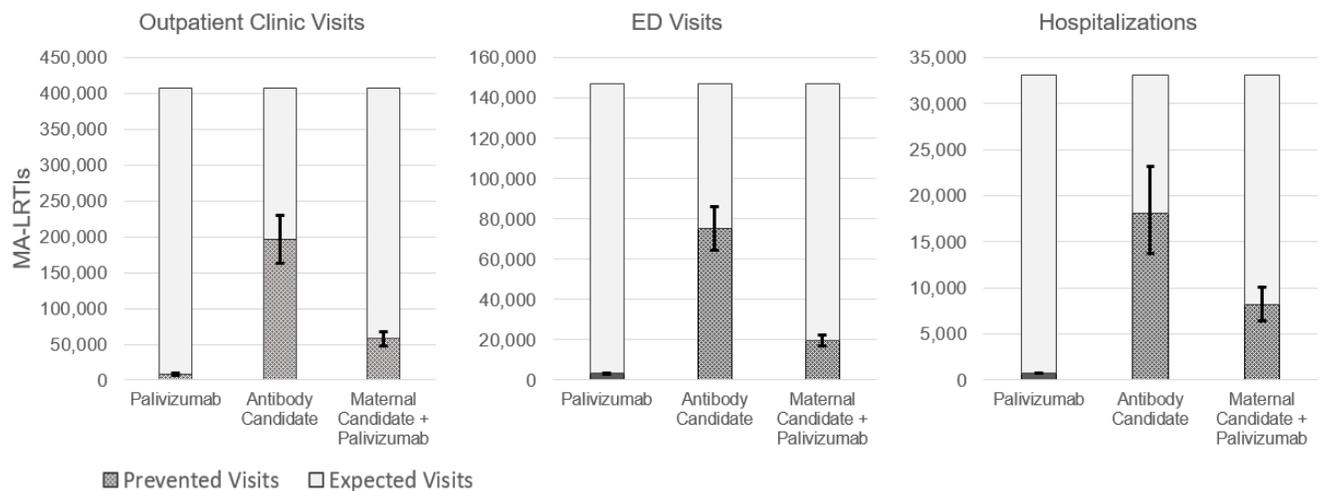
Notes: Error bars reflect uncertainty in the number of prevented MA-LRTIs associated with uncertainty in RSV rates. Uncertainty in the expected visits despite immunization is not shown.

3.3. Deaths with and without immunization

We estimated 33 deaths (range: 25-43) would occur annually among hospitalized infants in the US from RSV-associated LRTIs in the absence of immunization and following current recommendations for palivizumab use (Strategy I) prevents just one death. Eighteen in-hospital deaths (range: 14-23) would be prevented if immunization were implemented according to Strategy II, and eight in-hospital deaths (range: 6-10) prevented with Strategy III.

3.4. Sensitivity Analyses

The relative influence of individual parameters on our estimates of prevented LRTI-associated visits varied by immunization strategy and healthcare setting. In both Strategies II and III, uncertainty in the duration of immunization protection was the most influential parameter, except for the hospital setting, where uncertainty in RSV rates was more influential in Strategy II

(Figure 2). When results assuming 120 and 180 days of protection by the antibody candidate are compared, the estimated LRTI visits prevented differed by 3,080 in the hospital setting, 26,960 in the ED setting, and 79,070 in the outpatient clinic setting. When results assuming 60 and 120 days of protection by the maternal vaccine candidate are compared, the estimated LRTI visits prevented differed by 3,880 in the hospital setting, 20,950 in the ED setting, and 51,840 in the outpatient clinic setting. The more pronounced effects of immunization duration in Strategy III results from RSV rates peaking for the outpatient and ED setting at ages just after our baseline 90-day duration (Appendix 1, Table 1). Antibody candidate uptake exhibited the least influence on prevented LRTIs in Strategy II. In contrast, efficacy was the least influential parameter in Strategy III.

Figure 2. Sensitivity of Estimates of RSV-associated LRTI Visits Prevented to Select Model Parameters.
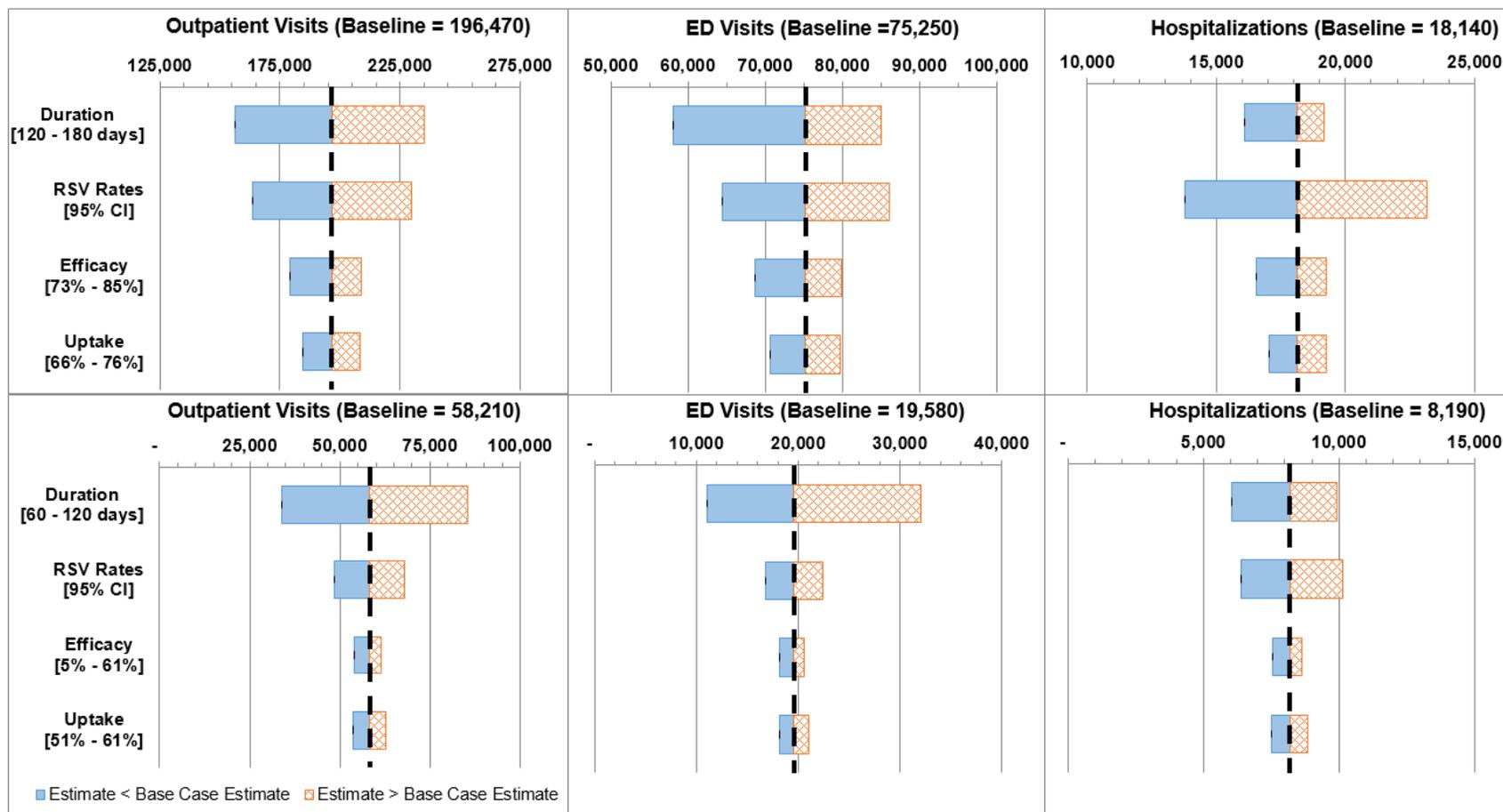
Notes: Top row: Immunization Strategy II (the "Antibody Candidate" Strategy). Bottom row: Immunization Strategy III (the "Maternal Vaccine Candidate + Palivizumab" Strategy). Parameter values not shown, provided in Table 2.

The results of our multivariable sensitivity analysis suggest changes in the antibody candidate uptake have a larger impact in preventing RSV-associated LRTI visits than would uptake changes in the maternal vaccine candidate. For every percentage point increase in uptake of the antibody candidate, we estimate 1,435 to 3,527 outpatient visits would be prevented, compared with 273 to 1,611 for the same increase in the maternal vaccine candidate. In the ED setting, a one percentage point increase in antibody candidate uptake is associated with 548 to 1,248 LRTI visits prevented, while the same uptake increase in maternal vaccine candidate would prevent between 82 and 588 LRTIs. In the hospital setting, a one percentage point increase in antibody candidate uptake is associated with 128 to 329 prevented LRTIs, and 58 to 215 prevented LRTIs for the maternal vaccine candidate.

DISCUSSION

Using the model and our best estimates of the parameters, we found that in the absence of an immunization, there are ~590,000 MA-RSV LRTIs among US infants and that new interventions that target all infants may prevent between ~86,000 to ~290,000 of those visits. These results indicate substantial RSV morbidity and associated healthcare utilization due to serious RSVi may be averted with new products under development. Few deaths (8-18), however, are averted, since few deaths in the US are attributed to RSVi. Of the candidates evaluated, administering an antibody candidate to all infants born during the season and at the season's start for those born outside the season, prevents the most MA-LRTIs. With this strategy, we estimate nearly 200,000 outpatient clinic visits, 75,000 ED visits, and 18,000 hospitalizations for LRTIs could be prevented annually; approximately 48-55% (across settings) of visits estimated to occur without

immunization. Our baseline estimates suggest this strategy may avert approximately 3.5 times the number visits for RSV-associated LRTIs to outpatient clinics and EDs, and two times the hospitalizations than a strategy in which a maternal vaccine candidate is offered to mothers year-round (in addition to palivizumab use per current US recommendations).

In our illustrative scenario, the difference in the number of prevented visits associated with candidates was largely attributable to the maternal candidate's duration of protection being less than the antibody candidates' duration of protection. This was especially pronounced in the outpatient clinic and ED settings, where the peak of incidence is beyond the 90 days of protection assumed for the maternal candidate. Consequently, changes to our duration assumptions for the maternal vaccine candidate had the greatest influence on product impact. Despite its lower impact, the maternal vaccine candidate has the potential to reduce MA-RSV LRTIs across all three settings by ~74,000 visits a year (beyond the ~12,500 visits prevented by palivizumab in our baseline scenario). Preliminary results suggest the efficacy of a maternal vaccine may be half what we assumed in our baseline estimates [20]. This would reduce visits prevented by the maternal vaccine candidate by about half, but not change the overall conclusion about the relative merits of the products and strategies evaluated.

Although uncertainty in factors over which public health practitioners have some influence, like uptake, had less impact on results, they were not trivial. For example, our multivariable sensitivity analysis suggests a 10% increase in uptake of the antibody candidate is associated with preventing an additional 14,350 to 35,270 outpatient clinic visits, 5,480 to 12,480 ED visits, and 1,280 to 3,290 hospitalizations for LRTIs. Similarly, a 10% increase in maternal vaccine candidate uptake is associated with preventing 2,730 to 16,110 outpatient clinic visits, 820 to 5,880 ED visits, and 580 to 2,150 hospitalizations for LRTIs. We also examined the influence of

the timing of maternal vaccine uptake, by altering the immunization schedule so that it optimized

the proportion of infants to whom antibodies successfully transfer (Appendix 1, Figure A2). The

difference between these results and our baseline results were negligible.

The relative impact of strategies on hospitalizations are similar to Cromer et al.'s findings (ED

and outpatients are not comparable) [13]. If we assume 100% uptake for both candidate products

and limit our evaluation to infants <6 months of age (to match Cromer et al.'s analysis) we find

the antibody candidate prevents 1.7 times more hospitalizations than the maternal vaccine

candidate, compared with a ratio of 1.8 in Cromer et al. Our findings are also in line with

previous studies examining the effect of a single type of vaccine with similar characteristics to

products we examined. For example, Regnier, using a decision tree model to examine a

theoretical vaccine for protecting infants in the US from birth, also estimated a 25% reduction in

hospitalizations, but with assumptions of 69% uptake, 50% efficacy, and a decaying exponential

distribution for the duration of protection with a 12-month median length [17]. And Hogan et al.,

employing a compartmental transmission model to examine maternal vaccine impacts in Western

Australia, similarly estimated a 25% reduction in hospitalizations when assuming a similar

immunization scenario of 50% uptake, 80% efficacy, and 3 months duration of protection [14].

A strength of our study is its simplicity. We focus on the impacts of products on infants who are

immunized, which will be of specific interest to policymakers developing RSV immunization

guidelines. We do not estimate the indirect effects of immunization in infants (i.e., secondary

infections prevented). However, this should not be seen as a limitation. Even Hogan et al.

concluded from their transmission model that herd effects due to the maternal vaccine were

modest and a simple cohort model would be a reliable alternative for estimating immunization

impacts among infants [14]. Additional strengths of our study include evaluation of multiple

candidate products, the separate consideration of infants with higher risk of healthcare use for RSV infection and the additional evaluation of the outpatient and emergency department settings.

RSV I^{2}M has limitations. Estimates of immunization impact are restricted to the season in which they are given. It is possible that these products will shift the demand for care to subsequent seasons, although there is evidence that primary infection with RSV beyond 12 months of age is less likely to result in an LRTI [21]. We also do not account for the possible protection of mothers against RSVi by the maternal vaccine candidate. As such, and because we do not account for herd effects, we may underestimate the actual benefit of immunizing mothers. Other limitations, however, may result in our overestimation of immunization benefits. For example, our assumption that effective immunization averts healthcare use does not account for the potential that some portion of immunized infants may still become infected with RSV, but require a lower level of care (e.g., shift from hospitalization to outpatient visit). We also assumed an additive effect of palivizumab on top of visits prevented by the maternal vaccine candidate in Strategy III, on the basis that the population of "high-risk" births may derive partial protection from the maternal vaccine and from palivizumab. Any overestimation from this limitation, however, is negligible (in the US at least), since <1% of births are affected. For jurisdictions that do not use palivizumab or who wish to see the potential impact of the maternal vaccine alone, users can set palivizumab uptake to 0%. It is worth noting that similar flexibility exists for analyzing impacts by setting: jurisdictions wishing to evaluate only the hospital setting can just input rates for this setting.

Our model provides decision makers with the ability to examine the impact of directly or indirectly immunizing infants against RSV infection with anticipated immunization products. As

such, local and national public health agencies may use it to evaluate jurisdiction-specific scenarios of impact. The findings can be used in economic analyses to understand the direct costs and benefits of these strategies and others. The results of our illustrative scenario underscore potential for these products to reduce serious RSV illness and the benefits of each. Although we found limited impact of these products on deaths averted in the United States, they may have greater impact in places where RSV-associated deaths are more common. As more data become available regarding immunization candidates (i.e., study results regarding efficacy and length of protection) and the burden of RSV infections, our tool permits rapid updating of results.

CHAPTER 3 – Study 2: A Dynamic Modeling Tool for Estimating Healthcare Demand in the Early Phase of the COVID-19 Pandemic and Evaluating Population-wide Interventions

On December 31, 2019, the regional office of the World Health Organization (WHO) was notified of a cluster of pneumonia cases of unknown origin associated with a market in Wuhan, China [26]. A novel coronavirus (SARS-COV-2) was identified as the cause of the infections [26] and has since spread worldwide. Just five months later, by May 7, 2020, more than 3.6 million cases of COVID-19 (illness caused by SARS-COV-2) had been reported in 184 countries and territories, including ~250,000 deaths [27, 28]. At that time, the pandemic had overwhelmed both national and local healthcare capacity in several countries [29, 30], and was projected to do so in many others. Low- and middle-income countries are particularly vulnerable [31], since financial and logistical challenges may hinder their ability to augment treatment capacity. As such, many countries resorted to societal-wide social distancing interventions in the hopes of reducing morbidity and delaying the demand for healthcare resources, to gain time to increase treatment capacity.

Numerous modeling efforts began forecasting the spread of the outbreak and examined the potential benefits of social-distancing interventions [29-32]. While informative, those efforts were limited to specific nations and snapshots in time and public health officials were reliant on the authors for updated estimates as the pandemic evolved. Other internet-based tools offered public health users the ability to generate estimates on their own, but these were limited in their practical utility because their assumptions and desired results did not necessarily match the specific needs of jurisdictions and public health decision makers, or they required coding knowledge to access or modify the calculations [33, 34]. These considerations are more critical

in low and middle-income countries, which may not have the resources to complete or modify such analyses on their own.

We sought to provide decision makers with the ability to examine the impacts of the early COVID-19 pandemic in their jurisdictions and evaluate the effects of various social-distancing mitigation strategies and augmenting treatment capacity on morbidity and mortality. Therefore, we developed a modeling tool for use by practicing public health officials to estimate the future impact of the COVID-19 outbreak on the demand for healthcare resources in their jurisdictions and for examining the costs and benefits of various intervention strategies. Once downloaded, the model can be used without an internet connection, to assist public health officials with choosing locally applicable intervention strategies and by how much to increasing hospital treatment capacity. For illustration, we apply the model to Chile, a Southern Hemisphere country where the virus was generating local transmission in the middle of 2020[2] and compare various interventions options in the three most affected regions of the country.

METHODS

Tool Overview

We created a spreadsheet-based tool that uses a Susceptible-Latent-Infectious-Recovered (SEIR) Compartmental Model to project the future impact of a COVID-19 epidemic among any population of interest (Appendix 2). The model requires information that is typically available for public health officials, including the number of cases in their jurisdiction, the size and demographics of their at-risk population, healthcare capacity, expectations for healthcare use, and choices of societal-wide social-distancing mitigation strategies users wish to evaluate. Model

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[2] at the time of initiation of this study

outputs reflect the potential demand on the healthcare system due to severely ill individuals with and without user-specified mitigation strategies, as well as deaths averted through treatment and excess deaths due to healthcare demand exceeding capacity. The demand for healthcare resources is measured as the estimated number of COVID-19 patients requiring critical-care or Intensive Care Unit (ICU) beds, hospital beds (non-ICU), and mechanical ventilators over the course of the outbreak and the maximum occupancy at the outbreak's peak. The tool offers users the ability to evaluate various intervention strategies currently under consideration and in use worldwide [29, 30, 35]. These interventions comprise five mitigation-type interventions which focus on slowing epidemic spread and reducing its burden on the healthcare system, and one suppression-type strategy, which employs aggressive interventions aimed at reversing epidemic growth (Table 3). Users can download the model (link in Appendix 2) and readily update all input values themselves as new data become available or reflect a jurisdiction's specific epidemiologic profile of disease and policy considerations. All calculations can be readily modified by users (although no modifications are necessary for tool use).

Table 3. COVID-19 Social-Distancing Intervention Strategies and Effects on Transmission

Strategy Name (Strategy Type)	Description	Reduction in R_0[a]	
		Low[b]	High[b]
Case isolation (mitigation)	Symptomatic cases stay at home for 7 days, reducing non-household contacts during this period. Household contacts remain unchanged.	15.8%	18.6%
Closing Schools and Universities + Telework (mitigation)	Closing Schools/Universities: Physical closure of all schools and universities (or move to virtual learning environment). Assumes some increase in contacts in the household and the community during the closure, partially offsetting reductions in transmission at schools and universities. Telework: All government switches to telework to the maximum extent possible and private businesses are encouraged to telework, resulting in 50% of the working population teleworking.	15.8%	16.8%
Case isolation + Household quarantine (mitigation)	Case isolation: same as above Household quarantine: Following identification of a symptomatic case in the household, all household members voluntarily remain at home for 14 days. Increased transmission between household members during the quarantine period will partially offset transmission reductions in the community.	25.4%	30.0%
Case isolation + Household quarantine + Social distancing of >70s + Telework (mitigation)	Case isolation: same as above Household quarantine: same as above Social Distancing of >70s: Reduce contacts among older individuals (>70 years of age) because of their increased risk for severe outcomes and healthcare resource requirements. These individuals reduce contacts outside the home by 50%. Telework: same as above	41.9%	47.7%
Lockdown (suppression)	Population-wide social distancing by forced quarantine of all households and workplaces, and border closed to travel. Only essential outings from the home are permitted (e.g. food/supplies purchases) and for employees working at businesses deemed essential for continued operation.	57.7%	68.2%

Notes

[a] R_0 = *basic reproduction number*. It represents the average number of people who will be infected by any given infected person at the early stages of disease spread when there are no control measures.

[b] High and Low values of the reduction in transmission associated with each strategy were used to account for uncertainty in societal compliance and strategy effectiveness. These reductions were based on equivalent reductions in Critical Care Bed Occupancy published in Ferguson et al. (2020), [29, Appendix 2]. We added 10 percentage points to reduction values for strategies including telework, based on Willem et al. (2020) [35].

Calculations: Transmission with and without intervention

Our SEIR model tracks the number of individuals transitioning between disease states every day of the outbreak. The initial number of susceptible individuals is set as the population minus the cumulative number infected since the outbreak's start. Transmission occurs through contacts between susceptible and infectious individuals, and we assume an equal probability any one person has contact with another ("homogenous mixing"). We also assume transmission chains generated by infected travelers entering the population are minimal compared to existing transmission in the community. As a result, the number of new infections each day is the product of the proportion of the population that is susceptible, the number of infectious persons on a given day, and the average number of new infections each infected person causes over the span of their illness (the reproduction number; hereafter, "R") divided by the duration (in days) of the average infectious period. Infectiousness is assumed to occur five days after infection [36] and lasts 11 days [37]. Upon recovery from infection, individuals are assumed immune to re-infection during the timespan modeled (through December 2020). In the absence of intervention R is 2.0 (low estimate) and 2.8 (high estimate), approximately spanning the middle 50% of the gamma distribution of R (95% intervals: 1.4-3.8) estimated from the early growth-rate of the epidemic in Wuhan [38, 39]. To account for uncertainty in R, all results are depicted as a range based on these low and high estimates for R. During time periods where interventions are applied, we reduce the low and high estimates of R by the values in Table 3. Upon mitigation concluding, R returns to pre-mitigation levels to illustrate the potential consequences of shorter duration interventions. However, advanced users can alter the tool so that when one mitigation strategy concludes, another begins. Finally, we do not account for any vaccine as it was unlikely

to be available within the modeled time frame [40]. All equations governing dynamics of the system are provided in Appendix 2.

Calculations: Hospitalizations and ICU admissions with and without intervention

In our model, all symptomatic persons with an illness severe enough to warrant hospitalization will seek healthcare and the risk for hospitalization is age-dependent (Table 4) [41]. Similarly, the percentages of individuals admitted to the hospital requiring ICU care and fatality are also age-dependent (Table 4), while the likelihood of patients admitted to the ICU who require mechanical ventilation is assumed the same (63.2%) for all ages [42].

Based on observations for COVID19, we assume individuals seeking hospital care do so 11 days after infection (five days incubation + six days of symptoms) [38, 43-45]. We calculate hospital (non-ICU) bed occupancy based on a ten-day length of stay for patients treated entirely in non-critical hospital wards [46, 47] and ICU bed occupancy based on a ten day length of stay when critical care is required [41, 45]. We assume a four-day lag from hospital admission to ICU admission [45, 47]. When mechanical ventilation is required, we assume the duration of use is nine days, based on expert clinical opinion that ventilation is necessary for the duration of ICU stays other than two days (one-day lag post ICU admission to initiate ventilator use plus 1 day in the ICU post-use) and another day required for ventilator cleaning/re-equipping.

Table 4. Risk of Healthcare Use and Outcomes Among COVID19-Infected Individuals

Age group	% Infected, Hospitalized[41]	% of Hospitalized, Admitted to ICU[41]	% ICU patients needing ventilation[a]	Infection Fatality Ratio (IFR)[41]	Fatality Increase if Demand>Capacity[b]
0-9	0.01%	5.0%	63.2%	0.002%	1.000%
10-19	0.04%	5.0%	63.2%	0.006%	1.000%
20-29	1.10%	5.0%	63.2%	0.030%	1.000%
30-39	3.40%	5.0%	63.2%	0.080%	1.000%
40-49	4.30%	6.3%	63.2%	0.150%	1.000%
50-59	8.20%	12.2%	63.2%	0.600%	1.000%
60-69	11.80%	27.4%	63.2%	2.200%	1.000%
70-79	16.60%	43.2%	63.2%	5.100%	1.000%
80+	18.40%	70.9%	63.2%	9.300%	1.000%

[a] Based on ICNARC (2020)[42]. Alternative estimates include 60% (Meltzer et al., 2015)[48] and 71.1% (Yang et al., 2020)[49].
[b] Percentage points increase in fatality when hospitals are overwhelmed. We assumed a 1% increase in the IFR to approximately double the population-weighted age-based IFR in Chile, based on data from COVID19 in China (Zhang Zuqin et al., 2020)[50].

To estimate the impact of interventions on hospital resource requirements we calculate two measures for each of the three resources tracked in the model: 1) the reduction in peak occupancy between the projected outbreak without intervention and when interventions are employed, and 2) the number of weeks peak occupancy is delayed due to employed interventions.

Calculations, Deaths with and without intervention

We assume all deaths occur in the hospital unless treatment capacity is overwhelmed, and that it takes the same time for an individual to recover and die, despite some preliminary evidence that deaths occur faster [44, 46]. As such, we might be overestimating the healthcare resources needed to treat the most critical patients (namely ventilators). Given the limited evidence for outcome-based durations of resource use, we took a more conservative approach, assuming planners would prefer to overestimate resources needs than under-prepare.

With treatment, fatality among infected (IFR) is age-dependent [41] (Table 4). When hospital capacity is overwhelmed, we assume a 1% increase in the IFR, chosen to approximately double the IFR in Chile, based on the observed reduction in IFR in China after treatment capacity was augmented to meet demand [50]. We also chose to base our mortality increase for untreated CoVID-19 patients on hospital bed availability (versus critical care beds or ventilators) since the vast majority of cases do not require critical care (~90% of cases in Chile). When more data become available, these assumptions can be updated. Finally, we assume when beds become free at overwhelmed hospitals, new admissions are not associated with a patient's potential outcome. To estimate the impact of interventions on deaths we calculate infection fatality rates with and without interventions and the number of estimated deaths averted, as the difference in our estimates of cumulative deaths with and without interventions.

Illustrative Scenarios and Sensitivity Analyses

To illustrate the model, we estimated the impact of implementing three intervention strategies in three regions of Chile with the most detected cases through April 6, 2020: Región Metropolitana (RM), an urban region with the largest population including the country's capital Santiago, and Araucanía and Ñuble, two of the least dense urban regions in Chile, but which had experienced rapid growth in late March and were reporting treatment capacity was already strained. We implemented the following three intervention strategies (Table 5) in each region, beginning April 1: Strategy 1) Closure of schools and universities and Telework for 8 months; Strategy 2) Case isolation, home quarantine, social distancing of individuals >70 years, and Telework for 8 months; and Strategy 3) Lockdown for 2 months (6 months shorter duration than the other strategies because the social and economic costs of this suppression strategy are not considered

sustainable for the long-term). We chose these strategies because they were in use to some

degree in all three regions [51-53] (Appendix 2).

Table 5. COVID19 Healthcare Demand Model Inputs, by Region for all Illustrative Scenarios

	Region			Source
	Metropolitana	Araucanía	Ñuble	
Population[a]	7,112,808	957,224	480,609	[53]
COVID-19 reported cases[b]				
Cumulative	20,590	1,907	1,107	[51]
2 weeks through 05/04/20	12,487	364	133	[51]
R_0	2.0 - 2.8	2.0 - 2.8	2.0 - 2.8	[39]
Intervention Strategy				
School closures, telework	4/1-12/1/20	4/1-12/1/20	4/1-12/1/20	Assumed
Case isolation, home quarantine, social distancing>70, telework	4/1-12/1/20	4/1-12/1/20	4/1-12/1/20	Assumed
Lockdown	4/1-6/1/20	4/1-6/1/20	4/1-6/1/20	Assumed
Disease severity				
Infected who are hospitalized[c] (%)	4.5%	4.8%	5.1%	[41]
Hospitalized, admitted to ICU[c] (%)	11.4%	12.2%	12.7%	[41]
Infection Fatality rate[c] (%)	0.8%	0.9%	0.9%	[41]
ICU patients needing ventilator (%)	63.2%	63.2%	63.2%	[42]
Healthcare resources[d]				
Hospital (non-ICU) beds	18,522	2,671	1,010	[55]
In-use by Non-COVID Patients (%)	71%	71%	71%	[56]
In-use by COVID Patients (%)[e]	3%	3%	3%	[51]
Critical Care Beds	2,326	215	60	[55]
In-use by Non-COVID Patients (%)	71%	71%	71%	[56]
In-use by COVID Patients (%)[e]	14%	14%	14%	[51]
Ventilators	867	80	22	[55]
In-use by Non-COVID Patients (%)[f]	40%	40%	40%	[57]
In-use by COVID Patients (%)[g]	19%	19%	19%	Assumed

[a] Population distributed by age groups are shown in the Appendix 2, based on Instituto Nacional de Estadísticas's Housing and Population Census, 2017 [53].

[b] Scaled counts to account for assumed 40% under-reporting in reported cases (based on 60% reported by Wang et al. (2020)[47] minus 20% to account for improvements in case-detection in Chile since the outbreak's start).

[c] Estimates differ by region due to age structure of the populations (Appendix 2).

[d] All beds available in the healthcare system, from public and private hospitals, are now part of the "Sistema Integrado COVID-19" under the centralized administration of the Ministry of Health. An ICU bed consists of a cot with a monitor, healthcare professionals and medication to treat patient. Some have a mechanical ventilator. There are an estimated 1,847 mechanical ventilators; 850 currently available and 997 were acquired in January 2020 [55]. We assumed the distribution of mechanical ventilators was proportional to the number of critical beds in each region: Metropolitana,47.0%; Araucanía, 4.3%; Ñuble, 1.2%. (Appendix 2)

[e] Based on the reported number hospitalized in "basic beds" (1,216) and in "critical care beds" (699) in all of Chile by the Ministry of Health as of May 4, 2020, out of the total existing beds nationally in March 2020 plus anticipated beds being added to expand pandemic treatment capacity: 41,706 and 4,954, respectively [55].

[f] Availability of mechanical ventilators was based on a three-year study of 97 ICUs in the US [57].

[g] Calculated by applying the % ICU patients needing ventilation (Table 4) to the number of COVID patients in critical care beds (see note e) and dividing the result by the total ventilators in Chile (see note f).

We conducted two sensitivity analyses to evaluate the effectiveness of varying the
implementation of mitigation strategies. First, we evaluated the influence of shortening the
duration (by 2, 4, and 6 months) of mitigation strategies by which successfully reduced our
healthcare demand estimates to within the range of treatment capacity. This analysis was chosen
since policymakers may be pressured to lift mitigation strategies as early as possible due to their
social disruption and economic costs. Then we evaluated the impact of combining the Lockdown
strategy with all other strategies, so that when the Lockdown strategy ends, another begins and
lasts 6 months. This analysis is intended to address the potential for the outbreak to rebound in
the absence of an intervention after a lockdown is lifted [29, 30].

RESULTS

3.1. Infections and Deaths without intervention

We estimate in the absence of any interventions, 5,682,168 to 6,592,016 infections would occur
over the course of the epidemic period modeled (5/5 – 12/31/20) in RM, 766,015 to 889,054
infections in Araucanía, and 384,509 to 446,285 infections in Ñuble (Figure 3 and Appendix 2).
These projected counts reflect the possibility that 80% to 93% of the populations in these regions
may be infected in the absence of any control measures or changes in individual behaviors.
Under such a scenario, the number of deaths is projected to be between 106,558 to 125,373 in
RM (1.9% IFR), 13,860 to 16,378 deaths in Araucanía (1.8% IFR), and 7,247 to 8,520 deaths in
Ñuble (1.9% IFR).

3.2. Hospital Resource Demands with and without interventions

Without intervening to control the outbreak, demands for all three of the healthcare resources
evaluated by our model are projected to exceed capacity sometime in June in RM (Figure 3 and

Appendix 2), and peak sometime between the end of July and mid-August. Araucanía and Ñuble

are projected to exceed capacity in July and peak sometime in August or September

(approximately one month after RM on both metrics). The degree to which demand is projected

to exceed supplies differs by region. In RM, peak demand across all resources is 6 to 18 times

the projected maximum supplies available. The situation is similar in Araucanía and Ñuble for

hospital beds and ventilators but is more dire for ICU beds: in both regions the unmitigated peak

ICU bed demand is between 13 and 47 times the supply.

Among the two mitigation strategies we evaluated (versus the suppression-type Lockdown

strategy), Strategy 2 reduced the burden on the healthcare system the most. In RM, compared to

the no intervention scenario, this strategy reduced peak hospital bed occupancy demands by a

range of 16,024 to 57,225 (35.4-69.2%), ICU bed occupancy between 2,945 to 8,270 beds (44.8-

69.0%), and the number of ventilators needed by 1,572 to 4,237 (47.1-69.3%). This strategy

would also push the peak demand for healthcare resources back between 7 and 27 weeks,

affording policymakers more time to plan or acquire more capacity. Greater percent reductions

but similar delays in the peak demand were observed for Araucanía and Ñuble (Appendix 2).

Our results suggest that this strategy can ease the demands for healthcare to levels below

projected capacity constraints when the effectiveness of this strategy is at the higher end of our

assumed range (i.e., reductions in R_0 approach 47.7%) (Table 1, Figure 3).

For policymakers willing to consider more restrictive measures, our results for the Lockdown

strategy, suggest it is an incredibly effective strategy, even for its short duration. The pandemic is

quickly subdued and remains so for the duration of the lockdown period in all three regions, with

the numbers of cases in treatment remaining relatively flat at levels well below treatment

capacity. However, once the lockdown is lifted the number of infected begins to rise again,

resulting in demand curves similar in size to the no-intervention scenario, but peaking later:

sometime between mid- August and late September (Figure 5, panel A).

Figure 3. Projected occupancy demands and capacity for hospital (non-ICU) beds in Región Metropolitana with and without intervention.
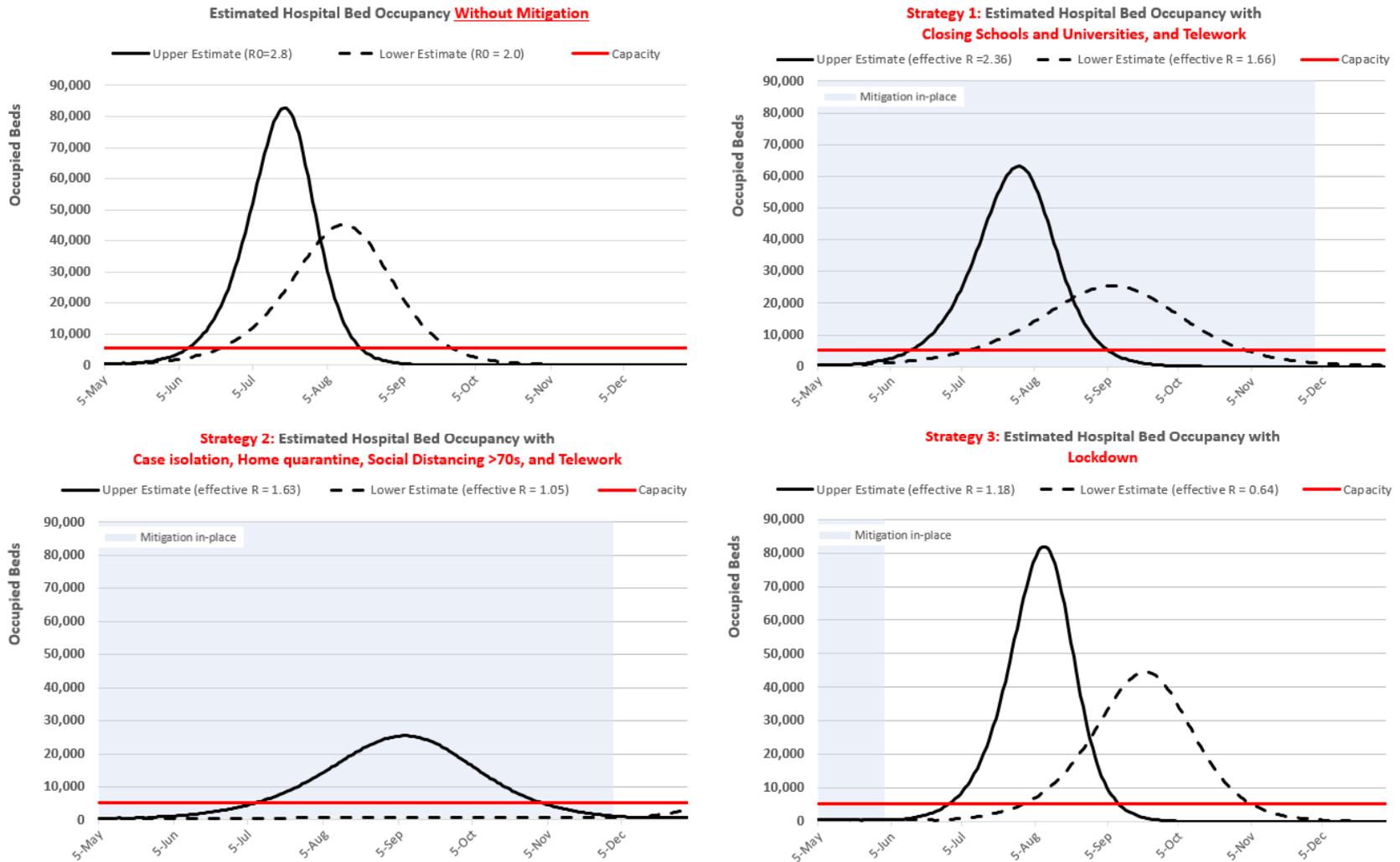
Notes. Solid curves: projections using the high estimate for the reproduction number. Dashed curves: projections using the low estimate for the reproduction number. Table 3 contains all reproduction numbers. Horizontal Red line: Hospital bed capacity. Blue shaded region: interventions in place.

3.3. Deaths averted with intervention

Based on the projected capacity to treat COVID patients in each region, the number of deaths resulting from patients being unable to obtain healthcare was 53,515 to 63,836 in RM, 7,130 to 8,567 in Araucanía, and 3,657 to 4,354 in Ñuble. With Strategy 2, the estimated number of deaths averted in RM ranged from 39,006 to 79,233 (36.6-63.2%), between 4,885 and 12,622 in Araucanía (35.2-77.1%), and 2,018 to 6,742 in Ñuble (27.8-79.1%) (Table 4). Lockdown eliminates between 99.8% and 99.9% of expected deaths in all three regions during the lockdown period, but deaths rise afterwards with the subsequent rebound of transmission.

3.4. Sensitivity Analyses

Figure 4 depicts the effects of shortening the duration of intervention Strategy 2 on hospital bed occupancy demands in RM to two (A), four (B), six (C) months of implementation versus our initial eight month (D) duration. Similar to our baseline results for Strategy 3 (Lockdown), these results show that effectiveness of interventions depends upon the length of time they overlap the epidemic period. Specifically, if too many susceptible individuals remain (i.e., insufficient herd immunity) at the time interventions are lifted, transmission will return. Even when interventions are less effective (R is higher), if the intervention remains in place past peak demand, the resulting outbreak may be smaller than when the same strategy is more effective (R is lower) but lifted prior to peak demand (Figure 4, Panel C).

Figure 4. Sensitivity analysis: Effects of the Duration of COVID19 Intervention Strategy 2 (case isolation, home quarantine, social distancing of population >70 years of age, and telework) on Hospital Bed Occupancy Demands in Región Metropolitana.
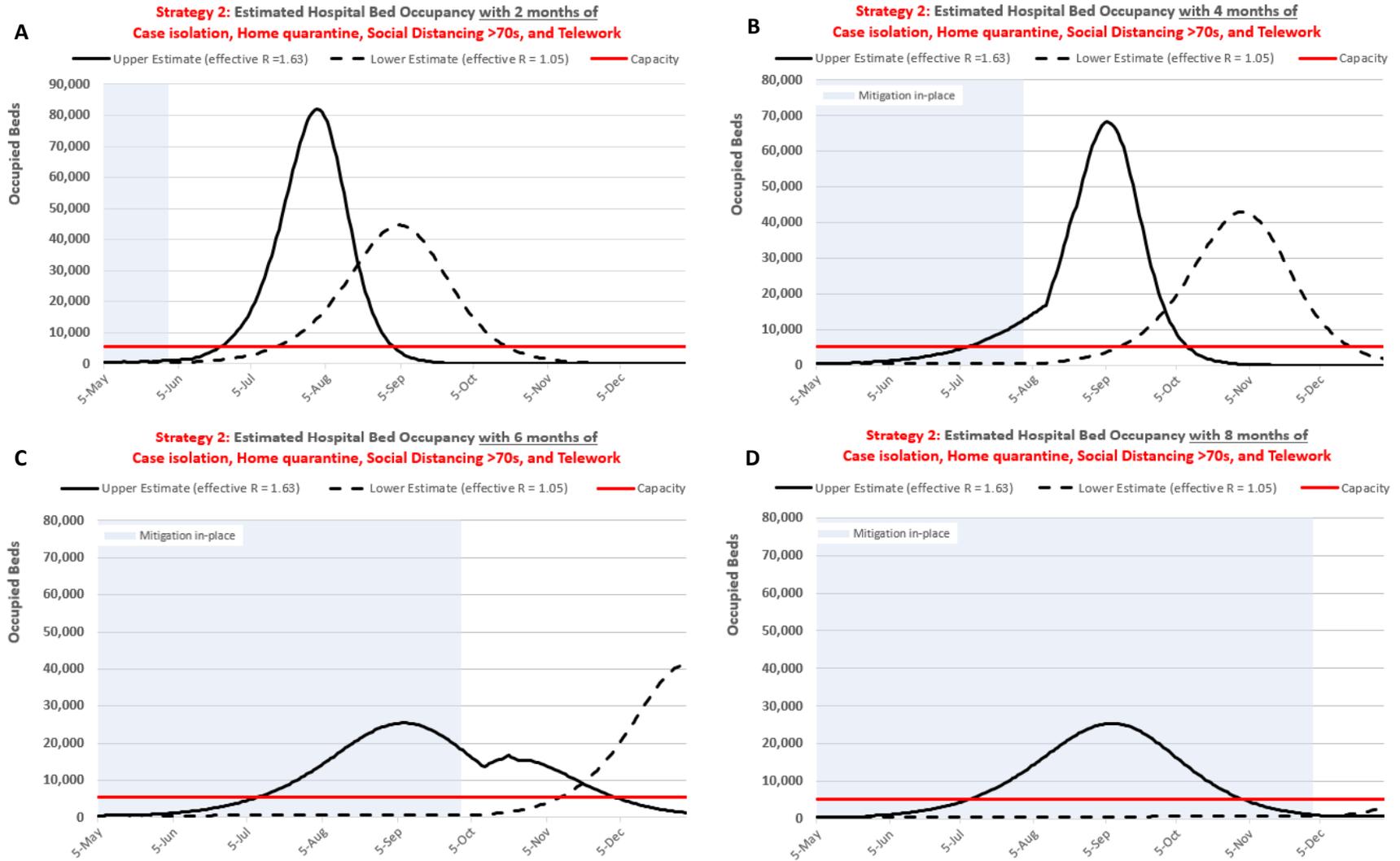
Notes: Duration for two months (A), four months (B), six months (C), and eight months (D) (and initiated on April 1, 2020). Solid and dashed curves reflect uncertainty in the effectiveness of intervention strategies (Table 3).

Figure 5. Sensitivity Analysis: Effects of a 2-month Lockdown Suppression Strategy alone (A) and followed by various mitigation strategies (C-D) for 6 months on Hospital Bed Occupancy Demands by COVID19 Cases.
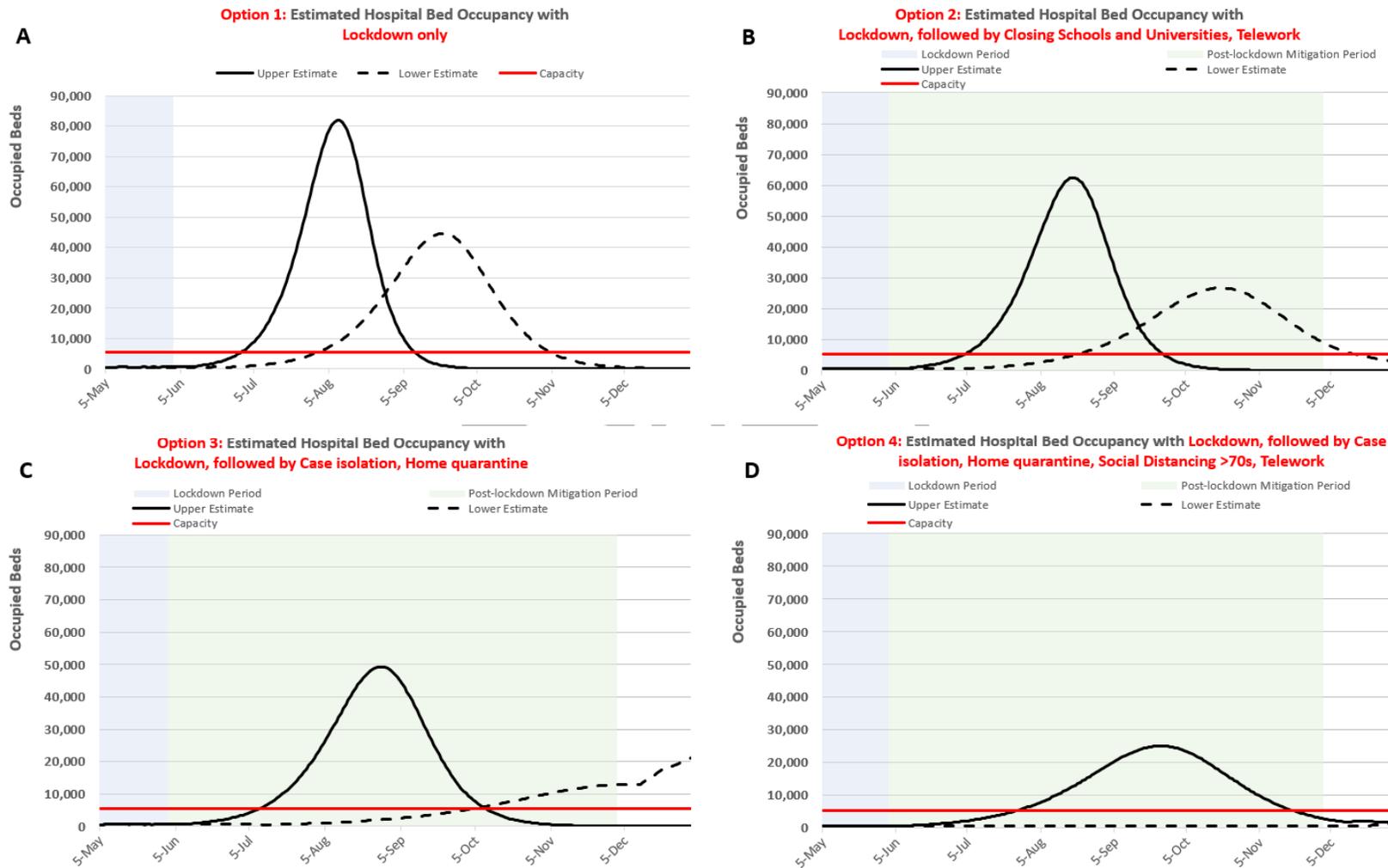
Notes: The various mitigation strategies following Lockdown Alone (A) include: Closing Schools and Universities + Telework (B), Case Isolation + Household Quarantine (C), and Case isolation, Household Quarantine, Social Distancing of >70 years of age, and Telework (D) Solid and dashed curves reflect uncertainty in the effectiveness of intervention strategies during both the Lockdown period and Post-lockdown intervention period per Table 3.

Figure 5 illustrates the results for combining a Lockdown suppression strategy with subsequent

mitigation strategies in RM. The benefit of this approach are an additional one to two months

delay in peak demand timing beyond delays afforded by each of the mitigation strategies on their

own. This approach, however, has no effect on the amount of demand (i.e. peak demand is

similar to the mitigation strategy without lockdown).

DISCUSSION

In the absence of immunization, our illustrative results suggest the number of severely ill patients

could overwhelm treatment capacity as early as late May to mid-June in all three regions of Chile

we evaluated. Our projections also suggest that with immediate aggressive action to implement

several combinations of interventions the current amount of hospital beds and critical care beds

may be sufficient. In specific circumstances, regional authorities may find it easier to augment

their current capacity (e.g., ventilators in Ñuble) along with some mitigation strategies to meet

demand versus strictly burdening society with disruptive mitigations. Policymakers should be

aware, however, that our results indicate that more effective intervention strategies at temporarily

suppressing transmission can also result in larger epidemics upon lifting the strategy than less

effective, longer-lasting strategies (in the absence of vaccine and changes in individual

behavior). As such, it may be necessary to keep societal-wide interventions in place, or

intermittently start and stop them again based on active monitoring of cases counts and treatment

capacity, until a vaccine or treatment that can be administered outside of the hospital setting are

available.

While our projections are reasonable estimates for how the pandemic may play out given our

current understanding of SARS-CoV-2, they should not be considered as forecasts of what will

occur. This is due to the uncertainty in our understanding of an outbreak that is still unfolding, the application of experiences of other countries to Chile (such as case severity, resource use by non-COVID patients, intervention effectiveness, compliance over time), simplifying assumptions (such as homogenous mixing), and case surveillance uncertainty. We assumed homogenous mixing to make implementing our model in a spreadsheet more tractable, but as a result, do not reflect potential important variabilities in contact patterns stemming from population social and spatial structures or behavior differences that can affect population disease dynamics. Since obtaining accurate data regarding contact patterns during an ongoing outbreak is challenging and because these patterns may evolve with the outbreak, we chose to focus on producing the simplest useful model. To address case surveillance uncertainty, users can scale upwards or downwards their case count inputs occurring over the prior two weeks based on perceived underreporting or overreporting and examine the influence on outputs (as we did in our illustrative scenario). Similarly, all assumptions and sources are explicitly presented in the tool, and all can be readily modified by the user to reflect their interests and as new information comes to light. Therefore, users should consider the value of this tool as its ability to support the evaluation of relative differences in results associated with "what-if" scenarios.

Our model has other limitations worth noting. Our estimates of beds and ventilators needed, and the number of deaths averted, also depends on associated resources not modeled here. Such resources include trained staff (respiratory therapists, nurses, and physicians) for the successful clinical management of hospitalized and ventilated patients and ancillary supplies associated with a bed or ventilator (e.g., electric circuits, oxygen). Furthermore, these resources may be impacted by the pandemic itself: staff absenteeism due to illnesses [58] and supply-chain disruptions in personal protective equipment (PPE) for healthcare personnel may further

exacerbate the situation. The effects of seasonality on the transmission dynamics of COVID19

remains unclear, but the transmission of similar respiratory illnesses (e.g., influenza, syncytial

virus) peaks in the wintertime [59, 60]. If COVID19 exhibits similar seasonality, or patients with

these other illnesses place additional demands on the healthcare system, there may be even fewer

resources available to treat COVID19 patients at the epidemic's peak. Finally, we do not

differentiate between specialized pediatric and non-pediatric resources. While this is justifiable

because the current pandemic does not appear to pose a great enough risk to children to

overwhelm pediatric healthcare capacity [39, 41, 61], users of the tool should take note of this

meaningful difference when inputting resource amounts.

Our model provides decision makers with the ability to examine the impacts of the current

COVID-19 pandemic in their jurisdictions and evaluate the effects of various social-distancing

mitigation strategies and augmenting treatment capacity on morbidity and mortality. The results

of our illustrative scenario underscore the need for policymakers to take immediate and

aggressive actions, and if they do so, substantial morbidity and mortality may be averted. As

more data become available (e.g., new treatments or healthcare capacity is augmented) and the

pandemic evolves (e.g., COVID case counts), our tool permits rapid updating of results

applicable for making decisions.

CHAPTER 4 – Study 3: Estimated COVID19 Cases and Hospitalizations Averted by Case Investigation and Contact Tracing in the US

INTRODUCTION

Reducing exposure to persons with communicable diseases through isolation and quarantine are basic tenets of transmission prevention. Public health programs regularly conduct case investigation and contact tracing (CICT) as a means of notifying persons infected with or exposed to communicable diseases and, often, of their need to isolate or quarantine. However, evidence of CICT's role in mitigating the COVID-19 pandemic thus far is lacking [62]. We recently showed, using data from 14 US jurisdictions (five states and nine local health districts), that CICT programs were effective at reducing SARS-CoV-2 transmission [63]. Despite these findings, the impact and consequent value of CICT remains controversial [64-66]. Some claim that the benefits are limited due to difficulty in scaling up services during COVID-19 case surges, or community reticence to participate in CICT, curtailing meaningful engagement between health departments and cases and their close contacts [64,67,68]. Between June 2020 and March 2021, the US Centers for Disease Control and Prevention (CDC) distributed more than $40 billion to state, local, and territorial health departments to support COVID-19 response activities, with a notable portion directed toward CICT activities [66]. A national review of these efforts from November 2020 to March 2021, indicates that upwards of 42,000-55,000 case investigators and contact tracers (per month) interviewed 9.1 million cases and identified and sought to notify 10.7 million contacts [66]. Given the unprecedented funding and effort surrounding CICT and continuing debate surrounding its value it is important to quantify for public health decision makers the benefits associated with sustaining and/or improving CICT programs.

We sought to provide public health practitioners with a model that allows them to estimate on their own the health impacts of CICT programs in their jurisdictions. We also use this model to present an expanded profile of national CICT impacts in the US at its busiest point of the pandemic before vaccination was available: 60 days from November 25, 2020, to January 23, 2021. Our analysis combines primary CICT implementation data with mathematical modeling to estimate the number of cases and hospitalizations averted by COVID-19 CICT programs across US states and territories.

METHODS

We used CDC's COVIDTracer Advanced modeling tool [69] in combination with data from CICT programs to estimate cases and hospitalizations averted by CICT activities among states and territories funded by CDC's Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases (ELC) program. We focused on the 60-day period from November 25, 2020 to January 23, 2021.

Data

Sixty-four health departments receiving CICT funding report to CDC's ELC program monthly on the performance of their CICT programs [66]. We used reported metrics from each jurisdiction to derive its CICT effectiveness for the 60-day analysis period: the proportion of cases and contacts that entered isolation and quarantine because of CICT efforts, and the days required to do so (Appendix 3, *Case Investigation and Contact Tracing Effectiveness* section and Figure A2). Reported metrics used to calculated CICT effectiveness include the proportions of cases interviewed, contacts notified or monitored, and number of days from testing to case and

contact notification. A summary of these data and assumptions used to calculate a range of CICT effectiveness values for each jurisdiction are detailed further below and in Appendix 3 (*Case Investigation and Contact Tracing Effectiveness* section and Table A4). We limited our analysis to those jurisdictions that reported all the required metrics and passed our data quality checks (*e.g.,* the number of contacts identified ≥ number cases that provided at least one contact, the number of contacts identified ≥ contacts notified; Figure A3 in Appendix 3).

Model Use

COVIDTracer Advanced is a deterministic Susceptible-Exposed-Infectious-Recovered (SEIR) epidemiological model that illustrates the spread of COVID-19 and impact of interventions in a user-defined population. The tool allows users to attribute reductions in transmission to either CICT or to a combination of vaccination and all other non-pharmaceutical interventions (other NPIs), such as facemask policies, large gathering restrictions, and school/business closures (Appendix 3, *COVIDTracer Advanced Model* section, Tables A1-A3, Figure A1). Estimates of reductions in transmission from CICT were obtained by first entering each jurisdiction's CICT effectiveness into COVIDTracer Advanced. After inputting the CICT effectiveness values for a jurisdiction, we estimated reductions in transmission due to other NPIs and any inceptive vaccination efforts. We accomplished this by "fitting" the curve of cumulative cases modeled by COVIDTracer Advanced to the jurisdiction's reported cases [70] by altering the percentage reduction in transmission ascribed to vaccine and other NPIs. The value that minimized the deviation (mean-squared error) between the fitted and reported case curves was our estimated effectiveness of vaccine and other NPIs. Then we "switched off" CICT (by setting CICT

effectiveness to zero) while maintaining the estimated effectiveness of vaccine and other NPIs. This simulated what would have happened if CICT had not occurred.

Outcome Measures

Estimates of CICT-averted cases were obtained by taking the difference between the model-simulated curve without CICT and jurisdictions' actual cumulative cases. We also calculated averted hospitalizations by multiplying the estimated number of averted cases by age-stratified infection-to-hospitalization rates (Table A3 in Appendix 3). In addition to calculating the absolute number of cases and hospitalizations averted by CICT in each jurisdiction, we calculated two measures of CICT impact to allow comparison among jurisdictions: 1) averted cases and hospitalizations per 100,000 population, and 2) the proportion of cases or hospitalizations averted by CICT out of the remaining cases, after accounting for the impact of vaccination and other NPIs. This latter measure may be interpreted as the number of cases (or hospitalizations) averted by CICT among every 100 cases (or hospitalizations) that were not prevented by vaccination and other NPIs. Finally, we grouped jurisdictions by their US Census Region and compared the group medians of cases averted per 100,000 population to assess whether CICT impact differed among regions [71].

Range of estimates

Jurisdictions did not report the proportions of cases that effectively isolated and contacts that correctly quarantined. Absent compliance data, we generated a range of averted cases and hospitalizations to circumscribe the possible impact of CICT. High estimates were calculated by assuming all the cases a jurisdiction interviewed and all the contacts it actively monitored fully complied [63] with CDC-recommended isolation and quarantine guidelines (Table 6) [72]. In our

high estimate scenario, we also assumed that contacts who were notified but not actively

monitored did not quarantine. That is, we assumed that the cases and contacts CICT programs

engaged either fully complied or not at all in this scenario. To produce our low estimates,

however, we altered the effect of CICT program's engagement by lowering the proportions of

cases/contacts entering isolation or quarantine based on values derived from the literature

(*Isolation/Quarantine Compliance* section in Appendix 3) [68,73,74. Specifically, we assumed

80% of cases that completed interviews, 80% of monitored contacts, and 30% of notified

contacts (that were not actively monitored) fully complied with isolation and quarantine

guidance (Table 6).

Table 6. Assumed proportions of confirmed COVID19 cases and their contacts that effectively isolated or quarantined in each analysis scenario.

	Low impact Scenario (%)	High impact Scenario (%)	Sensitivity Analysis (%)
Confirmed Cases that completed interviews	80	100	100
Confirmed Cases that did not complete interviews[a,b]	0	0	0
Contacts that were notified and monitored	80	100	100
Contacts that were notified but not monitored	30	0	100
Contacts that were not notified by their health department[b]	0	0	0

Notes: Each row is a mutually exclusive group of cases or contacts. The sum of each row (or column) does not add up to 100%, as the numbers represent the assumed compliance within each group. 0% compliance means none of the cases or contacts in a group isolated or quarantined effectively. 100% means all the cases or contacts in a group isolated or quarantined effectively after being interviewed or notified.
[a] Includes cases that weren't reached and those that were reached but who did not agree to be interviewed.
[b] Compliance was set to zero for these case/contact group categories because any transmission reductions from quarantine and isolation are not attributable to direct interactions with health department's CICT staff, and, therefore outside of the scope of this analysis. Their inclusion here is to help distinguish between the various cases/contacts types.

In our model, and irrespective of the above scenarios, infected individuals may transmit to others until interactions with their health department prompt them to isolate or quarantine. Also, both estimates do not include unmeasured changes in behavior from sources of information other than phone calls/texts from CICT programs (*e.g.,* cases informing their own contacts), as measuring the influence of such factors are beyond our estimation goals.

We also conducted two sensitivity analyses. The first evaluated a scenario in which all interviewed cases and all contacts notified of their exposure fully complied with CDC-recommended quarantine guidelines. We chose this aspirational scenario to understand the potential impact of CICT assuming maximum community cooperation. Our second sensitivity analysis evaluated the effects of assuming a background amount of isolation and quarantining would have occurred without direct interactions with health departments. That is, instead of setting CICT effectiveness to zero to simulate an epidemic curve without CICT, we assumed 20% of interviewed cases would have isolated anyways, and 2.5% of notified contacts would have learned of their exposure via other means (*e.g.,* parents receiving notice of their child's exposure at school) and acted on this knowledge by effectively quarantining. It should be noted that these values represent a hypothetical counterfactual scenario as there is no data on what interviewed cases and notified contacts would have done in the absence of their interactions with their health departments.

RESULTS

Twenty-two US states and one territory met our data requirements for inclusion in the analysis (Figure A3 in Appendix 3). These 23 jurisdictions had a combined population of approximately 140 million persons, covering 42.5% of the entire US population and all 4 census regions [71].

Jurisdictions in our analysis reported metrics (% of cases interviewed and contacts notified, and contact notification speed) that were similar to those reported by all 64 federally funded CICT programs (Table A4 in Appendix 3).

We estimated that CICT averted 1.11 to 1.36 million cases and 27,231 to 33,527 hospitalizations from November 25, 2020, to January 23, 2021, across all 23 jurisdictions analyzed (Figure 6 and Figure A4 and Table A5 in Appendix 3). The lower estimates assume fractions of interviewed cases and contacts complied with isolation and quarantine guidelines, while the upper estimates assume all interviewed cases and monitored contacts did so (Table 6). The median number of estimated cases averted per 100,000 population ranged from 704 (low impact scenario) to 895 (high impact scenario). After accounting for the impact of vaccination and other NPIs, the median estimate of the percent of cases averted was 19.1% (range: 1.3 – 65.8%) in the low impact scenario and 23.5% (range: 1.6 – 58.7%) in the high impact scenario (Table A5 in Appendix 3).

On average, the number of estimated cases averted was greater among jurisdictions with larger populations, with more jurisdictions in the top half of Figure 6, Panel A having greater populations than those in the bottom half: the median population size of jurisdictions in the top half was 6.4 million (IQR: 4.8 – 9.2 million) and 3.2 million (IQR: 1.0 – 6.0 million) for the bottom half. However, per our estimates, CICT programs in jurisdictions with smaller populations often averted more cases on a per population basis (Figure 6, Panel B). Jurisdictions in the smallest population category (less than 1 million) averted the most cases per population (median: 1,714 – 1,875 per 100k population); more than twice the overall median (704 - 895 per 100k population).

We estimate that jurisdictions in the Midwest US averted the most cases on a per population basis because of CICT, averting between 1,444 cases per 100,000 population (in our low impact scenario) and 1,600 (in our high impact scenario) (Table 7). CICT programs among jurisdictions in the Western US were the least effective by our estimates, averting 488 cases per 100,000 (in our low impact scenario) to 568 (in our high impact scenario).

When we maximized compliance among interviewed cases and notified contacts (Table 6), we estimated that CICT could have averted 1.72 million cases and 42,2631 hospitalizations (approximately 26% greater than our high baseline estimate) across the 23 jurisdictions during the 60-day study period. And, when we accounted for the potential that some cases and contacts would have isolated and quarantined even without CICT program interviews or notification, we estimated that CICT would have averted 0.77 to 1.01 million cases and 18,998 to 24,845 hospitalizations (30% and 26% less than our baseline low and high impact estimates, respectively).

Figure 6. Estimated COVID-19 Cases Averted by Case Investigation and Contact Tracing, by Jurisdiction, November 25, 2020-January 23, 2021 (60 days)
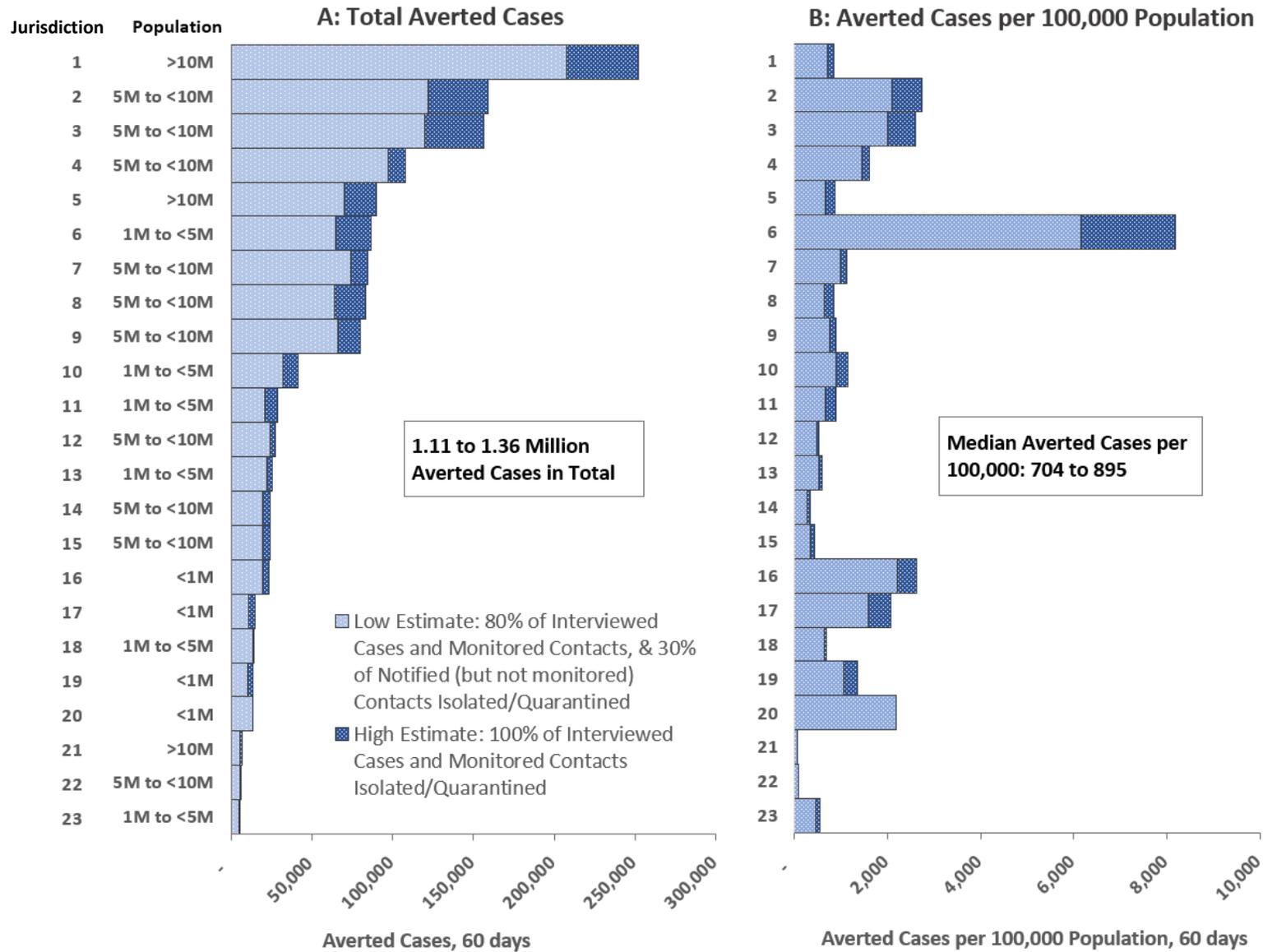
Table 7. COVID19 Case Investigation and Contact Tracing Effectiveness and Health Impacts, by US Census Region (from 11/25/20 – 1/23/21)

US Census Regions	No. States[c]	Total Population	Daily COVID-19 Incidence per 100k, mean (Range)	CICT Effectiveness[b], Median (Range)			Estimated Cases Averted, Median (Range)		Estimated Cases Averted per 100k Population, Median (Range)	
				Days from infection to isolation	Cases isolated, low (%)	Cases isolated, high (%)	Low	High	Low	High
Midwest	5	30,947,757	58 (42-75)	7 (6-7)	17 (15-25)	19 (18-28)	73,780 (19,577-121,865)	84,523 (23,221-158,766)	1,444 (639-2,213)	1,600 (838-2,727)
Northeast	5	25,348,752	59 (19-92)	7 (6-10)	16 (4-35)	19 (5-34)	32,084 (5,921-66,362)	41,194 (7,005-86,692)	900 (53-6,139)	1,155 (62-8,183)
South	7	33,384,859	55 (22-88)	8 (7-12)	19 (14-41)	24 (16-49)	21,170 (5,466-120,157)	27,473 (6,452-156,557)	670 (80-1,987)	895 (94-2,590)
West	6	49,893,913	61 (28-94)	8 (7-9)	14 (4-23)	17 (5-24)	19,484 (4,858-207,417)	24,326 (5,721-252,325)	488 (271-704)	568 (336-856)
Total	23	139,575,281	58 (19-94)	7 (6-12)	17 (4-41)	19 (5-49)	22,014 (4,858-207,417)	27,473 (5,721-252,325)	704 (53-6,139)	895 (62-8,183)

Notes: Range = minimum and maximum values
[a] Defined by the US Census Bureau [71].
[b] Days from infection to isolation calculated using jurisdictions' reported days from testing to case and contact notification, the COVID-19 incubation period, and assumptions regarding the timing of entry into isolation/quarantine after notification. Percent cases isolated calculated from jurisdictions' reported metrics on CICT program performance, such as the proportions of cases interviewed, and contacts notified or monitored. The lower estimates assume a fraction of interviewed cases and contacts complied with isolation and quarantine guidelines, while the high estimates assume all interviewed cases and monitored contacts did so (Table 6 and Appendix 3).
[c] Includes 22 states (3 with a major city excluded) and 1 territory.

DISCUSSION

In this decision analytical model study, we estimated that CICT programs in 23 US jurisdictions potentially averted 1.11-1.36 million cases and 27,231-33,527 hospitalizations in a 60-day period during the 2020-21 winter surge. There were 5,269,390 total cases reported across these jurisdictions during the same 60-day period, suggesting that CICT may have reduced the COVID-19 burden by 17 to 21%. Our range of estimates reflect uncertainties regarding the proportions of cases and contacts that effectively isolated or quarantined because of interactions with their health departments. Despite this uncertainty, our estimates of CICT impact were substantial, with averted cases exceeding 1 million across the 23 jurisdictions in our low impact scenario.

While our aggregate estimated impact was sizeable, it was uneven across the jurisdictions: In the lowest performing jurisdiction, we estimated that CICT averted 1 out of every 100 remaining cases not prevented by nascent vaccination efforts and other NPIs, and as many as 66 cases in the highest performing jurisdiction. We also found that population size was correlated with our estimates of CICT impact. On average, our estimates suggest that jurisdictions with larger populations averted more cases, although this was expected given their larger populations eligible for protection. Conversely, the smallest jurisdictions averted the most cases on a per-population basis. This result may reflect, in part, that smaller jurisdictions were able to rely on existing CICT staff who had community knowledge and experience connecting with the population, while the caseloads in larger jurisdictions required hiring temporary, less experienced staff. A multivariable analysis, using data from several months of the pandemic, is needed to tease apart the effects of such factors. For example, population size alone cannot explain the variability in our estimated impacts. Jurisdictions 5, 6, and 7 were in different

population categories (with jurisdiction 5 being 10 times larger than jurisdiction 6), but all three jurisdictions averted approximately 87,000 cases under our high impact scenario (Figure 6, Panel A). Jurisdiction 6's CICT program is also notable for averting the most cases per 100,000. This result reflects the jurisdiction's success at interviewing cases (79% interviewed and >50% named at least 1 contact) and being among the fastest to notify contacts (6 days after cases were likely infected).

We also found regional differences in CICT impact. Based on the median averted case estimates per 100,000 population, Midwest jurisdictions' CICT programs performed the best, while CICT programs in Western jurisdictions were least impactful. Future studies exploring the potential reasons for these differences may consider incidence, factors affecting public acceptance of CICT (*e.g.,* sociodemographic makeup and cultural norms), and aspects of program implementation (*e.g.,* staffing levels and efficiency).

Our sizeable estimates of averted cases are partially due to the success of the analyzed CICT programs at suppressing the transmission not controlled by vaccination and other NPIs, compounded over approximately 10 generations of infection during our 60-day observation period. For example, at jurisdiction 1, where our estimates of the absolute impact of CICT was greatest, CICT was responsible for just a 3.0 to 3.5% reduction in new infections per case (Table A5 in Appendix 3). However, jurisdiction 1 also had a very large burden of infectious cases at the start of our 60-day period and was one of the largest jurisdictions. This example shows that even when the percentage reduction in transmission from CICT is in the low single digits, when applied to large populations, the influence over multiple generations of cases is meaningful. This analysis was possible because of the rich and unique programmatic data provided by jurisdictions and the use of assumptions to address key uncertainties, such as the compliance

with public health recommendations. Still, important information was absent. As such, our results of CICT's impact may over- or under-estimate the true impact. Our impact estimates may be low because we do not account for the indirect effects of CICT programs on transmission reductions. For example, due to their interactions with health department staff, cases and contacts may have additionally notified and motivated isolation/quarantining among close contacts whom, themselves, were not contacted by the CICT program. And some individuals may have isolated/quarantined without being contacted, because of CICT program-funded ad campaigns or information obtained from their health department's website. Other factors may have affected our estimates, although the direction of their effect is less clear. For example, we may have over- or under-estimated CICT's impact if the calculated number of contacts per case for each jurisdiction (Appendix 3, Term B.1.1), the timing of testing and initiation of isolation/quarantine, or the compliance with public health recommendations differed from our examined scenarios.

This study was performed before the Delta or Omicron variants dominated transmission in the US, and before vaccine was widely available. Increasing vaccination may be expected to reduce the absolute number of cases eligible to be averted by CICT. However, CICT's effectiveness (*i.e.,* percent of cases isolated by CICT) would increase if jurisdictions are able to prioritize notification and monitoring of unvaccinated or under-vaccinated populations, especially during periods of high caseloads. Further, the impact of CICT can be potentially reduced when Delta or Omicron variants are predominately circulating due to their earlier and shorter duration of infectiousness. Alternatively, the higher transmissibility of the Delta and Omicron variants potentially increases CICT's impact since each averted case prevents more new infections than we originally allowed. The degree to which these factors offset one another is unclear.

Our study has several strengths. Foremost, the breadth of data on CICT implementation enabled

us to generate a profile of CICT impact for nearly half of the US. By anonymizing jurisdictions

and assessing the same time frame, we were able to present and compare the range of impacts

among 23 CICT programs spanning the country. Further, this work can be replicated for other

jurisdictions and time periods. The tool that we used, COVIDTracer Advanced [69], is provided

(Appendix 4) and designed for use by practicing public health officials. Jurisdictions can conduct

site-specific analyses using these methods to estimate prevention impact, guide local public

health programming, and reflect on resource utilization (*e.g.,* hospital beds).

Our study also has limitations. Jurisdictions' self-reported CICT performance measures were not

intended for this analysis. Although we employed the previously described data quality checks

(Figure A3 in Appendix 3), the reported measures that we used were likely influenced by

differences in jurisdictions' surveillance systems, CICT platforms and protocols (*e.g.,* how they

defined, enrolled, and monitored contacts). The extent to which these differences affected our

results is unclear. We also only assess the impact over two months (60 days) of the pandemic and

in 23 US jurisdictions. Results may differ for other jurisdictions and periods (*e.g.,* during the

Delta or Omicron surges and wider use of vaccine). Because cases were spiking across the entire

US during the period that we analyzed and the vaccine had not yet been widely administered, it

is likely that our estimates provide an upper limit of cases averted by CICT during the pandemic

as of this writing (August 31, 2021). Also, because we used statewide data, our results dilute

potentially meaningful differences in CICT performance within jurisdictions (*e.g.,* rural versus

urban counties). Finally, the accuracy of our results may be affected by our model's design. For

example, the COVIDTracer Advanced model assumes homogeneous mixing among individuals

in the population and does not account for any age- or location-based heterogeneities in

transmission (such as within and between households or schools), or variations in the effectiveness of vaccine and other NPIs over the study period. The extent of the influence of these factors, however, appears limited and would not appreciably alter our estimates or their implications for public health policy makers (see Appendix 3, *Additional Results and Commentary, Effect of alternate fitting methods,* Figure A5 and Table A6).

Our analysis combined primary implementation data with mathematical modeling to estimate the health impact of COVID-19 case investigation and contact tracing programs across nearly half of US state and territory. The volume of estimated cases and hospitalizations averted underscores the critical role CICT programs play in curtailing the pandemic, while differences among jurisdictions illustrate the opportunities to further improve effectiveness. Case investigation and contact tracing remain CDC-recommended practices for personally communicating individualized prevention activities against COVID-19 [75]. This work quantifies for public health decision makers the benefits from sustaining and improving these programs.

CHAPTER 5 – Dissertation Summary and Future Directions of Research

The results of studies in this dissertation demonstrates the value of the biological and public health sciences and the benefits of investing in public health infrastructure and programs. We estimated millions of averted healthcare visits across all three studies by employing the immunizations and non-pharmaceutical interventions examined. Additionally, our evaluation of CICT is the first (to our knowledge) to offer policy makers with a profile of this intervention's impact across the US.

With the provided models, each study enables decision makers to rapidly evaluate on their own, locally applicable policy scenarios and their effects on healthcare capacity, both now and in the future. For example, the illustrative results produced with our RSV I^2M, can be updated by using the results of future clinical studies on the efficacy and length of protection offered by the immunization products evaluated, even post-licensure. And, even though we found limited impact of the evaluated products on deaths averted in the United States, our analysis can be re-run in other countries where RSV-associated deaths are more common. Similarly, our models examining the effects of non-pharmaceutical interventions such as social distancing measures and contact tracing on COVID19 healthcare utilization were able to be rapidly updated by public health practitioners. Practitioner's ability to evaluate "what-if" scenarios as they arise is paramount in the early phase of outbreak, where a delay in decision-making may be more costly than the choice of intervention itself (as we showed). And this flexibility may be useful in the future too as the models in our latter studies can be reused for the next respiratory disease outbreak. Future enhancements to these models can include an accounting for vaccination or variabilities in contact patterns associated with population social and spatial structures that can affect disease dynamics. Our analysis of CICT revealed large variabilities in the performance of

states. Future research should endeavor to understand these differences and the extent to which they are associated with either programmatic implementation options (under the control of public health officials) or societal characteristics that dictate public reception to phone calls from health departments and isolation/quarantine guidance. Additionally, this analysis can be replicated for periods where other COVID variants (i.e., Delta or Omicron) dominated transmission.

The models in this dissertation were developed with the intent that practicing public health officials would use them to assist with decision-making. This aim steered us to make several methodological and practical choices during their development that distinguish them from models, for example, that are produced for the purposes of academic research. The guiding attributes we used are provided in Table 8 and may be considered as a subjective list that define a "good" model from the public health practitioner perspective. In this table, attributes are assigned to either improving model utility, trust in the model, and/or accessibility. Model utility refers to the degree to which model outputs satisfy questions public health practitioners desire to answer with the model. A useful model is one that provides practitioners with a complete understanding of how to interpret the results, along with any uncertainty and limitations associated with them. Trust in the model refers to the practitioners' confidence that the methods employed sufficiently account for all the critical features of disease dynamics and interventions considered and that the results are valid. Finally, accessibility refers to the ease with which users can use the model to produce results. This entails the cost to run a model (when specific software must be purchased) and the time needed to learn how to use the model, including the time needed to familiarize oneself with the navigation of the interface, input and output definitions, assumptions, and obtaining the necessary input data.

Table 8. Model attributes associated with useful, trusted, and accessible models from a public health practitioners' perspective.

Model Attributes	Example from the three dissertation studies	Utility	Trust in the Model	Accessibility
Software-related				
Transparent and modifiable calculations	No programming language knowledge needed to review formulas or logic		X	X
Free, ubiquitous, & familiar platform	We used spreadsheets for all models		X	X
Model framework – related				
Use the simplest useful model	1) Employed a Cohort-type model to evaluate RSV immunization effects versus a model that accounts for few anticipated herd effects. 2) Assumed homogenous population mixing for both COVID19 models versus parameterizing complex and uncertain contact structures.		X	X
Results/Outcomes are understandable	Use of averted healthcare visits and hospitalizations as outcomes from all models are easy to explain and justify to non-modelers (e.g., politicians and the public).	X		X
Key inputs are values familiar to public health officials	CICT evaluation model inputs on program performance were generated by health departments, the intended audience (versus parameters on disease dynamics [e.g., infectivity distribution] which were provided).	X	X	X
Calculations rely on algebraic math	Discretized the time step of analyses in compartmental models versus relying on differential equations.		X	X
How the models accommodate desired use				
Model's purpose is clear, designed to answer just a few, focused questions	The stated goal for RSV I^{2}M clarifies the intended beneficiary of the intervention (infants < 1yr), the time horizon evaluated (their first RSV season), and the measure of efficacy (medically attended LRTI visits).	X	X	
Model deals with uncertainty	1) The range of CICT's estimated impact was based on the degree of isolation/quarantine compliance, an unknown quantity. 2) COVID19 forecasts of healthcare use were produced for a range of social-distancing effects	X	X	
Assumptions and sources explicitly presented in the modeling tools			X	
Support examination of multiple scenarios that interest practitioners	COVIDTracer Advanced allows users to enter up to 3 contact tracing effectiveness scenarios simultaneously and compare the associated simulated epidemic curves	X		
Models can be readily updated with new data	Users of RSV I^{2}M can easily toggle uptake, efficacy, and duration of protection values	X		

Those who wish to produce their own models for public health officials may evaluate their

efforts by considering Table 8 as a checklist of sorts, seeing how many of the listed attributes

describe their model. Ultimately, however, models should be evaluated on whether they are used

or not and on feedback received from the intended audience. The RSV I^2M model was used by

coauthors to generate results on averted healthcare visits that were presented to the US Advisory

Committee on Immunization Practices (ACIP), the body which develops recommendations for

U.S. immunizations, including ages when vaccines should be given, number of doses, time

between doses, and precautions and contraindications. And coauthors of the model evaluating

social-distancing impacts on COVID19 transmission presented results to the Chilean Ministry of

Health soon after the model was developed. Those results contributed to decisions to

aggressively implement and expand various social distancing measures in Chile. Finally, this

model's calculations served as the basis for CDC's COVIDSurge model, one of three models

produced by CDC, including COVIDTracer Advanced used in study 3, that were downloaded

more than 100,000 times over the course of the pandemic (CDC, unpublished).

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APPENDICES

APPENDIX 1 – Additional Methods and Results for Study 1

RSV I²M can be downloaded here: https://ars.els-cdn.com/content/image/1-s2.0-
S0264410X19313866-mmc1.xlsx

Illustrative Scenario Inputs

Table 2 in the main text outlines the major inputs and parameter values used in this illustration. Our modeled annual birth cohort was 3,945,875, based on the 2016 Vital Statistics Report [22]. The proportion of high-risk births was based on a recent study that assessed palivizumab utilization [23]. Hospitalization rates for high-risk infants were based on hospitalization rates found amongst those who did not receive palivizumab in the original clinical trials [31, 32]. We obtained all-risk rates of MA-RSVi from population-based surveillance data published by the New Vaccine Surveillance Network (NVSN, Table A1) [4, 5]. We based the proportions of outpatient clinic and ED visits resulting in an LRTI on the average proportion of lab-confirmed RSV visits in NVSN from 2002-2009 with any of the following diagnoses: croup, bronchiolitis, bronchitis, pneumonia, or asthma (CDC, unpublished). All hospitalized patients were assumed to have an LRTI. Case fatality ratios among hospitalized infants were based on estimates for high income/industrialized countries [1]. The RSV season was determined by the monthly distribution of outpatient, ED and hospital visits across NVSN during the 2000-2009 seasons (CDC, unpublished; Figure A1). The estimate for palivizumab uptake (38%) is based on a recent study that defined compliance as receipt of all recommended doses [24, 25]. For the Antibody Candidate (anticipated to be a single injection), we assumed 71% uptake among low-risk newborns, based upon vaccination rates for the birth dose of hepatitis B vaccine [27], and 80% among high-risk newborns, which is an estimate of the percent of high-risk newborns that receive at least one dose of palivizumab [23]. For the Maternal Vaccine Candidate, we based uptake (56%) on TdaP (tetanus, diphtheria, and pertussis) immunization in pregnant women because, like the maternal RSV vaccine, it is also given in the third trimester of pregnancy [28]. The efficacy used for palivizumab (51%) was based on a meta-analysis of randomized controlled trials among high-risk infants where the endpoint was hospitalizations [29]. For the model, we assumed palivizumab reduces outpatient clinic and ED visits by the same percentage as hospitalizations. For the antibody candidate, we based efficacy (80%) against inpatient and outpatient MA-RSVi on findings from a clinical trial in term infants

of an antibody product similar to palivizumab [30]. Since maternal vaccine also provides passive antibody protection to infants, we used the same efficacy for this product. We used 0.919 for the maternal vaccine reduction factor, which accounts for the percentage of infants acquiring antibodies successfully from their mothers (see Appendix 2 section "Maternal Vaccine Candidate"). Duration of protection was based on the endpoints of the clinical trials for each of the products (Table 2, main text) [10, 11, 31, 32].

Table A1
US Population-based Rates per 1000 for Medically-Attended RSV infections by health care setting and month-of-age

| Age (months)	Outpatient Clinic Visits [5]		Emergency Department Visits [5]		Hospitalizations [4]	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
0	85.2	(71.0-99.3)	19.6	(16.8-22.4)	13.5	(10.3-17.1)
1	187.9	(156.6-219.1)	64.2	(54.9-73.4)	25.9	(21.3-30.8)
2	234.2	(195.2-273.1)	72.4	(62.0-82.9)	14.3	(11.1-17.8)
3	232.6	(194.0-271.3)	105.2	(90.1-120.4)	10.3	(7.7-13.5)
4	265.0	(221.0-309.1)	116.0	(99.3-132.7)	8.9	(6.3-11.8)
5	289.2	(241.1-337.2)	71.3	(61.1-81.6)	4.8	(2.9-7.0)
6	264.7	(220.7-308.7)	81.8	(70.1-93.6)	4.1	(2.5-6.2)
7	207.2	(172.8-241.7)	56.1	(48.0-64.2)	5.6	(3.6-8.0)
8	277.8	(231.7-324.0)	55.6	(47.6-63.5)	3.4	(1.8-5.2)
9	227.2	(189.4-264.9)	55.6	(47.6-63.6)	3.8	(2.1-6.0)
10	241.7	(201.5-281.8)	40.4	(34.6-46.2)	3.7	(2.0-5.7)
11	258.1	(215.2-301.0)	55.6	(47.6-63.6)	2.9	(1.5-4.8)
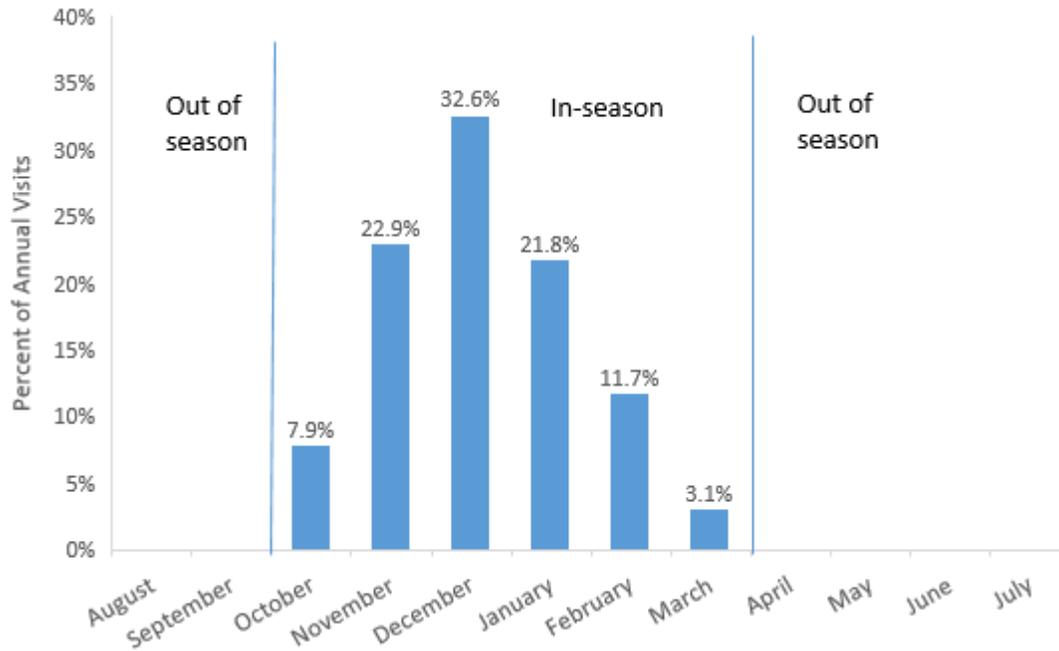
Figure A1. Seasonal Distribution of Medically-Attended RSV infections in the US (National-level). Source: CDC, unpublished

"High-Risk" births and RSV risk

In our analysis "high-risk births" refers to infants who are recommended to receive palivizumab under current guidelines [8] and in our strategies I and III. In our illustrative scenario we calculated that 0.98% of all births are eligible to receive palivizumab in the US [23]. 0.98% is the sum of the percent of all births with the following three conditions associated with elevated RSVi risk: 1) hemodynamically significant congenital heart disease (CHD), 2) chronic lung disease of prematurity (CLD), and 3) prematurity (defined as <29 weeks gestation) without CHD or CLD (Table A2). We then obtained the hospitalization rates for each high-risk condition from hospitalization rates found amongst those who did not receive palivizumab in the original clinical trials [31, 32]. Next, we multiplied the percent of infants with each condition who are hospitalized with RSV by the proportion of all US births with the condition to determine the % of all live births for each high-risk condition that are hospitalized (Table A2). The sum of this product across all three conditions was 0.0913% and represents the percentage of live births with a high-risk condition that are hospitalized due to RSV. RSV I^2M permits users to redefine high-risk conditions as they wish, accounting for up to four such conditions.

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Table A2
Conditions Associated with Elevated Risk for RSV Infection and Percent Hospitalized

High-Risk condition	%, live births [23]	%, with condition hospitalized for RSV [31, 32]	%, live births with condition hospitalized for RSV*
Hemodynamically significant congenital heart disease (CHD)	0.39%	9.7%	0.0378%
Chronic lung disease of prematurity (CLD)	0.12%	12.8%	0.0154%
Prematurity (<29 weeks gestation), without CHD or CLD	0.47%	8.1%	0.0381%
% of live births with a high-risk condition hospitalized due to RSV (column sum)→			0.0913%

* Product of row data in prior two columns

Proportion of high and low risk infants

Although there was a placebo-controlled trial that showed palivizumab reduces MA-RSVi without hospitalization in preterm infants 33-35 weeks [33], there are no data available regarding the efficacy of palivizumab in reducing MA-RSVi in the outpatient clinic and ED settings among infants we define as "high-risk". Therefore, we assumed the ratio of rates between high- and low-risk infants in the outpatient clinic and ED settings is the same as the ratio of hospitalization rates for high- and low-risk infants, and that palivizumab would have the same efficacy for preventing cases in these settings. We obtained the ratio of hospitalization rates for high- and low- risk infants by subtracting the expected number of high-risk hospitalizations from the expected number of all-risk hospitalizations. Expected all-risk hospitalizations were obtained by multiplying the birth cohort times the age-based rates in Table A1 and expected high-risk hospitalizations were obtained by multiplying the birth cohort times the percent of live births with a high-risk condition hospitalized due to RSV (0.0913%, from Table A2). These calculations resulted in a ratio of 8.4 low-risk visits for every high-risk visit (range 5.9 to 11.4, when using the 2.5 and 97.5 percentiles values from Table S1 for all-risk rates).
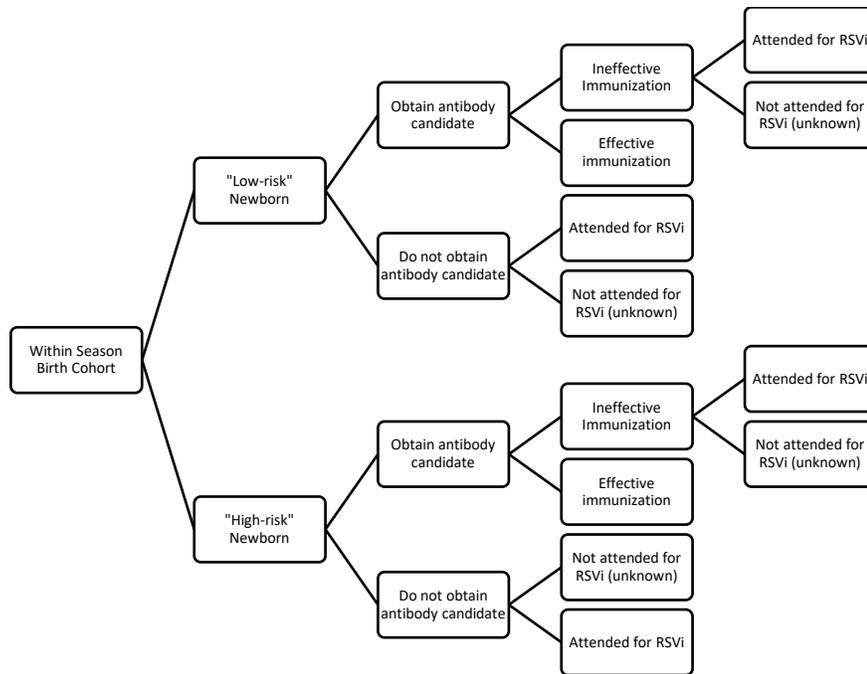
Within Season Birth Cohort

"Low-risk" Newborn

Obtain antibody candidate — Ineffective Immunization — Attended for RSVi / Not attended for RSVi (unknown)

Effective immunization

Do not obtain antibody candidate — Attended for RSVi / Not attended for RSVi (unknown)

"High-risk" Newborn

Obtain antibody candidate — Ineffective Immunization — Attended for RSVi / Not attended for RSVi (unknown)

Effective immunization

Do not obtain antibody candidate — Not attended for RSVi (unknown) / Attended for RSVi

Figure. A2. Example Decision Tree Model Schematic. This schematic illustrates one of the decision trees used to track monthly birth cohorts in RSV I^{2}M. This tree schematic is for within-RSV-season births evaluating Strategy II. Different tree structures were used for births occurring out of RSV season and the other evaluated Strategies. All trees are accessible in the RSV I^{2}M modeling tool (S1). The probabilities associated with branching of a cohort are described in the main methods text (Table 2, main text).

Maternal Vaccine Candidate: Proportion of infants successfully immunized

In our model, the percentage of antibodies that successfully transfer from mothers receiving the maternal vaccine candidate was dependent upon a combination of the timing of vaccination relative to the infant's birth, and the infant's gestational age at birth. We assumed there would be a partial (50%) transfer two weeks post-vaccination and full (100%) transfer by four weeks post-vaccination, and that maternal antibodies would not wane prior to birth (Table S3) [34, 35]. Additionally, we took into account the fact that the efficiency of placental transfer of antibodies is dependent on gestational age. We assumed that the amount of antibody transfer would be ineffective before 33 weeks gestational age and only partially effective (50%) between 33-36 weeks gestational age. At term, the transfer would be fully effective [36]. Taking into account the distribution of gestational ages of when births occur [22] and when mothers receive TdaP vaccination (CDC, unpublished), we calculated that ~92% of antibodies that are needed to protect the cohort of infants would be successfully transferred across the immunized population. Since the protective level of antibodies needed to offer full protection has not been established,

we used this value as a proxy reduction factor for maternal vaccine efficacy. That is, we multiplied the percent protected by maternal vaccine by 0.92 to obtain the overall efficacy of maternal vaccine.

Table A3.
Proportion of maternal vaccinations with successful transfer of antibodies to the infant, by gestational age at immunization and birth

	Gestational Age, Birth (weeks)	Percent of Births	Percent of Vaccinations Administered (2nd row) by Gestational Age in weeks (top row)									
			<28	28	29	30	31	32	33	34	35	36
			3.0%	14.4%	14.4%	14.4%	14.4%	14.4%	12.0%	10.0%	3.0%	0.0%
High-risk births	<28	0.68%	0%	NA	NA	NA	NA	NA	NA	NA	NA	NA
	28	0.23%	0%	0%	NA	NA	NA	NA	NA	NA	NA	NA
Pre-term births	29	0.23%	0%	0%	0%	NA	NA	NA	NA	NA	NA	NA
	30	0.23%	0%	0%	0%	0%	NA	NA	NA	NA	NA	NA
	31	0.23%	0%	0%	0%	0%	0%	NA	NA	NA	NA	NA
	32	0.59%	0%	0%	0%	0%	0%	0%	NA	NA	NA	NA
	33	0.59%	50%	50%	50%	50%	25%	0%	0%	NA	NA	NA
	34	2.36%	50%	50%	50%	50%	25%	25%	0%	0%	NA	NA
	35	2.36%	50%	50%	50%	50%	50%	25%	25%	0%	0%	NA
	36	2.36%	50%	50%	50%	50%	50%	50%	25%	25%	0%	0%
Full-term births	37	12.74%	100%	100%	100%	100%	100%	100%	100%	50%	50%	0%
	38	12.74%	100%	100%	100%	100%	100%	100%	100%	100%	50%	50%
	39	28.97%	100%	100%	100%	100%	100%	100%	100%	100%	100%	50%
	40	28.97%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	41	6.38%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	42+	0.35%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Proportion vaccinated with successful Ab transfer* -->			2.8%	13.5%	13.5%	13.5%	13.4%	13.3%	11.0%	8.4%	2.3%	0.0%

* Calculated by 1) summing the product of the percent of births [22] and the proportion of antibody transfer in each row, then 2) multiplying the result by the percent of vaccinations administered for a given gestational age (percent value at top of each column, based on TdaP uptake [CDC, unpublished]), and 3) taking the sum of the column totals on the bottom row. This results in a total 91.9% successful transfer rate.

We also conducted a sensitivity analysis examining the influence of our assumption regarding the timing of immunization on the proportion of infants to whom antibodies successfully transfer. In this analysis we altered the immunization schedule so that it optimized the proportion of infants to whom antibodies successfully transfer. This was achieved when 100% of mothers receiving the maternal vaccine candidate are immunized when the fetus is exactly 29 weeks of gestational age. This improved the proportion of infants to whom antibodies successfully transfer by 2.1 percentage points to 94.0%. When this transfer proportion was used in our baseline illustrative scenario for the US (and all other parameters values in Table 2 remained the same), our estimated number of MA-LRTI hospitalizations prevented by the

maternal vaccine candidate increased by 170 (from 8,190 to 8,360), prevented MA-LRTI ED visits increased by 380 (from 19,580 to 19,960), and prevented MA-LRTI outpatient clinic visits increased 1,140 (from 58,210 to 59,350).

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APPENDIX 2 - Additional Methods and Results for Study 2

SEIR Model (Available for Download here: **https://ars.els-cdn.com/content/image/1-s2.0-S1201971220303507-mmc1.xlsx**)

The model consists of individuals who are either *Susceptible* (S), *Infected* but not yet Infectious (E), Infectious (I), Total *Recovered* and Died (D). It projects and tracks the number of individuals moving between these categories every day of the outbreak. Projections begin on the day following the date input by users for the last day of the most recent 2-weeks of cases available. On this date, there are only Susceptible and Infectious individuals. The epidemic then proceeds via a growth and decline process: As the number of susceptible individuals is depleted (once individuals are infected) the spread of the infection slows. Individuals in the Infectious (I) category includes those who are not yet symptomatic (pre-symptomatic) but will become symptomatic, those who are symptomatic, and those who are infectious yet not exhibiting symptoms (asymptomatic). The dynamics are given by the following equations such that on any given day t, the number individuals Susceptible (S), Infectious (I), Recovered (L), and Died (D) are:

$$S_t = S_{t-1} - \left(\frac{R}{\gamma} * S_{t-1} * \frac{I_{t-1}}{N} \right)$$

$$I_t = \sum_{i=t-(1/\gamma)-\kappa-1}^{t-(1/\gamma)-1} \frac{R}{\gamma} * S_{t-1} * \frac{I_{t_i}}{N}$$

$$L_t = \left(\frac{R}{\gamma} * S_{t-(\kappa+1/\gamma)-1} * \frac{I_{t-(1/\gamma)-\kappa-1}}{N} \right)(1-\alpha)$$

$$D_t = \left(\frac{R}{\gamma} * S_{t-(\kappa+1/\gamma)-1} * \frac{I_{t-(1/\gamma)-\kappa-1}}{N} \right)\alpha$$

where:

N is the population size,

R is the number of new infections each infected persons causes with $R = R_0$ when no mitigation strategy is in place and $R=R_e$ when a mitigation strategy is being used, and

κ is the number of days needed to become infectious after being infected.

$1/\gamma$ is the number of days needed to recover (or die) once infectious.

α is the proportion of infected that die (i.e., infection fatality rate (IFR)) with $\alpha = \alpha_1$ when hospitals have capacity to treat and $\alpha = \alpha_2$ when capacity is overwhelmed

Note: The Infected but not yet Infectious state (E) is not calculated each day in our tool (i.e., not given its own data column), but still contributes to the model by delaying when infected persons begin to contribute to the force of infection.

Reductions in R_0 Associated with Interventions

We chose the reductions in R_0 for each intervention strategy by determining the reduction applied to $R_0 =2.4$ (no intervention) in our model which produced comparable percent declines and delays in peak critical care (ICU) bed occupancy from the "do nothing scenario" observed in Ferguson et al.'s [1] Figure 2. Table S1 shows how these were determined.

Table A1. **Summary of values used for determining the reductions in R associated with interventions**

Intervention Strategy	Observed in Figure 2 of Ferguson et. al.				Observed in our model			
	(A) Peak Occupancy	(B) Weeks peak is delayed (compared to "Do Nothing")	(C) Beds Occupied	(D) Reduction in Beds Occupied (compared to "Do Nothing")	(E) Median R_0	(F) Peak Occupancy	(G) Weeks peak is delayed (compared to "Do Nothing")	(H) Reduction in Beds Occupied
Do Nothing	5/19/2020	--	2700	--	2.4	19,538*	--	--
Closing Schools and Universities	5/26/2020	1	2400	11.1%	2.25	1087	1	10.9%
Case isolation	6/1/2020	2	1850	31.5%	1.98	831	3	31.9%
Case isolation + household quarentine	6/7/2020	3	1300	51.9%	1.74	590	5	51.6%
Case isolation, home quarantine, social distancing of >70s	6/10/2020	3	920	65.9%	1.57	417	8	65.8%
Lockdown	4/15/2020	-5	5	99.8%	0.9	3	-11	99.8%

Notes

* Generated using 2,793 cases through March 31 for all of Chile (per population 17,574,003), and interventions beginning the next day (4/1/20) and continuing through the calendar year

A-C: Estimated from Figure 2 Ferguson, Laydon [1].

D: $(C_{Do\ nothing}-C_{intervention})/ C_{Do\ nothing} * 100$

E: Manipulated manually in our model until columns E and G approximated columns B

F-G: Observed in our model

H: $(F_{Do\ nothing}-F_{intervention})/ F_{Do\ nothing} * 100$

Interventions Application Timeline in Chile [2,3]

Closure of all daycares, schools, and universities was mandated across all of Chile on March 16; followed by case isolation, and mandatory home quarantine for CoVID19 patients on March 19, and the implementation of flexible work schedules and telework for government workers began March 20. Social distancing measures across Chile include bans on nursing homes visits (03/16), closures of non-essential business (03/20, e.g., restaurants, pubs, night clubs), night curfews (03/22), and bans on meetings and events ≥50 people (03/24). Additionally, since March 28, two major cities in Araucanía, and seven municipalities in Santiago are under a mandatory lockdown.

Table A2. Demographics of the Chilean population in the three study regions

Age group	Chile	Metropolitana XIII	Ñuble XVI	Araucanía IX
0-9	2,376,335	937,432	61,464	133,392
10-19	2,392,112	933,218	66,179	137,493
20-29	2,861,972	1,238,583	66,985	144,782
30-39	2,501,414	1,066,451	60,993	124,652
40-49	2,359,266	951,497	67,450	128,716
50-59	2,232,733	889,726	66,574	120,577
60-69	1,499,917	579,388	46,661	84,658
70-79	879,498	333,994	29,403	53,289
80+	470,756	182,519	14,900	29,665
Urban	15,424,263	6,849,310	333,680	678,544
Rural	2,149,740	263,498	146,929	278,680
Total	**17,574,003**	**7,112,808**	**480,609**	**957,224**

Notes. Chile has a total of 16 regions. Here we include the three regions that have been more heavily affected by CoVID-19 as of April 5th, 2020, since the first case was reported in march 2, as an illustration of the potential uses of the tool. Estimates for all regions have been reported to the Ministry of Health.
Source: CENSO 2017.[4]

Table S3. Reported cases of COVID-19 by region

Region	N	Total	Two weeks
Metropolitana	XIII	2350	1810
Araucanía	IX	612	553
Ñuble	XVI	522	417
Chile		5116	4194

Notes. Total reported CoVID-19 cases as of April 5, 2020
Source: Ministry of Health[5]

Table A4. Healthcare capacity: basic and intensive care beds by region, public and private hospitals

	Basic beds			Beds/	Intensive care			Beds/	Mech.
	Current	Increase†	Total	100k	Current	Increase†	Total	100k	Ventilator
Metropolitana	16,596	1,926	18,522	260.4	1,937	389	2,326	32.7	867
Ñuble	942	68	1,010	210.2	38	22	60	12.5	22
Araucanía	2,202	469	2,671	279.0	136	79	215	22.5	80
Chile	37,777	3,929	41,706	227.2	3,295	1,659	4,954	29.1	1,847

Notes.

†Increase refers to new beds in the health care system as a consequence of CoVID-19 response. All beds available in the healthcare system, from public and private hospitals, are now part of the "Sistema Integrado COVID-19" under the centralized administration of the Ministry of Health. An intensive care bed (ICU) consists of a cot with a monitor, healthcare professionals and medication to treat patient. Some have a mechanical ventilator.

There are an estimated 1,847 mechanical ventilators; 850 currently available and 997 were acquired in January 2020.[6] We assumed the distribution of mechanical ventilators was proportional to the number of critical beds in each region. We assumed 60% of mechanical ventilators would be available based on a three-year study of 97 ICUs in the US, including 226,942 admissions to ICUs.[7]

Source: Latorre et al. 2020[6]

B. ADDITIONAL RESULTS
B.1.1 Región Metropolitana – Hospital beds

Estimated Hospital Bed Occupancy Without Mitigation
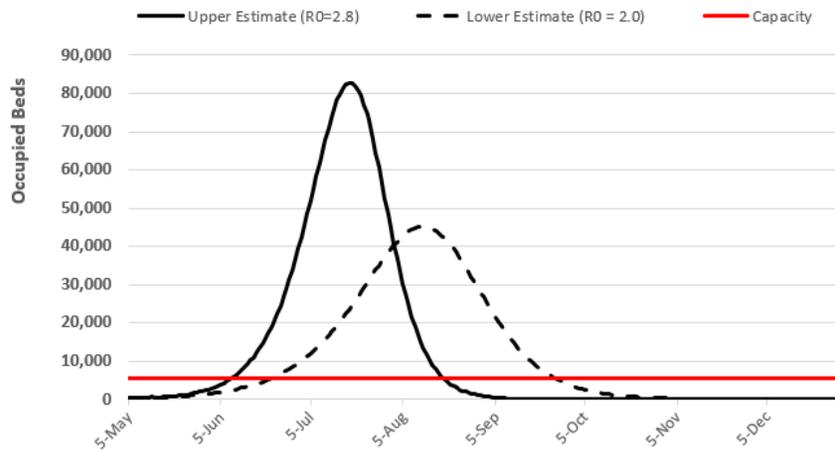
Strategy 1: Estimated Hospital Bed Occupancy with Closing Schools and Universities, and Telework
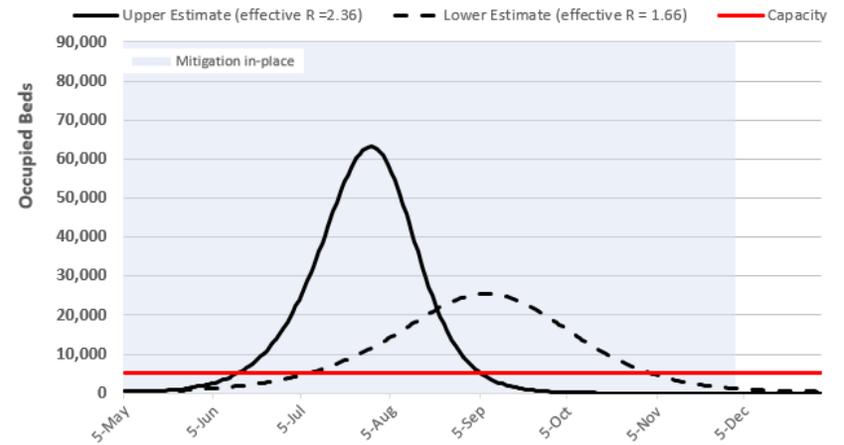
Strategy 2: Estimated Hospital Bed Occupancy with Case isolation, Home quarantine, Social Distancing >70s, and Telework
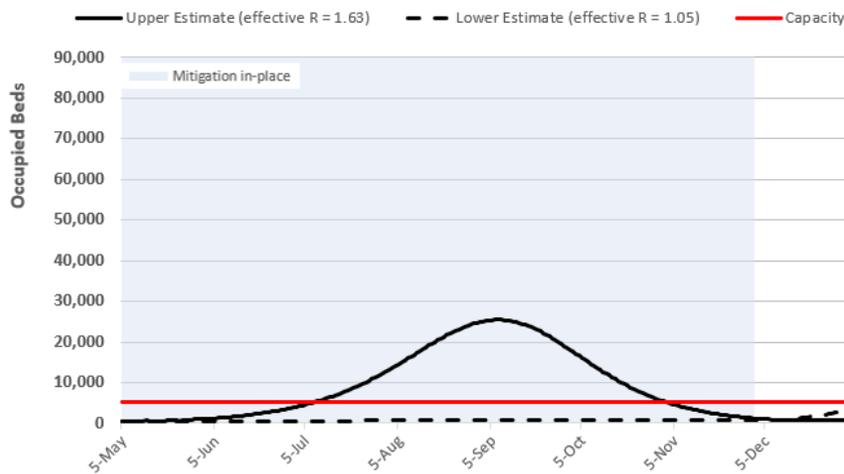
Strategy 3: Estimated Hospital Bed Occupancy with Lockdown
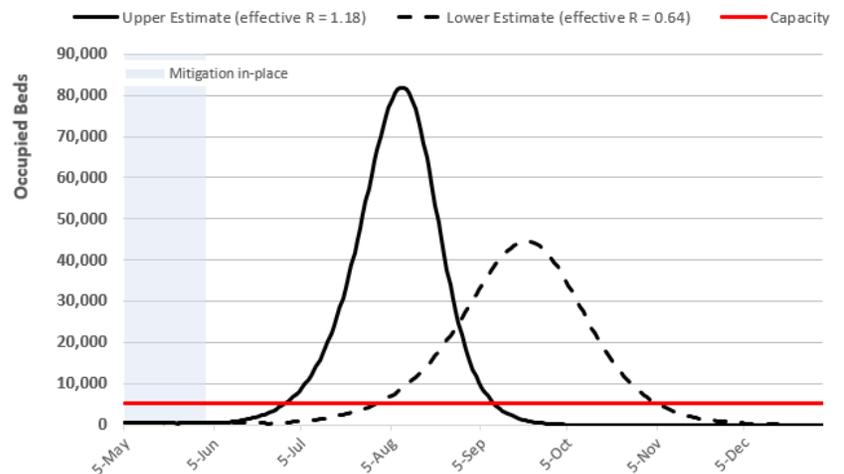
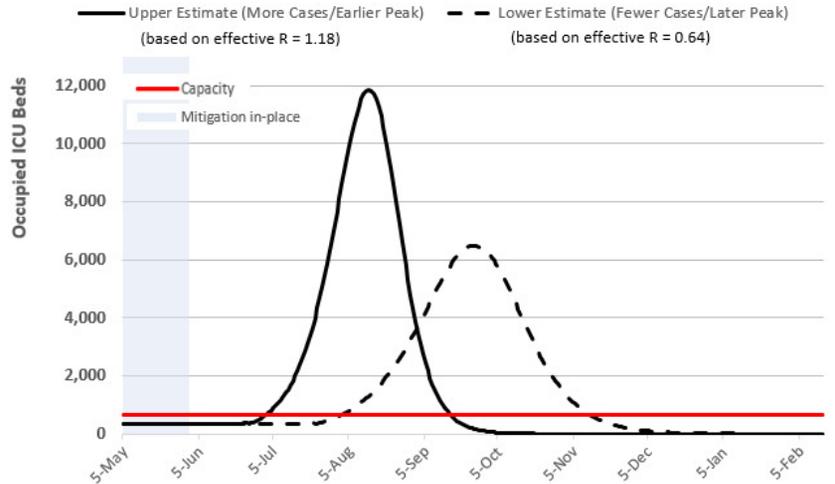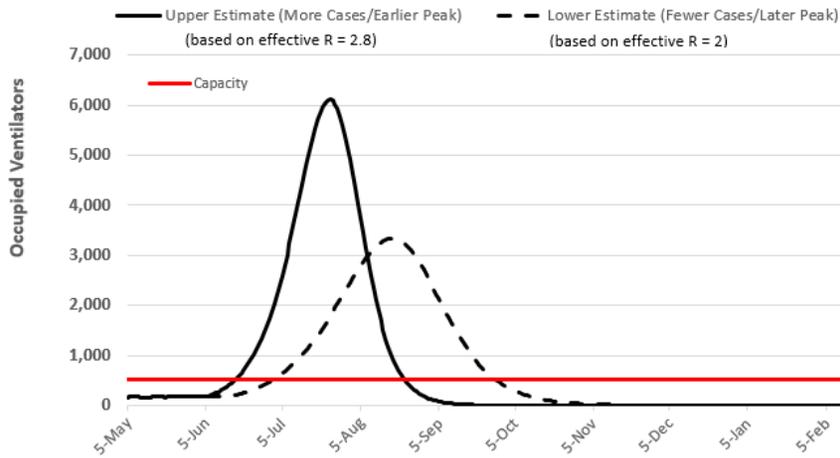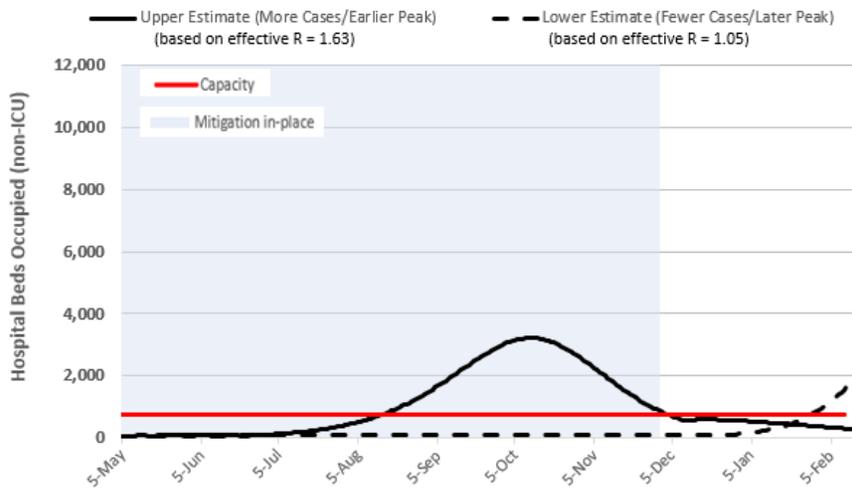## B.1.2 Región Metropolitana – ICU Beds

Estimated ICU Occupancy Without Mitigation
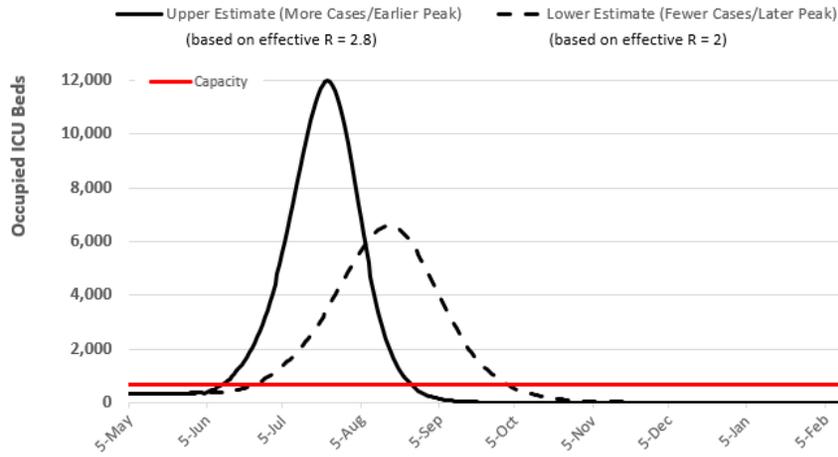
Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.8)
Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 2)

OPTION 1: Estimated ICU Occupancy with Closing Schools and Universities + Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.36)
Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.63)

OPTION 2: Estimated ICU Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.63)
Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.05)

OPTION 3: Estimated ICU Occupancy with Lockdown

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.18)
Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 0.64)
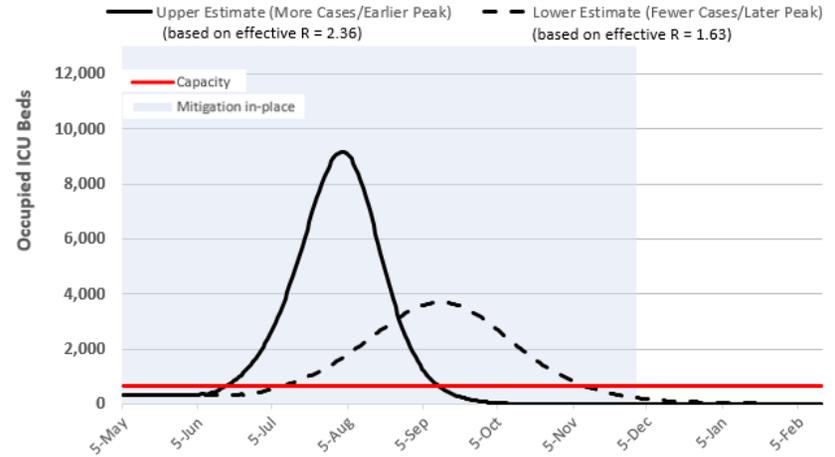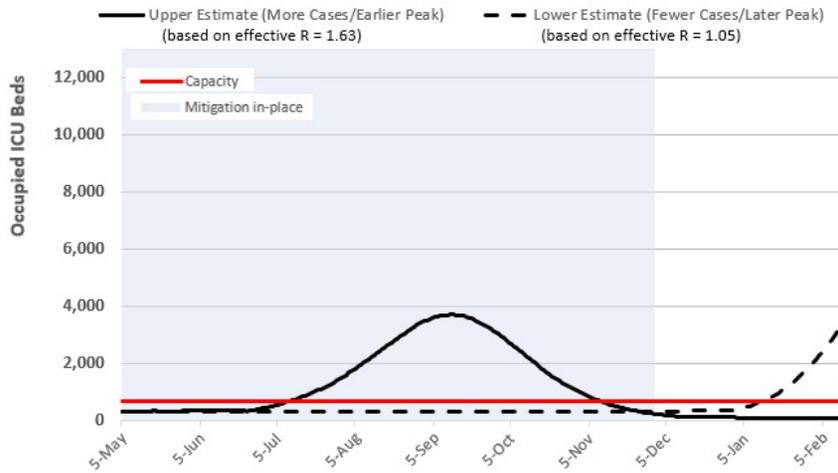
B.1.3 Región Metropolitana – Ventilators

Estimated Ventilators Occupancy Without Mitigation

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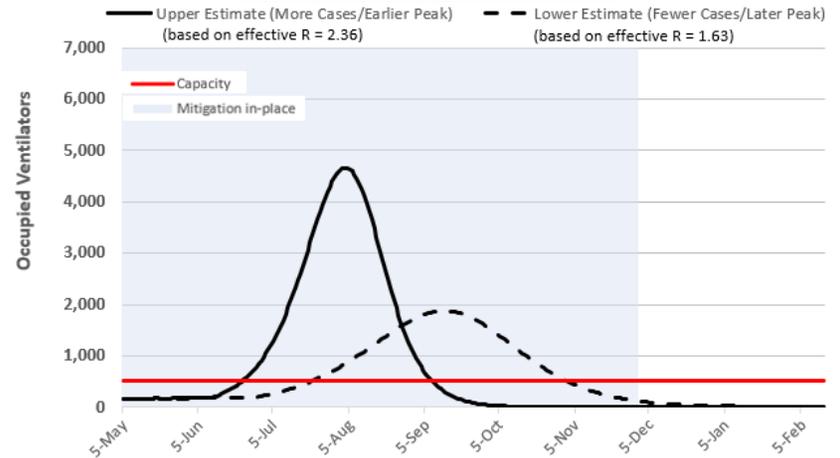
OPTION 2: Estimated Ventilators Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework
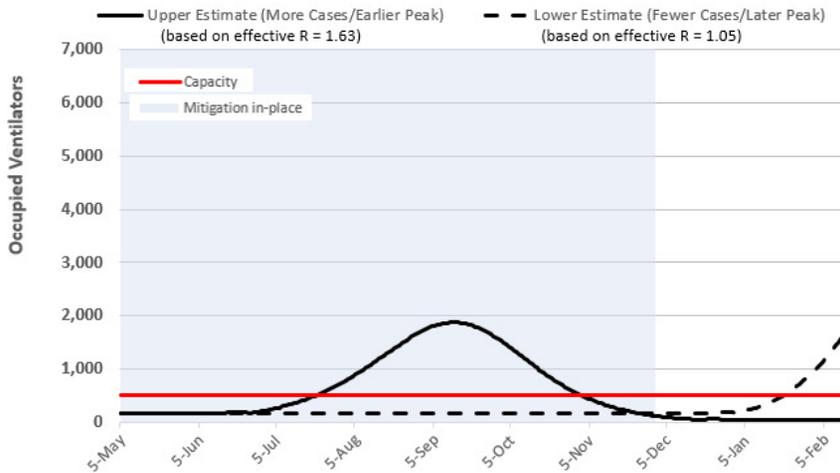
OPTION 3: Estimated Ventilators Occupancy with Lockdown
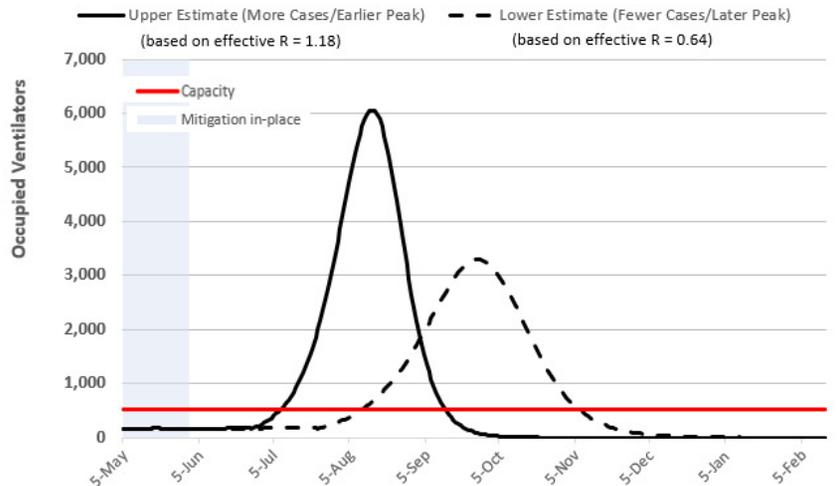
B.2.1 Región Araucanía - Hospital beds

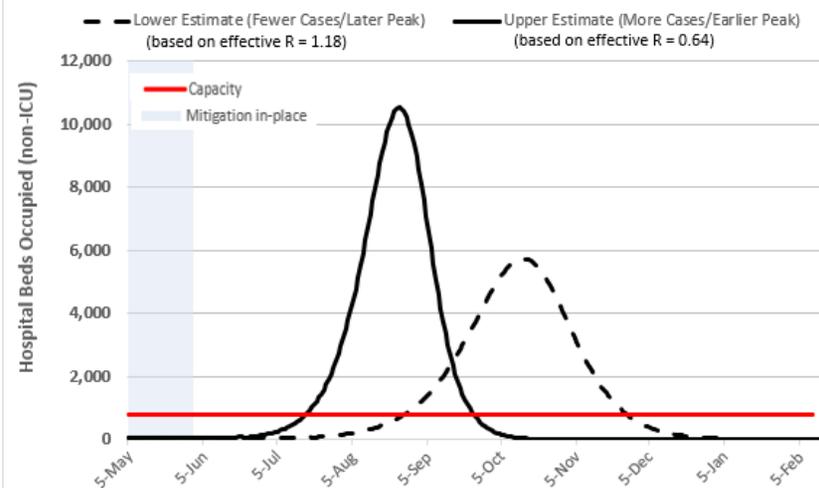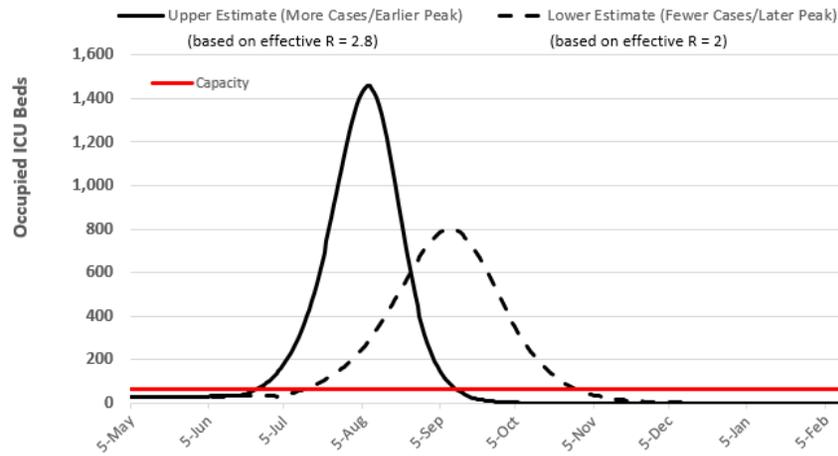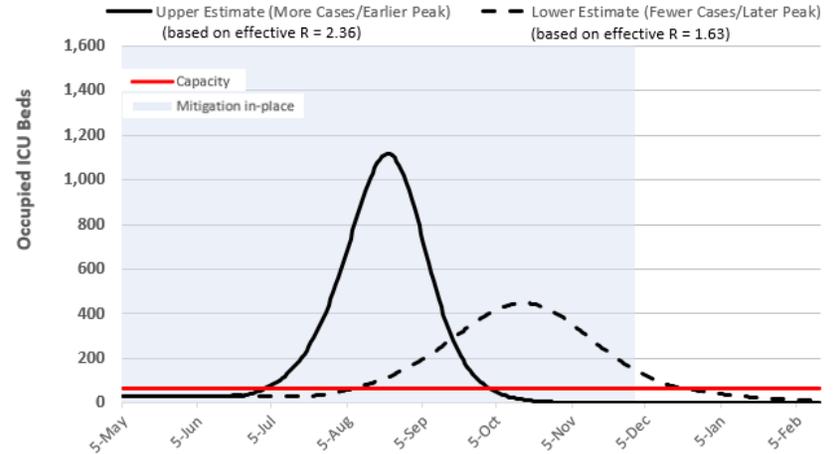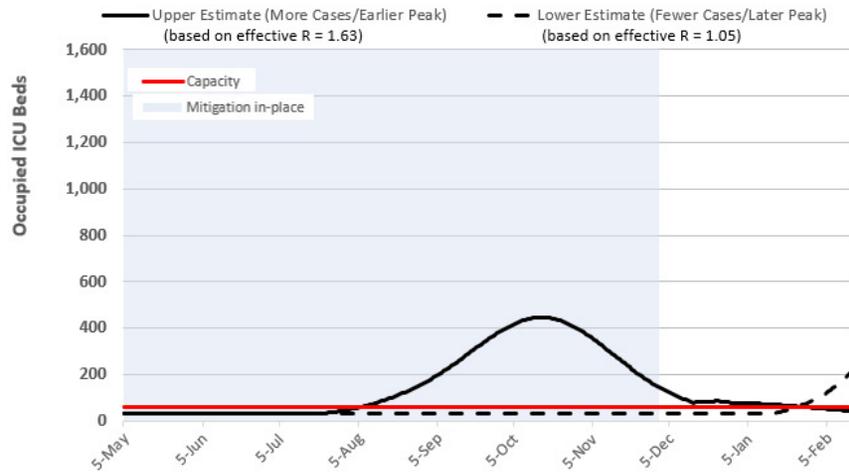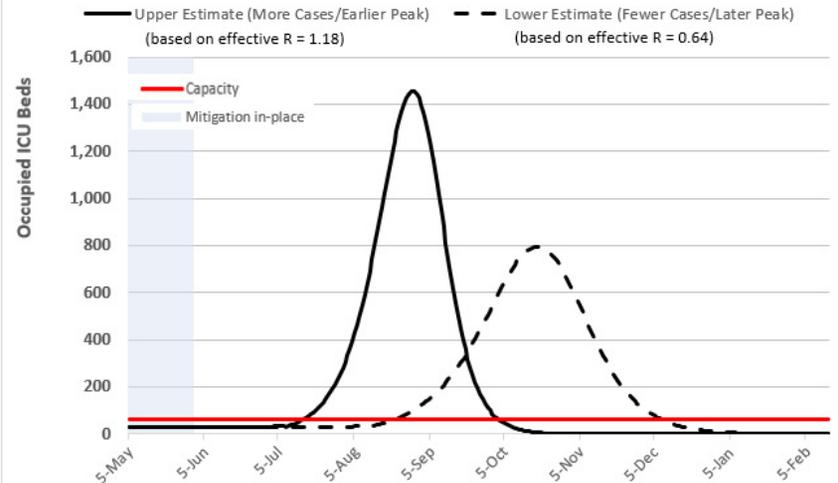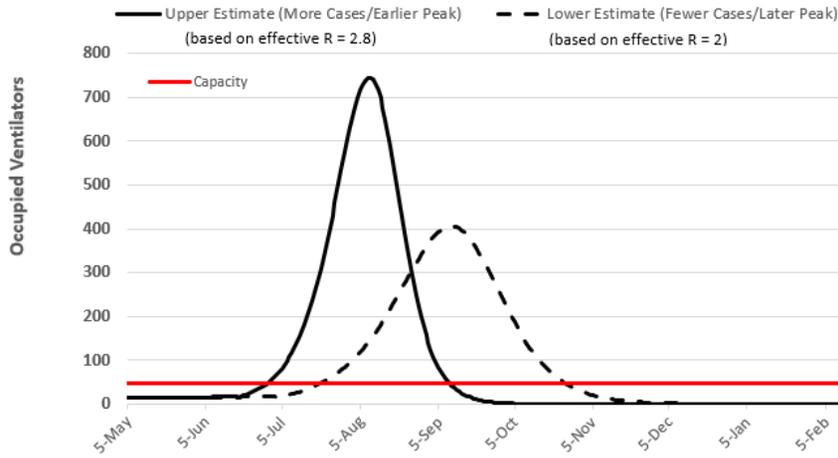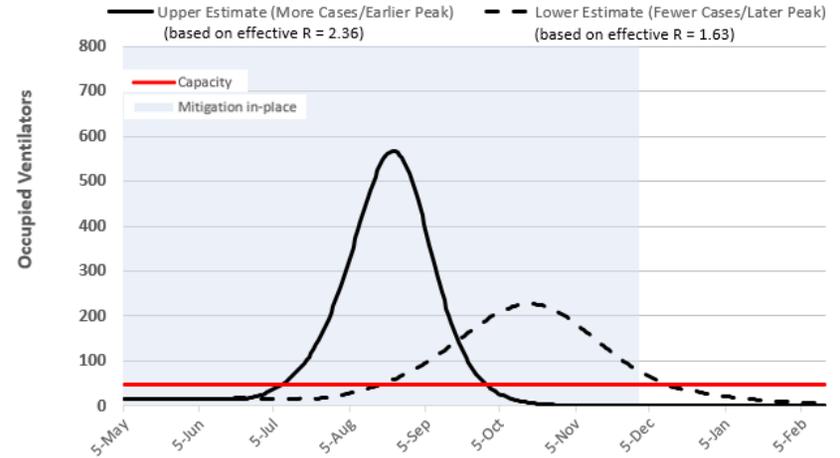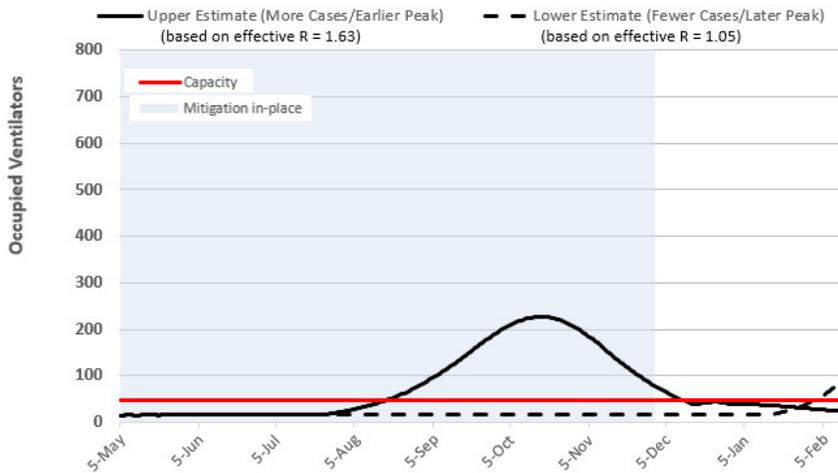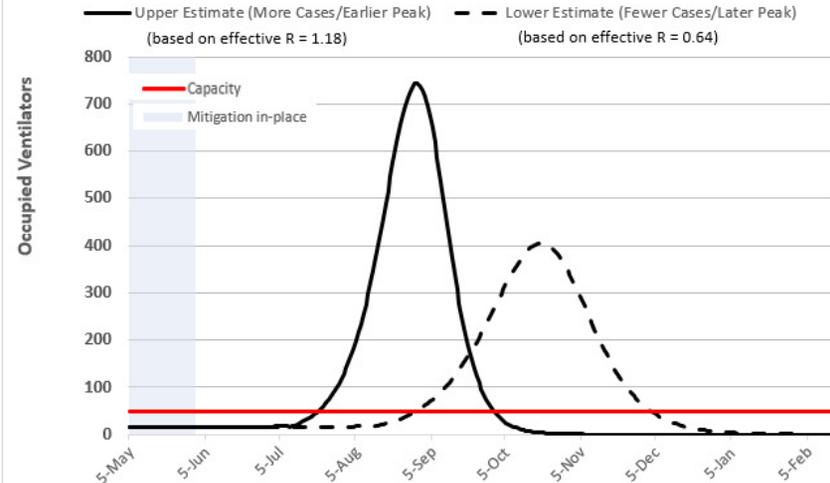**Estimated Hospital Bed Occupancy (non-ICU) Without Mitigation**
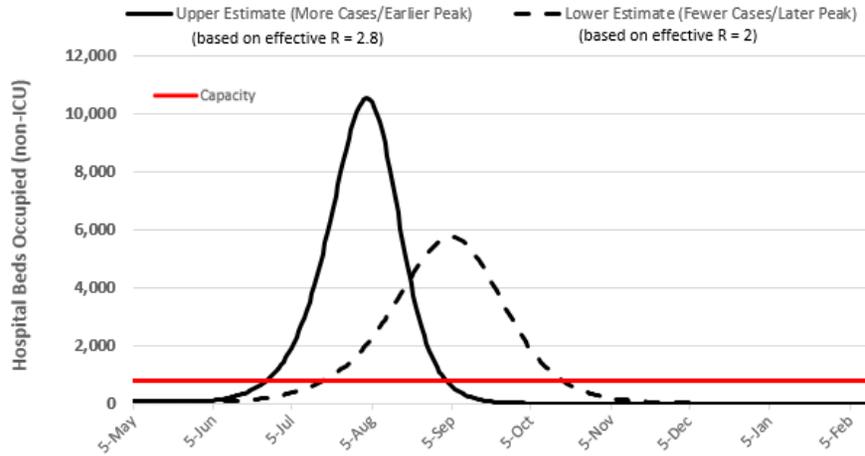
Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.8) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 2)

Capacity

OPTION 1: Estimated Hospital Bed Occupancy (non-ICU) with Closing Schools and Universities + Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.36) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.63)

Capacity
Mitigation in-place

OPTION 2: Estimated Hospital Bed Occupancy (non-ICU) with Case isolation, home quarantine, social distancing of >70s, Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.63) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.05)

Capacity
Mitigation in-place

OPTION 3: Estimated Hospital Bed Occupancy (non-ICU) with Lockdown

Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.18) — Upper Estimate (More Cases/Earlier Peak) (based on effective R = 0.64)

Capacity
Mitigation in-place
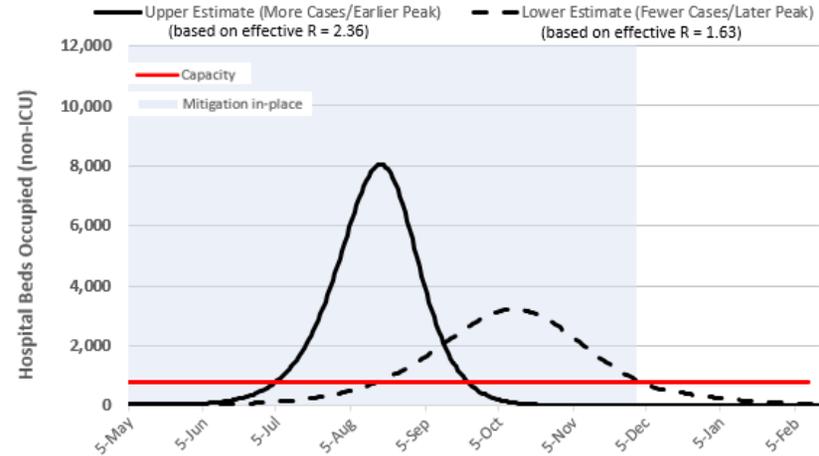
B.2.2 Región Araucanía - ICU beds

Estimated ICU Occupancy Without Mitigation

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.8)

Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 2)

Capacity

OPTION 1: Estimated ICU Occupancy with Closing Schools and Universities + Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.36)

Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.63)

Capacity

Mitigation in-place

OPTION 2: Estimated ICU Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.63)

Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.05)

Capacity

Mitigation in-place

OPTION 3: Estimated ICU Occupancy with Lockdown

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.18)

Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 0.64)

Capacity

Mitigation in-place

B.2.3 Región Araucanía - Ventilators

Estimated Ventilators Occupancy Without Mitigation

OPTION 1: Estimated Ventilators Occupancy with Closing Schools and Universities + Telework

OPTION 2: Estimated Ventilators Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework
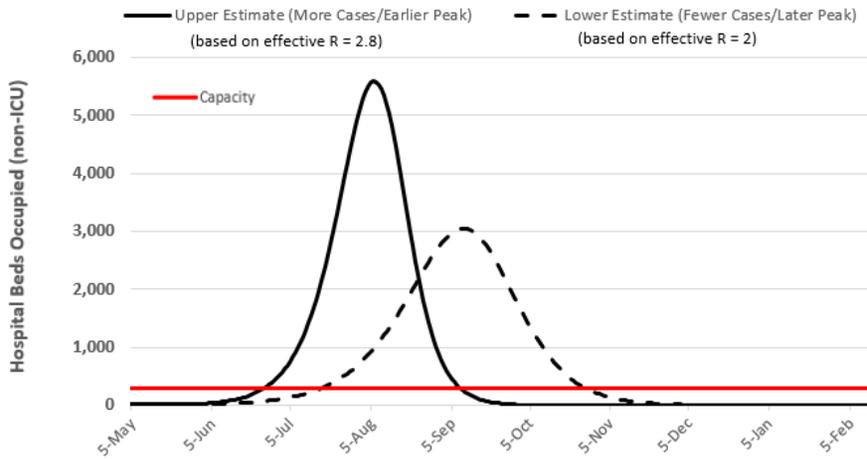
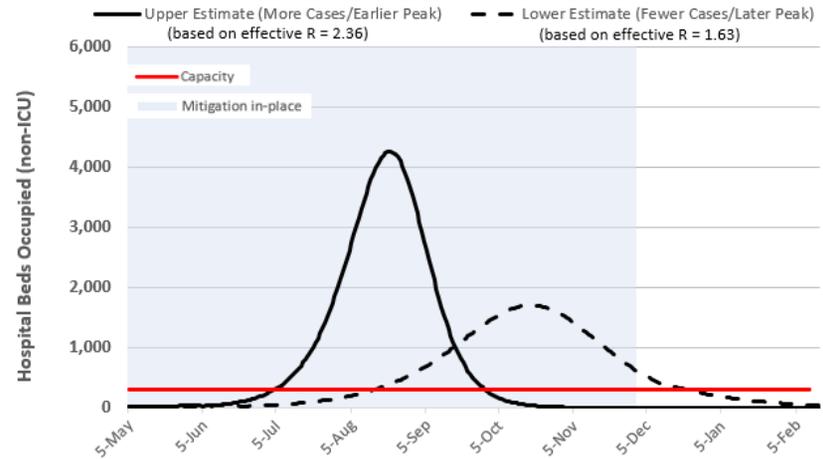**OPTION 3: Estimated Ventilators Occupancy with Lockdown**
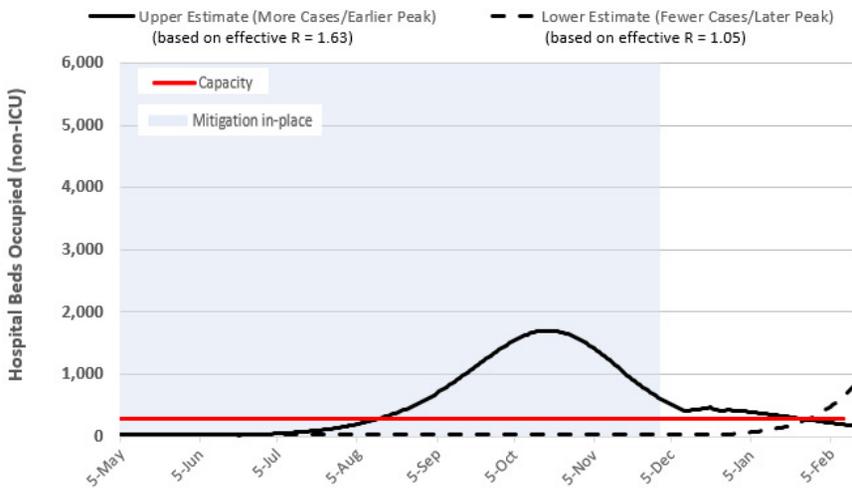
B.3.1 Región Ñuble - Hospital beds
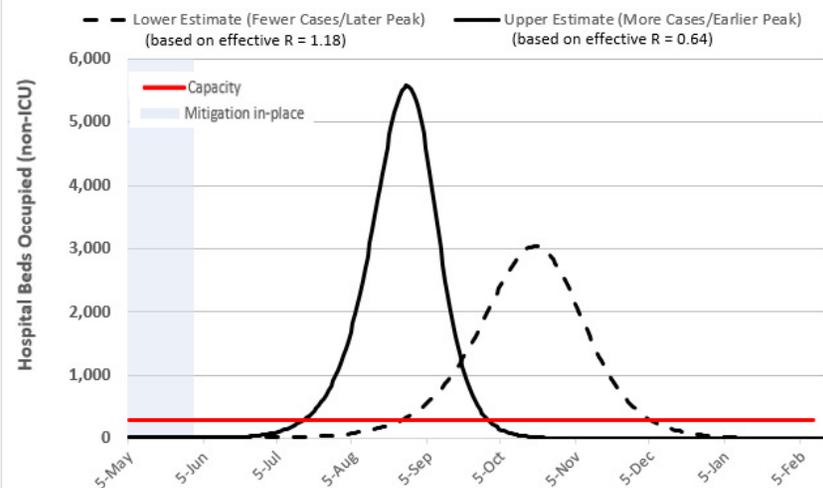

Estimated Hospital Bed Occupancy (non-ICU) Without Mitigation

OPTION 1: Estimated Hospital Bed Occupancy (non-ICU) with Closing Schools and Universities + Telework

OPTION 2: Estimated Hospital Bed Occupancy (non-ICU) with Case isolation, home quarantine, social distancing of >70s, Telework
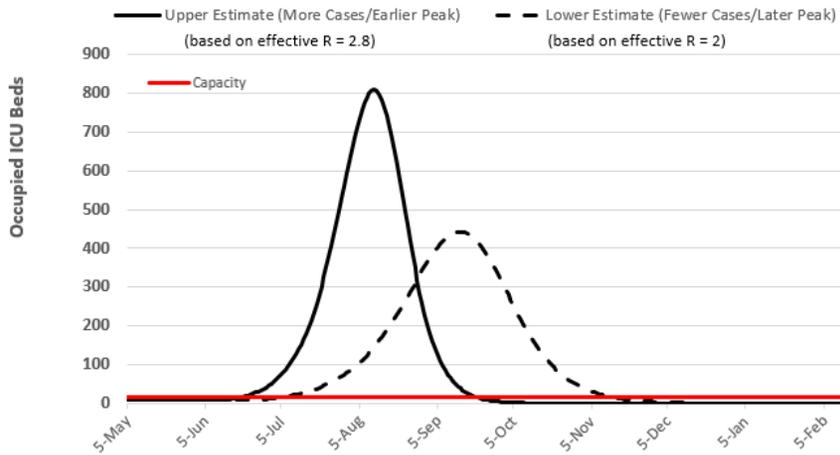
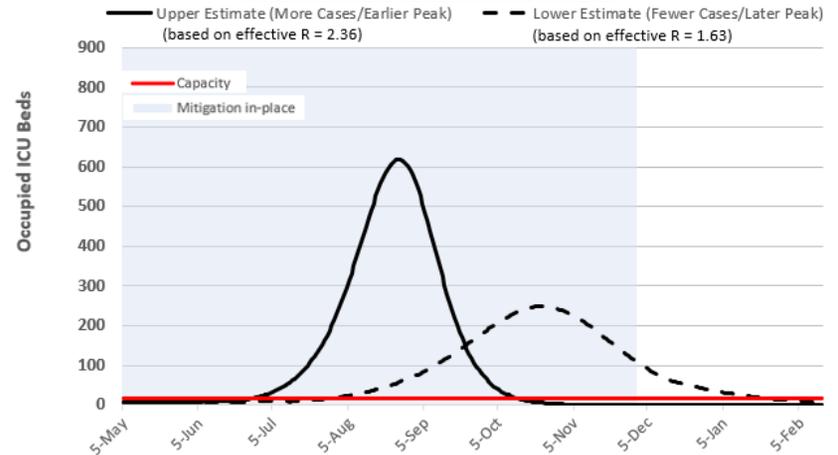**OPTION 3: Estimated Hospital Bed Occupancy (non-ICU) with Lockdown**
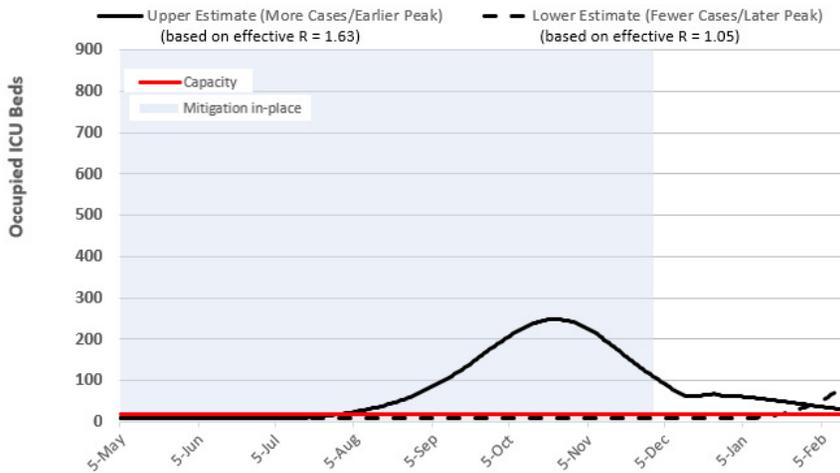
B.3.2 Región Ñuble - ICU beds

Estimated ICU Occupancy Without Mitigation
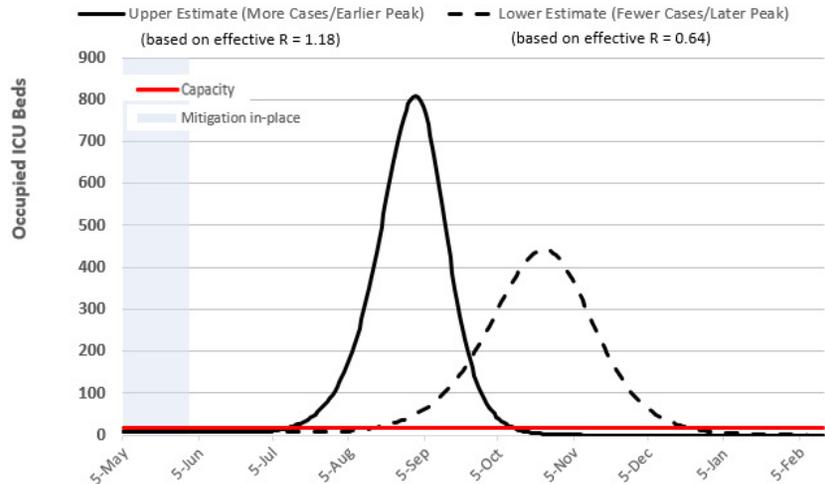
Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.8) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 2)

Capacity

OPTION 1: Estimated ICU Occupancy with Closing Schools and Universities + Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.36) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.63)

Capacity — Mitigation in-place

OPTION 2: Estimated ICU Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.63) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.05)

Capacity — Mitigation in-place

OPTION 3: Estimated ICU Occupancy with Lockdown

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.18) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 0.64)

Capacity — Mitigation in-place

B.3.3 Región Ñuble - Ventilators

Estimated Ventilators Occupancy <u>Without Mitigation</u>
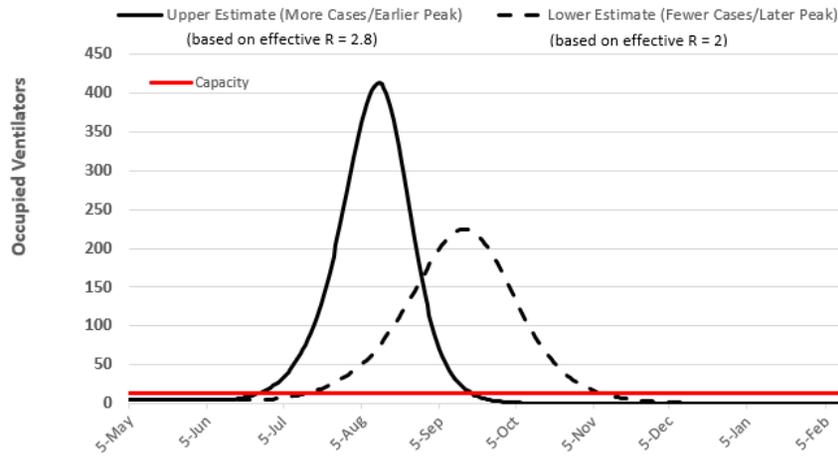
Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.8) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 2)

Capacity

OPTION 1: Estimated Ventilators Occupancy with Closing Schools and Universities + Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 2.36) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.63)

Capacity
Mitigation in-place

OPTION 2: Estimated Ventilators Occupancy with Case isolation, home quarantine, social distancing of >70s, Telework

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.63) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 1.05)

Capacity
Mitigation in-place

OPTION 3: Estimated Ventilators Occupancy with Lockdown

Upper Estimate (More Cases/Earlier Peak) (based on effective R = 1.18) — Lower Estimate (Fewer Cases/Later Peak) (based on effective R = 0.64)

Capacity
Mitigation in-place

97
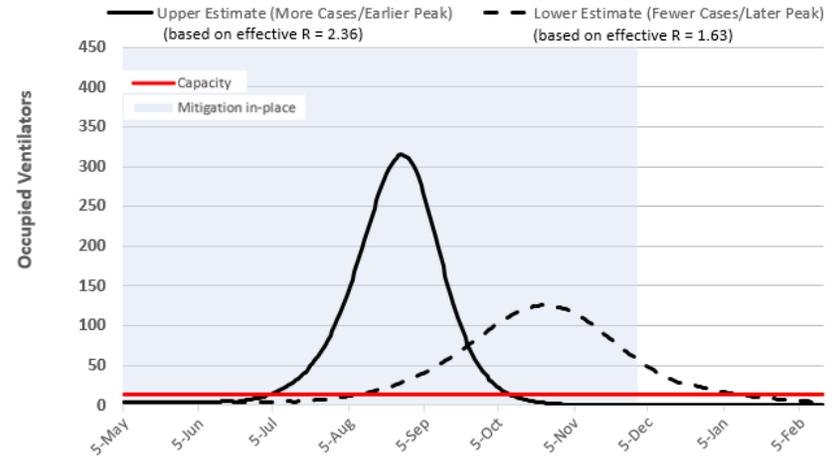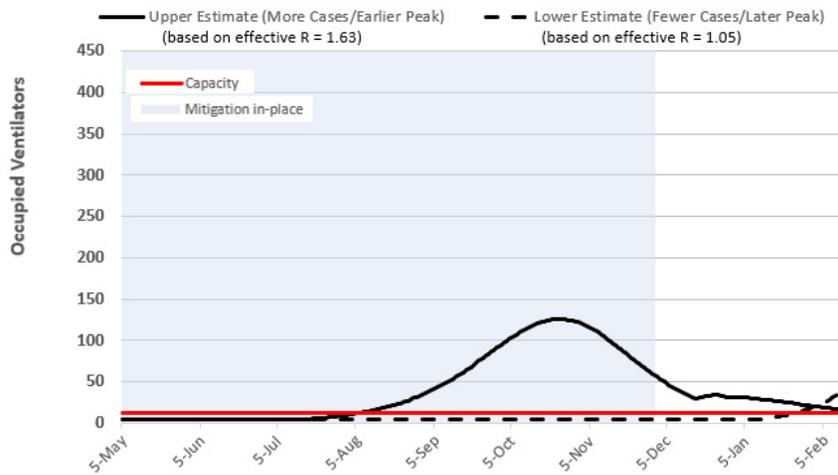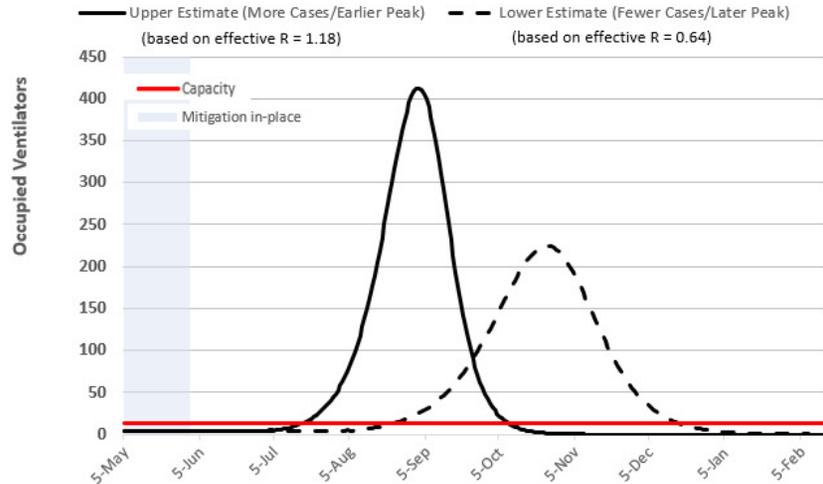
References - Appendix 2

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APPENDIX 3 – Additional Methods and Results for Study 3

Appendix 3 Table of Contents

COVIDTracer Advanced Model

COVIDTracer Advanced[1] is a spreadsheet-based compartmental Susceptible-Exposed-Infectious-Recovered (SEIR) epidemiological model, which illustrates the spread of a pathogen, resultant disease, and impact of interventions in a user-defined population. Readers can download the tool and enter input values of their choosing, exploring the impact of scenarios and assumptions beyond those covered in this manuscript. To model the clinical progression and transmission of disease using COVIDTracer Advanced, we used the following definitions and assumptions. A "case" was defined as a person who has been exposed, infected and subsequently becomes infectious, regardless of the presence of clinical symptoms. We assumed that for the first 3 days after infection, cases do not infect others. During days 4–5 post-infection, cases are pre-symptomatic but shed virus in amounts that may infect others.[2-5] During days 6–14, the infected person can be symptomatic and shedding virus, albeit during days 11–14 the risk of onward transmission is relatively low but non-zero (the complete infectivity distribution is given in Table A1). We assumed that approximately 40% of cases are asymptomatic during days 6-14 yet have a risk of onward transmission equal to 75% of symptomatic cases (Table A2) without vaccine or other non-pharmaceutical interventions (NPIs).[5] The model assumes homogeneous mixing among individuals and does not account for any age- or location-based heterogeneities in transmission.

Table A1. Daily percentage risk of transmission by infectiousness state and clinical symptoms.

Days post infection	Daily percentage risk of onward transmission[a] (%)	Infected person's state
1	0.00	*Infected,*
2	0.00	*not yet infectious*
3	0.00	
4	16.78	*Infectious,*
5	18.03	*pre-symptomatic*
6	17.07	
7	14.52	
8	11.27	
9	8.10	
10	5.48	*Infectious, symptomatic*
11	3.55	
12	2.26	
13	1.46	
14	1.48	
Total	**100**	

[a] Percentages show when onward transmission might occur by day of infectiousness
Sources: He *et al.*[2, 3] and Ferretti *et al.*[4] See also COVIDTracer Advanced manual.[1]

**Table A2. Epidemiological parameters, values, and sources.**

Parameter	Default Value	Source
Infected but not yet infectious period	3 days	CDC COVID-19 Pandemic Planning Scenarios[5]
Pre-symptomatic and contagious (infectious) period	2 days	He *et al.*[2, 3], Ferretti *et al.*[4]
Symptomatic and contagious (infectious) period	9 days	He *et al.*[2, 3], Ferretti *et al.*[4]
New infections per case (R_0)	2.5	CDC COVID-19 Pandemic Planning Scenarios[5]
% of cases that are asymptomatic	40%	CDC COVID-19 Pandemic Planning Scenarios[5]
Infectiousness of asymptomatic cases (relative to symptomatic cases)	75%	CDC COVID-19 Pandemic Planning Scenarios[5]

Table A3. Assumed[a] proportion of cases by age group and infection-to-hospitalization rate, default values in COVIDTracer Advanced and sources.

Age group (year)	% of Total Cases	Source	% of all cases admitted to hospital care	Source
0 to 17	15		0.21	CDC COVID-19
18 to 64	55	CDC COVID Data	2.17	Response Team[7], Wu
65+	30	Tracker[6]	4.12	*et al.*[8]

[a] derived September 2020 using sources available at that time

Figure A1. COVIDTracer Advanced Model Structure
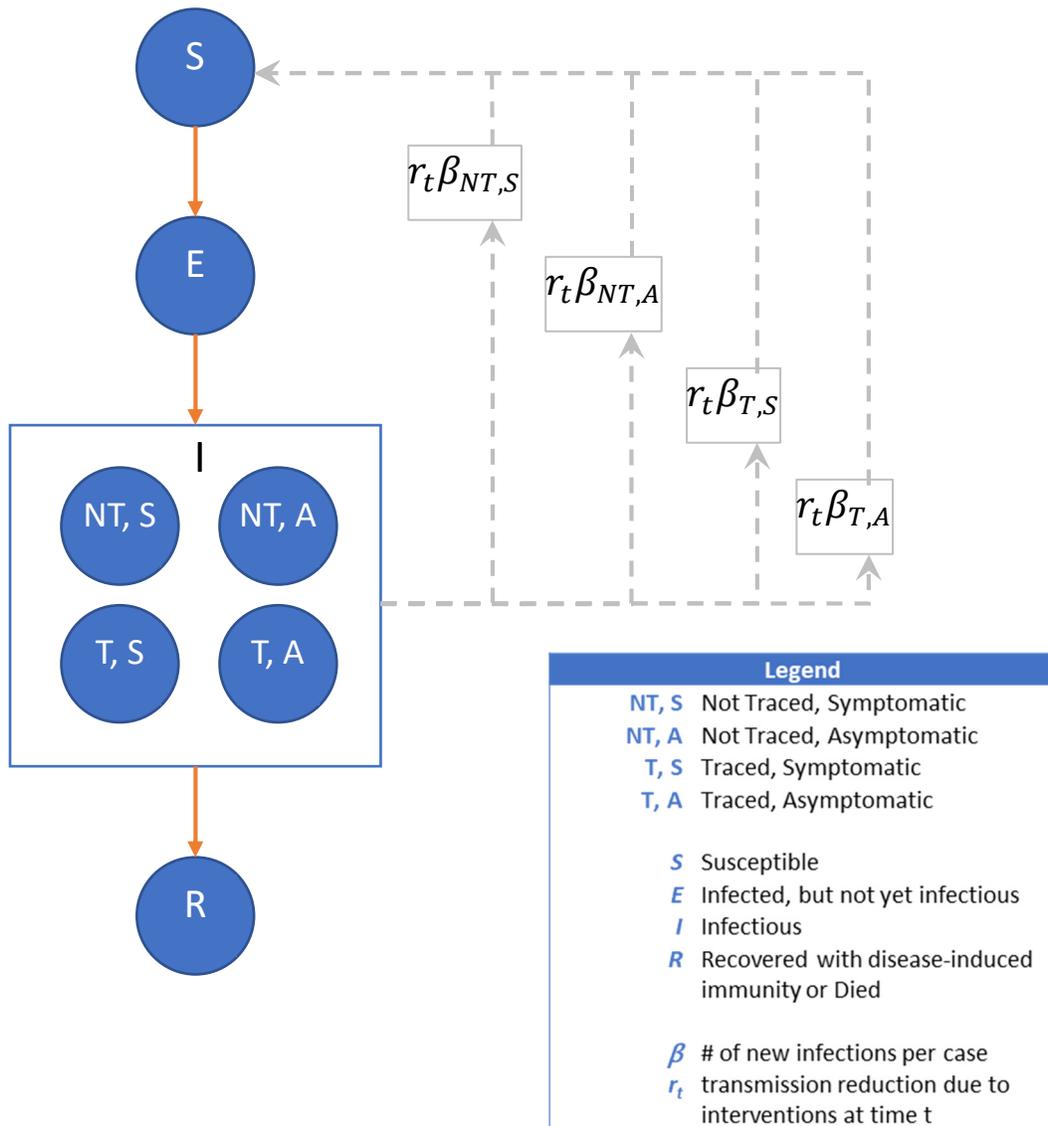
Notes: The model consists of individuals who are either *Susceptible* (S), *Infected but not yet Infectious* (E), *Infectious* (I), *Recovered or Died* (R). Individuals can move between these compartments as indicated by the orange arrows. The model tracks the number of individuals moving between these categories every day of the outbreak. The rate of new infections is influenced by the number of individuals in the *Infectious* (I) category (depicted by the light grey dashed lines). There are 4 types of *Infectious* individuals: cases (symptomatic or asymptomatic) who adhere to isolation guidelines because they were engaged by their health departments via case investigation and contact tracing efforts (CICT), and cases (symptomatic or asymptomatic) who do not participate in CICT efforts. The overall risk to the *Susceptible* population of onward transmission is dependent upon both the distribution of cases among these 4 infectious categories on each day, and any reductions in transmission associated with a jurisdiction's implementation of CICT, and vaccine and other non-pharmaceutical interventions.

Case Investigation and Contact Tracing Effectiveness

The effectiveness of case investigation and contact tracing (CICT) is determined by the proportion of cases and their infected contacts that are effectively isolated and quarantined, preventing further transmission in the susceptible population. The duration of quarantine and isolation is described in Centers for Disease Control and Prevention (CDC)'s guidance.[9] We assumed that confirmed cases are effectively isolated following case interviews. We further assumed that contacts are quarantined upon either contact notification or through active monitoring.

We calculated the average proportion of cases and contacts isolated and quarantined by CICT for each location as follows:

Step 1: We first calculated the proportion of cases that effectively isolated:

$$Compliance * \left(\frac{\text{\# Cases that completed case interview}}{Total\ number\ of\ cases} \right) \qquad Term\ A$$

Step 2: We then calculated the proportion of infected contacts that effectively quarantined:

$$Compliance * \%\ Contacts\ identified * \%\ Contacts\ notified \qquad Term\ B$$

Where:

$$\%\ Contacts\ identified = \frac{\text{\# Contacts named by interviewed cases}}{Total\ number\ of\ contacts} \qquad Term\ B.1$$

and

$$\%\ Contacts\ notified = \frac{\text{\# Contacts notified}}{\text{\# Contacts named by interviewed cases}} \qquad Term\ B.2$$

The "Total number of contacts" in *Term B.1* was the expected total number of contacts generated by all cases. We estimated it by multiplying the total cases reported by a jurisdiction by the average number of contacts per case as follows:

$$Total\ Cases * \left(\frac{Total\ \text{\# Contacts named by interviewed cases}}{\text{\# Cases that named at least 1 contact}} \right) \qquad Term\ B.1.1$$

Step 3: We took the weighted average between the results of steps 1 and 2 (Terms A and B) by weighting quarantined contacts by R_0, since undetected infected contacts will infect R_0 additional individuals on average (or 2.5 new infections per infected contact). This resulted in the final equation:

Average proportion of cases and contacts (which become cases) isolated by CICT = [% Cases interviewed*Compliance + (R_0 * % Contacts identified * (% Contacts monitored *Compliance + % Contacts notified but not monitored*Compliance))] / (1+R_0)

By populating this equation with the assumed compliance to isolation/quarantine guidance (described in Table 1), we assessed the following three scenarios.

Equation 1: Baseline Low Estimate

      80% of interviewed cases and monitored contacts, and 30% of notified contacts (who are not monitored), isolate or quarantine:

      Average proportion of cases and contacts (which become cases) isolated =
            [% Cases interviewed*0.8 + (R_0* % Contacts identified * (% Contacts monitored *0.8 + % Contacts notified but not monitored*0.3))] / (1+R_0)

Equation 2: Baseline High Estimate

      100% of interviewed cases and monitored contacts isolate or quarantine:

      Average proportion of cases and contacts (which become cases) isolated =
            [% Cases interviewed + (R_0 * % Contacts identified * % Contacts monitored)] / (1+R_0)

Equation 3: Sensitivity Analysis (Maximum CICT Impact) Estimate

      100% of interviewed cases and 100% of contacts isolate or quarantine:

      Average proportion of cases and contacts (which become cases) isolated =
            [% Cases interviewed + (R_0 * % Contacts identified * % Contacts notified)] / (1+R_0)

where R_0 is the assumed number of new infections per case without any interventions and when the population is entirely susceptible to infection (Table A2).

In addition, reducing the time from case identification to effective isolation is critical for case investigation and contact tracing to succeed. The longer the cases and contacts interact with the susceptible population, the greater the opportunity for onward transmission. In practice, cases with no known exposure are predominantly identified and isolated after symptom onset[3], and cases with known exposures (*i.e.,* contacts that eventually become infected cases) can begin quarantine upon contact notification (even potentially prior to symptom onset). We assumed asymptomatic cases can only be identified and isolated if they are notified through case investigation and contact tracing. For the purposes of our study, we assumed the proportions of cases with no known exposure and cases with known exposures were equal (*i.e.*, 50/50 breakdown) because we did not have data on what prompted case identification in each location. Therefore, for each location the days to effective case isolation was determined by taking the average of the days to effective isolation between case groups with known and no known exposures. The time to effective case isolation for each of the two case groups was determined as follows:

For symptomatic cases with no known exposures (*i.e.,* symptoms prompt identification):
  We assumed that cases experience a 5-day pre-symptomatic period (See Table A2), get tested the day after symptom onset (*i.e.,* 6 days would have transpired since infection at the time of testing). We then obtained the number of days from testing to result notification by adding the reported "*Median days from specimen collection to case reporting to the health department (HD)*". We also assumed that confirmed cases begin isolation the day after their result notification (*i.e.,* we added 1 to the total obtained above). Our assumptions regarding the "next-day" timing of testing and entry into isolation are based on symptoms and notifications beginning or occurring throughout the day, with a sizeable portion occurring sufficiently late enough in the day to prevent testing and entry into isolation the same evening. This assumption takes into account practical considerations such as time needed to find a testing site and arrange an appointment, and for notified individuals to prepare to isolate (*e.g.,*

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[3] Some cases can be identified before being symptomatic (*e.g.,* during screening for various reasons)

purchasing food or medications, setting up childcare, handling work or other commitments).

For cases with known exposures (*i.e.,* those who were notified they were a contact and eventually became a case):

We first calculated the days from index case testing to their exposed contacts' notification by summing jurisdictions' reported "*Median days from specimen collection to case report to the HD*", "*Median days from case report to the HD to the case interview completion*", and "*Median days from case interview completion to contacts notification*". We assumed that contacts begin quarantine the day after receiving exposure notification from their health department (*i.e.,* we added 1 to the sum above). The "next-day" timing of entry into quarantine is based on the same practical reasoning as cases needing time to prepare to isolate once notified (described above). We then used the resultant sum from the procedure above to estimate the time (in days) from exposure to quarantine for contacts. Because we did not have information on when exposures actually occurred for contacts, we assumed that these individuals' exposures occurred at the midpoint of their potential exposure window (in days). We identified the earliest date in this window as the first day of infectiousness among cases to which contacts were exposed. Based on our assumed 5-day pre-symptomatic period for symptomatic cases (described above), this was two days prior to the symptom onset date in cases exposing the contact. We identified the latest possible exposure as the date the cases exposing them were interviewed by the health department (because they began isolation the next day). See both "Contacts" rows in Figure A2 for a visual depiction of this timeline.

Figure A2. Illustrative example of the timing of COVID-19 case isolation and quarantine of contacts

	Day 1	2	3	4	5	6	7	8	Day 9	Day 10	Days from Exposure to Isolation
Index Case	Exposed			Contagious Period Begins		Symptom Onset	Tested	Result Notification & Case Interview	Begin Isolation		8
Contacts (Earliest possible exposure)				Exposed					Exposure Notification	Begin Quarantine	6
Contacts (Latest possible exposure)								Exposed	Exposure Notification	Begin Quarantine	2

Notes: In this hypothetical scenario, we assume a jurisdiction needed 1 day from specimen collection (testing) to result notification and 2 days from specimen collection to contact notification. The index case (symptomatic case with no known exposure) began showing symptoms on day 6 post-infection, got tested on day 7 and was notified of test result on day 8. The case's contacts (cases with known exposure) were exposed sometime between days 4 to 8 and notified of their exposure on day 9. Therefore, the index case began isolation on day 9 and contacts went into quarantine on day 10 (based on our assumptions above). To calculate the days from contacts' exposure to their quarantine, we took the average of the maximum days a contact was infected (6 days in this example based on the earliest possible exposure) and the fewest days the contact could be infected (2 days in this example, based on the latest possible exposure), and weighted each day span by the case's infectiousness on each of possible exposure days. The result is 3.9 days in this example, meaning the contact had been exposed for 3.9 days upon initiating quarantine. We then took the average between 8 days (index case) and 3.9 days (contacts) as the number of days from exposure to isolation (for both cases and contacts). This is 6 days in this example.
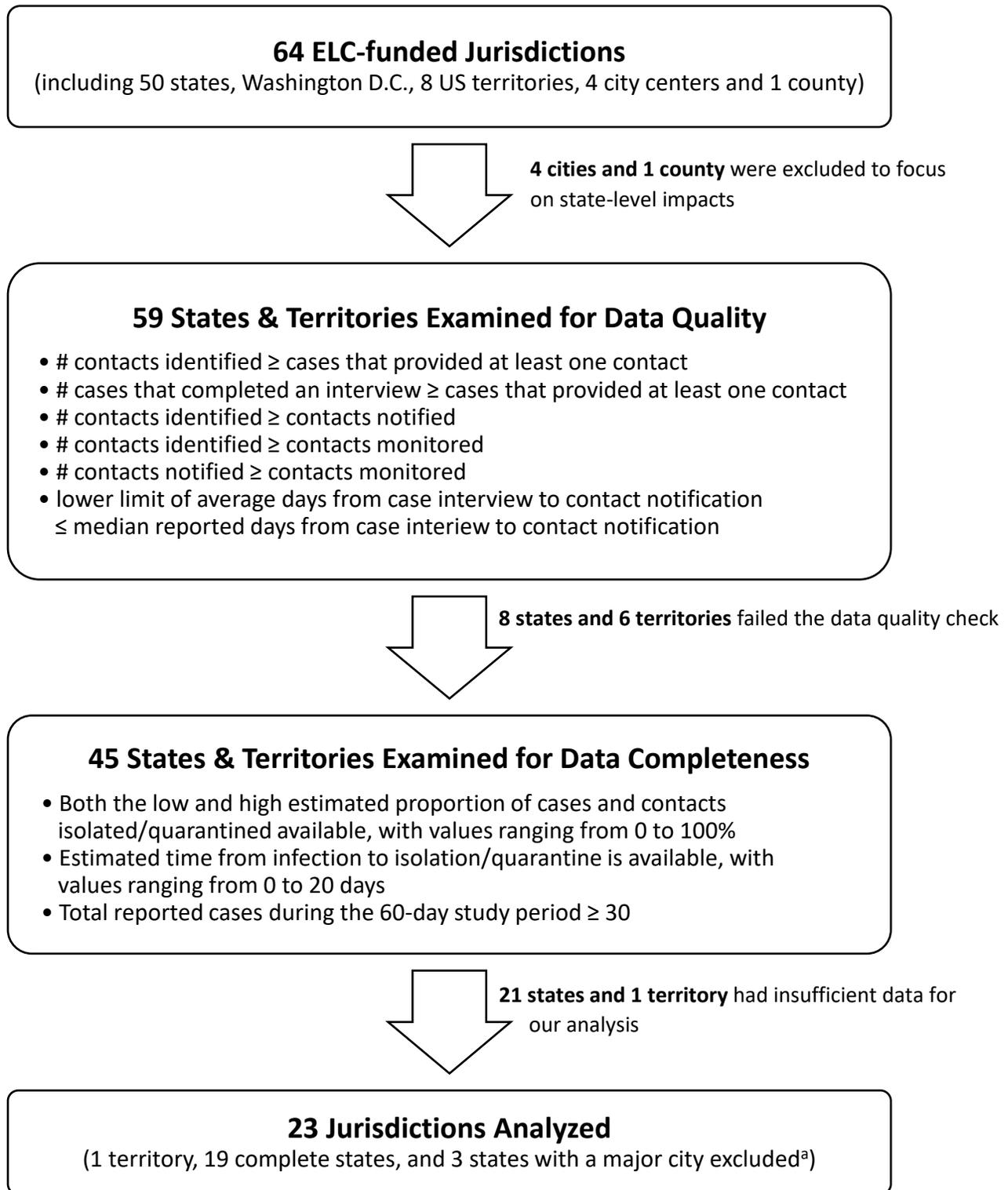
The days between cases with known exposures becoming infected and their exposure notification can vary from what we assumed. For example, cases may take longer to become symptomatic, or get tested the same day that they become symptomatic or begin their isolation on the same day as their results notification. Similarly, contacts who become cases may be exposed earlier or later than we assumed and may make up a larger or smaller share of the case pool. Readers interested in more detail of the influence of varying our assumed time to case isolation may wish to see Table A6 in the Technical Supplement of our 14-site study on CICT impact, containing results of a sensitivity analysis examining this topic in those jurisdictions.[10]

CDC's Epidemiology and Laboratory Capacity (ELC)-funded jurisdictions also reported the *Number of contacts that were notified within 1 day of case interview*, the *Number of contacts that were notified between 1-3 days after case interview*, and the *Number of contacts that were notified within 3 or more days after case interview*. We used these additional data elements as a quality check (Figure A3) of the reliability of jurisdictions' reported median values regarding notification timing (described above). We did this by calculating the lower limit of the average number of days from case interview to contact notification as follows:

$$0.5 \; days * (\% \; contacts \; notified \; within \; 1 \; day)$$
$$+ \; 2 \; days * (\% \; contacts \; notified \; between \; 1 - 3 \; days)$$
$$+ \; 3 \; days * (\% \; contacts \; notified \; 3 \; or \; more \; days \; after \; case \; interview).$$

This metric assumes that all contacts were notified within 3 days of the case interview. We used this metric to exclude jurisdictions from the analysis (*i.e.,* deemed reported data unreliable) when the lower limit of the average time to contact notification was greater than our calculated time to contact notification using reported median days AND the proportion of contacts that were notified 3 or more days after case interview was less than 10% of total contacts (*i.e.,* too few to exert enough influence on the average lower limit for it to plausibly exceed the median-based value).

Figure A3. Inclusion and Exclusion Criteria for Analysis of Jurisdictions

64 ELC-funded Jurisdictions
(including 50 states, Washington D.C., 8 US territories, 4 city centers and 1 county)

4 cities and 1 county were excluded to focus on state-level impacts

59 States & Territories Examined for Data Quality

- # contacts identified ≥ cases that provided at least one contact
- # cases that completed an interview ≥ cases that provided at least one contact
- # contacts identified ≥ contacts notified
- # contacts identified ≥ contacts monitored
- # contacts notified ≥ contacts monitored
- lower limit of average days from case interview to contact notification
  ≤ median reported days from case interiew to contact notification

8 states and 6 territories failed the data quality check

45 States & Territories Examined for Data Completeness

- Both the low and high estimated proportion of cases and contacts isolated/quarantined available, with values ranging from 0 to 100%
- Estimated time from infection to isolation/quarantine is available, with values ranging from 0 to 20 days
- Total reported cases during the 60-day study period ≥ 30

21 states and 1 territory had insufficient data for our analysis

23 Jurisdictions Analyzed
(1 territory, 19 complete states, and 3 states with a major city excluded[a])

[a] Three states included a major city or county that were separately funded by the CDC's ELC program. Their reported CICT metrics are exclusive of the separately funded locales.

Additional Results and Commentary

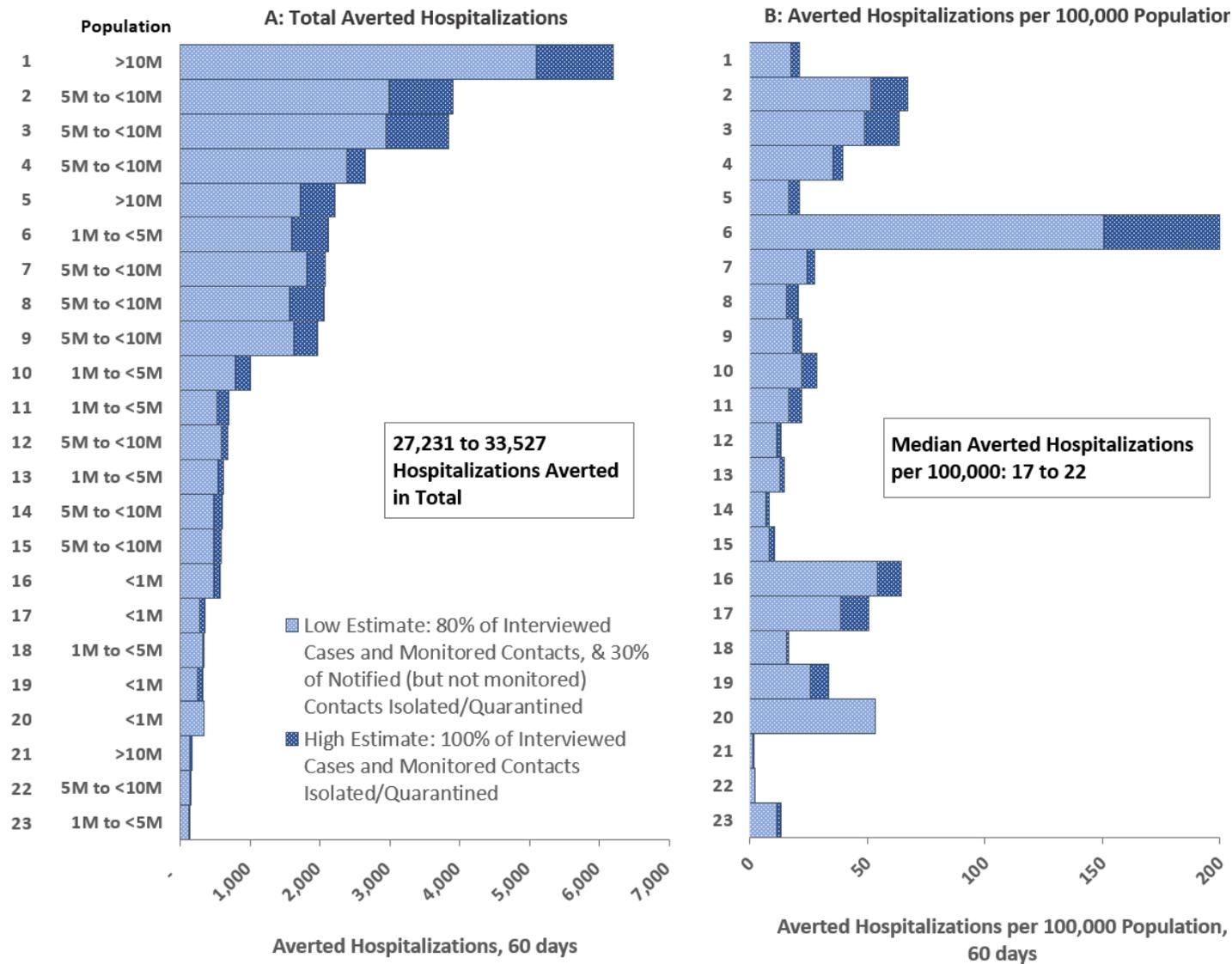**Figure A4. Estimated hospitalizations averted due to CICT programs from 11/25/20 – 1/23/21 (60 days)**

A: Total Averted Hospitalizations

B: Averted Hospitalizations per 100,000 Population

27,231 to 33,527 Hospitalizations Averted in Total

Median Averted Hospitalizations per 100,000: 17 to 22

Low Estimate: 80% of Interviewed Cases and Monitored Contacts, & 30% of Notified (but not monitored) Contacts Isolated/Quarantined

High Estimate: 100% of Interviewed Cases and Monitored Contacts Isolated/Quarantined

Averted Hospitalizations, 60 days

Averted Hospitalizations per 100,000 Population, 60 days

Table A4. Summary of reported case investigation and contact tracing (CICT) data reported to CDC's ELC program and calculated CICT effectiveness for the 23 jurisdictions analyzed and all funded jurisdictions, 11/25/20–12/24/20 (30 days)

Measures	Median (Interquartile Range)	
	23 Jurisdictions analyzed	**All Jurisdictions[a]**
Reported CICT ELC Program Data		
% of cases interviewed	49% (39 – 67%)	58% (39 – 74%)
% of interviewed cases who named their contacts	25% (15 – 35%)	27% (15 – 47%)
% of contacts who were notified	59% (37 – 72%)	64% (35 – 84%)
% of contacts who were monitored	32% (17 – 50%)	48% (29 – 78%)
Reported days from testing to case interview	3.5 days (3.0 – 5.0)	3.0 days (2.4 – 5.0)
Reported days from testing to contact notification	4.0 days (3.0 – 5.2)	4.0 days (3.0 – 5.7)
Calculated CICT Effectiveness		
% of cases and contacts isolated/quarantined (high)	19% (16 – 25%)	N/A
% of cases and contacts isolated/quarantined (low)	17% (14 – 22%)	
Calculated days from exposure to isolation/quarantine	7.0 days (7.0 – 8.0 days)	

[a] Out of 64 total ELC jurisdictions, 5 did not report CICT program data and 3 reported a zero COVID-19 case count. Summary metrics are based on the remaining 56 ELC jurisdictions that reported the following measures: % of cases interviewed (*n=54*); % of interviewed cases who named their contacts (*n=52*); % of contacts that are notified (*n=53*); % of contacts that are monitored (*n=43*); Reported days from testing to case interview (*n=48*); Reported days from testing to contact notification (*n=45*).

Table A5. Estimated impacts of case investigation and contact tracing (CICT) and other interventions from 11/25/20 – 1/23/21 (60 days), by jurisdiction and CICT impact scenarios.

Jurisdiction	Low CICT impact[b]					High CICT impact[b]				
	% Transmission reduction from		Cases Averted by CICT[e], 60 days	Hospitalizations Averted by CICT[e], 60 days	% Reduction in cases and hospitalizations by CICT[f], 60 days	% Transmission reduction from		Cases Averted by CICT[e], 60 days	Hospitalizations Averted by CICT[e], 60 days	% Reduction in cases and hospitalizations by CICT[f], 60 days
	Other NPIs & Vaccine[c]	CICT[d]				Vaccine & Other NPIs[c]	CICT[d]			
1[a]	53.6	3.0	207,417	5,097	12.8	53.3	3.5	252,325	6,200	15.1
2	53.6	8.7	121,865	2,995	37.5	52.6	10.5	158,766	3,901	43.9
3	51.6	9.8	120,157	2,953	42.6	50.5	11.8	156,557	3,847	49.1
4	56.5	5.7	97,231	2,389	23.8	56.3	6.2	107,689	2,646	25.7
5	54.1	3.5	70,297	1,727	15.8	53.8	4.3	90,217	2,217	19.4
6	49.4	13.6	65,037	1,598	51.6	47.8	16.2	86,692	2,130	58.7
7[a]	59.7	5.6	73,780	1,813	22.2	59.4	6.3	84,523	2,077	24.6
8	61.0	5.0	63,813	1,568	20.2	60.4	6.3	83,647	2,055	24.9
9	54.7	3.6	66,362	1,631	16.9	54.4	4.3	80,059	1,967	19.7
10	54.2	4.0	32,084	788	18.9	53.8	5.0	41,194	1,012	23.0
11	55.5	7.1	21,170	520	32.0	54.7	8.9	28,595	703	38.8
12	50.1	2.0	24,011	590	10.0	49.9	2.2	27,473	675	11.3
13	59.2	5.7	22,014	541	23.7	58.9	6.4	25,359	623	26.4
14	53.2	0.9	19,691	484	4.4	53.1	1.2	24,455	601	5.5
15	61.3	2.3	19,277	474	9.6	61.1	2.9	24,197	595	11.8
16	53.6	8.3	19,577	481	36.0	53.0	9.4	23,221	571	40.1
17	50.1	9.2	11,135	274	41.1	49.1	11.0	14,586	358	47.8
18	59.8	3.3	13,248	326	13.9	59.8	3.5	14,102	347	14.6
19	54.2	4.4	10,200	251	19.1	53.7	5.4	13,247	326	23.5
20	49.3	17.0	13,560	333	65.8	51.7	12.9	8,304	204	54.1
21[a]	60.4	0.4	5,921	145	1.3	60.4	0.4	7,005	172	1.6
22	58.6	0.4	5,466	134	1.5	58.6	0.5	6,452	159	1.7
23	62.9	3.4	4,858	119	13.1	62.7	3.9	5,721	141	15.1

[a] Single large city or county in these states were separate Epidemiology and Laboratory Capacity (ELC) jurisdictions and not included in this analysis.

[b] Low CICT impact scenario assumes only actively monitored contacts (who later became cases) effectively quarantined/isolated. High CICT impact scenario assumes notification prompted contacts (who later became cases) to quarantine effectively. In both scenarios we assumed interviewed cases fully adhered to isolation guidelines.

[c] Percent reduction in the number of new infections per case (R_t) due to a combination of vaccination and all other nonpharmaceutical interventions (NPIs; *e.g.,* masks use, social distancing, school/restaurant closures, etc. Calculated as the percent difference in R_0 and R_t after implementation of vaccine and other NPIs.

[d] Percent reduction in the number of new infections per case (R_t) due to CICT after the implementation of other NPIs. Calculated as the percent difference between R_t after implementation of other NPIs and R_t after implementation of both other NPIs and CICT.

[e] After accounting for the impacts from vaccination and all other NPIs.

[f] Cases or hospitalizations averted by CICT out of the estimated cases or hospitalizations remaining after the implementation of vaccination and other NPIs.

Alternate approaches to simulating Epi-curves without CICT and their results

We estimated the combined effectiveness of vaccine and other non-pharmaceutical interventions (NPIs) by fitting our model to cumulative cases and assuming that the effectiveness of NPIs remained constant over the course of our 60-day evaluation period. These choices enabled us to 1) avoid the influence of transient testing accessibility and test-seeking behaviors, or data reporting artifacts (observed in many locations around the Christmas and New Year's holidays), and 2) maintain COVIDTracer Advanced's accessibility and ease-of-use for practicing public health officials. However, fitting to cumulative cases weights early cases over later cases and can inflate model fit. Also, fixing the effectiveness of NPIs may result in an over- or under-estimation of impact. We, therefore, conducted an excursion analysis to examine the influence of these choices on our estimates of averted cases and hospitalizations.

We selected eight jurisdictions for this analysis: the five with the largest estimates of averted cases (accounting for 56% of total averted cases), and three others exhibiting clear and large changes in the overall trend of incident cases within our 60-day evaluation period (jurisdictions 1-5, 7, 12, and 20 in Table A5).

For these eight jurisdictions, we repeated our fitting process, but used the incidence epi-curves, and fit up to three periods using our low CICT impact scenario (Table 6, main text). The number of periods and their lengths (in days) were determined by visually examining and selecting inflection points in the 7-day moving average of the observed incidence curves of reported cases (Figure A5).

This fitting procedure reduced discrepancies between the observed cumulative case count and the fitted curve's count on the last day of our evaluation period (which we use for calculating CICT impact on cases) for 6 of the 8 evaluated jurisdictions (Figure A5). Based on the new fits, our averted case estimates decreased for five of the eight states and increased for the remaining three (Table A6). Across all eight states, we estimate that CICT potentially averted 713,752 cases and 17,539 hospitalizations, 2.0% fewer than our main estimates for the same scenario. The similarity of these results to those presented in the main text suggest our simplified fitting approach generates estimates of averted cases that are sufficiently accurate for policymakers to value the impact of CICT, while preserving a simple, easy-to-use model for public health practitioners.

Table A6. Effect of alternate fitting methods[a] on estimates of the impact of case investigation and contact tracing (CICT) from 11/25/20 – 1/23/21 (60 days), under "low" CICT impact scenario[b].

Jurisdiction	% Transmission reduction from Other NPIs & Vaccine[d]		Cases Averted by CICT[f], 60 days		Hospitalizations Averted by CICT[f], 60 days		% Reduction in cases and hospitalizations by CICT[g], 60 days	
	Main Results (Single, Constant NPI Effectiveness)	Alternate Fit (Up to three NPI Effectiveness Values[h])	Main Results	Results, Alternate Fit	Main Results	Results, Alternate Fit	Main Results	Results, Alternate Fit
1[c]	53.6	48.8, 55.2, 61.4	207,417	202,236	5,097	4,970	12.8	13.0
2	53.6	52.6, 59.1, 52.9	121,865	113,234	2,995	2,782	37.5	36.3
3	51.6	55.9, 47.9, 56.5	120,157	107,950	2,953	2,653	42.6	40.4
4	56.5	56.5, 53.9, 62.2	97,231	96,477	2,389	2,371	23.8	23.6
5	54.1	54.1	70,297	71,027	1,727	1,745	15.8	15.8
7[c]	59.7	59.6, 54.1	73,780	85,831	1,813	2,109	22.2	23.3
12	50.1	50.0, 48.4, 54.9	24,011	22,823	590	561	10.0	9.8
20	49.3	54.8, 34.4, 52.2	13,560	14,080	333	346	65.8	65.6

[a] Using the 7-day moving incidence average for fitting and up to three periods for each jurisdiction using our low CICT impact scenario (Table 1).

[b] Low impact scenario assumes 80% of actively monitored contacts (who later became cases), 30% of notified contacts effectively quarantined/isolated and 80% interviewed cases fully adhered to isolation guidelines.

[c] Single large city or county in these states were separate Epidemiology and Laboratory Capacity (ELC) jurisdictions and not included in this analysis.

[d] Percent reduction in the number of new infections per case (R_t) due to a combination of vaccination and all other nonpharmaceutical interventions (NPIs; *e.g.,* masks use, social distancing, school/restaurant closures, etc). Calculated as the percent difference in R_0 and R_t after implementation of vaccine and other NPIs.

[e] Percent reduction in the number of new infections per case (R_t) due to CICT after the implementation of other NPIs. Calculated as the percent difference between R_t after implementation of other NPIs and R_t after implementation of both other NPIs and CICT.

[f] After accounting for the impacts from vaccination and all other NPIs.

[g] Cases or hospitalizations averted by CICT out of the estimated cases or hospitalizations remaining after the implementation of vaccination and other NPIs.
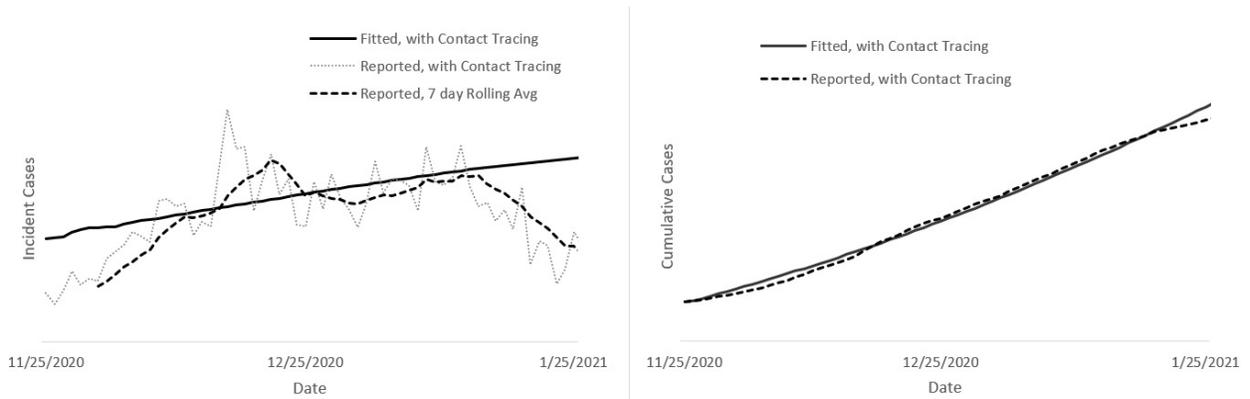
[h] See Figure A5 for fitted curves and periods used for fitting.

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Figure A5. Fitted epidemic curve outputs from COVIDTracer Advanced and observed data for the 60-day period, by jurisdiction and fitting approach
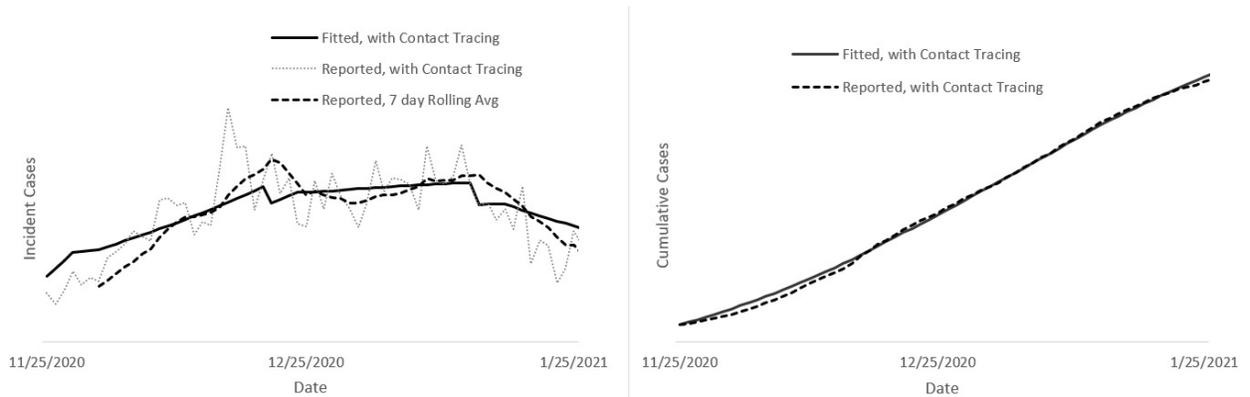
(Case counts excluded to maintain jurisdiction anonymity)
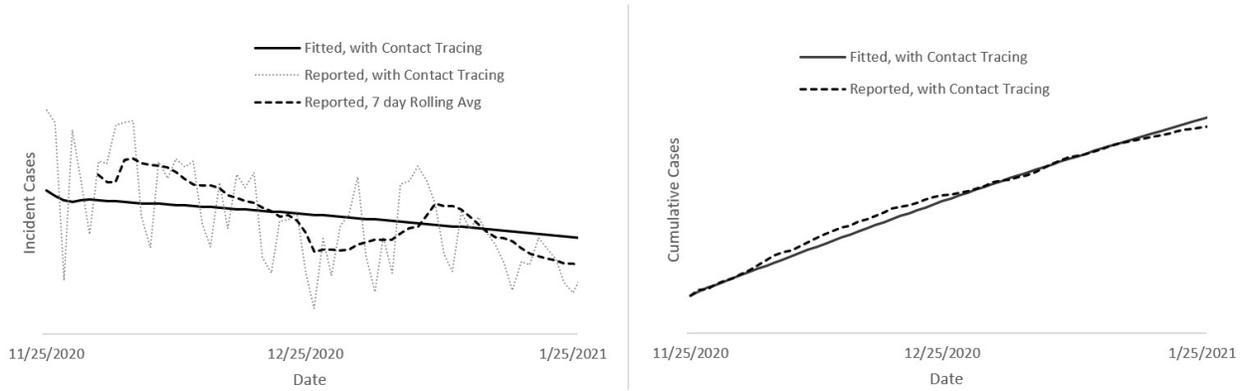
Jurisdiction 1

Fits Using Cumulative Cases

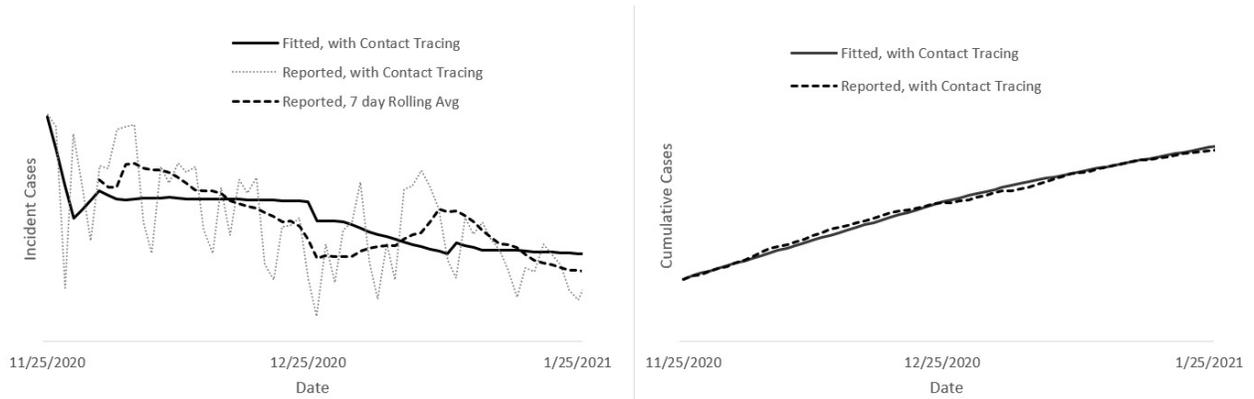### Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods

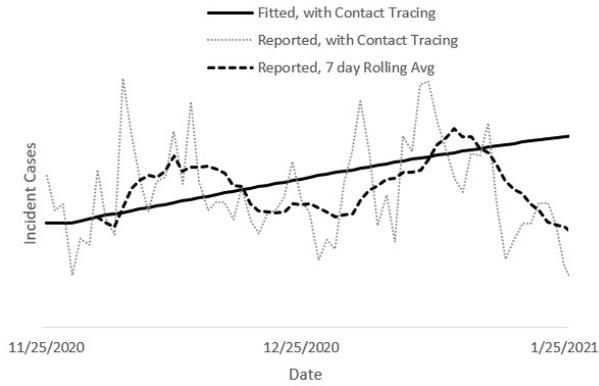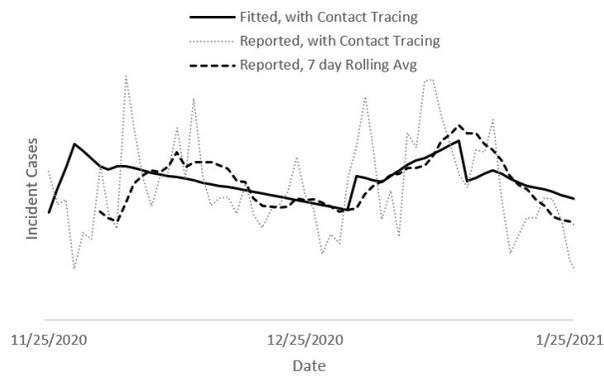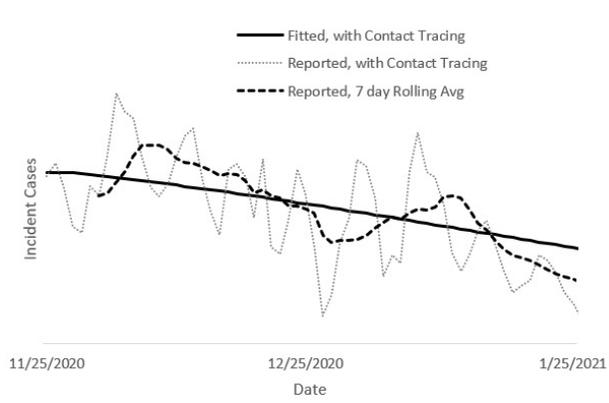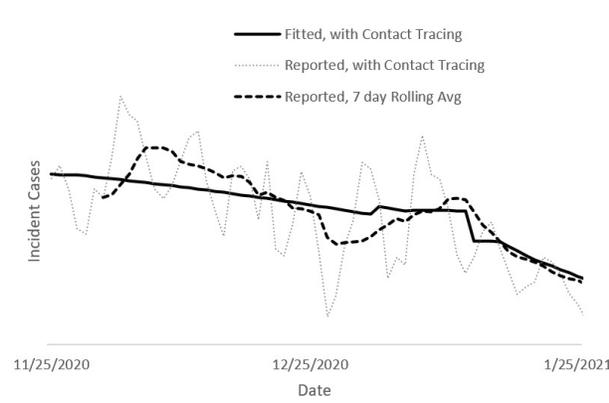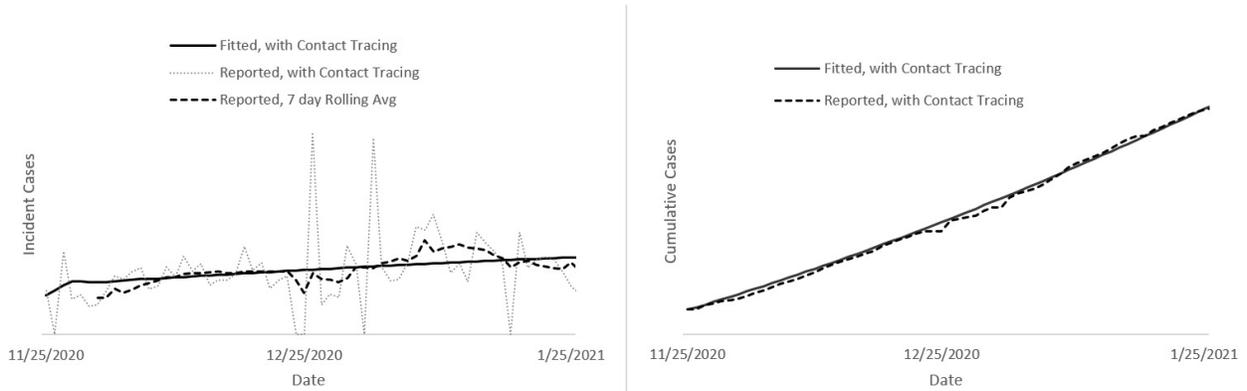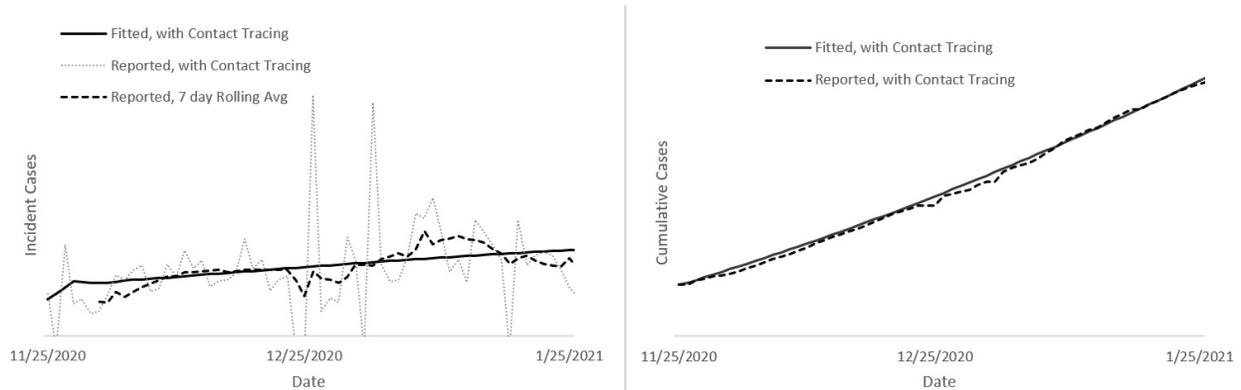## Jurisdiction 2

Fits Using Cumulative Cases

Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods
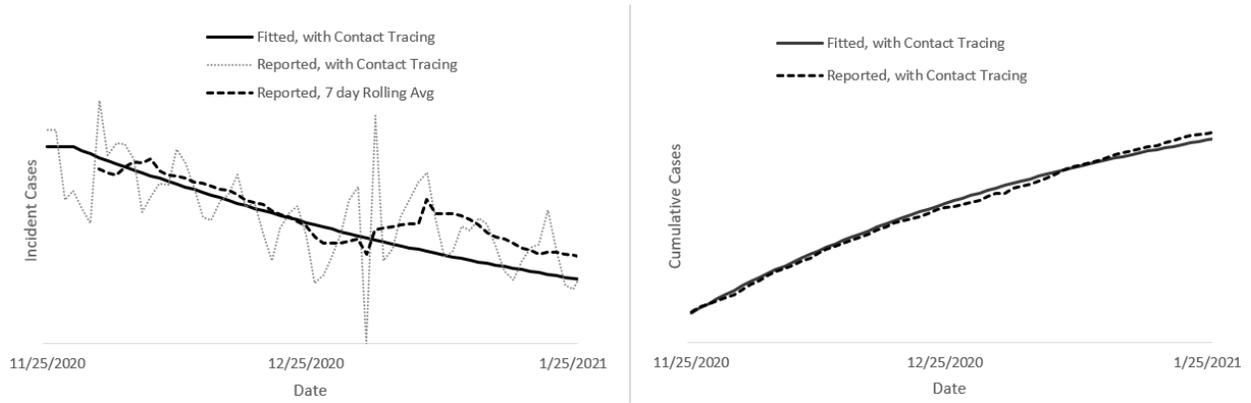
Jurisdiction 3

Fits Using Cumulative Cases

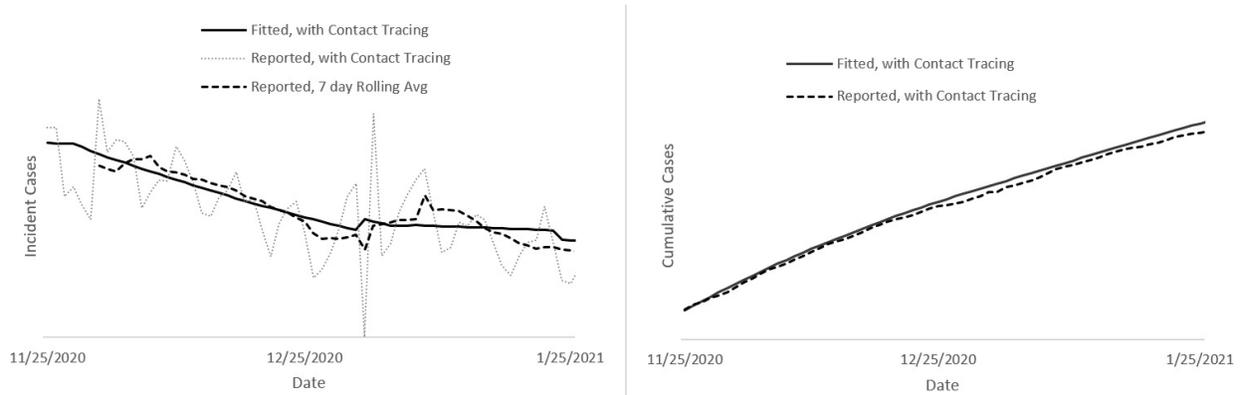**Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods**

Jurisdiction 4

Fits Using Cumulative Cases

Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods

Jurisdiction 5

Fits Using Cumulative Cases

Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods*

* A single fitting period spanning the entire 60-day evaluation period maximized fit for this jurisdiction.
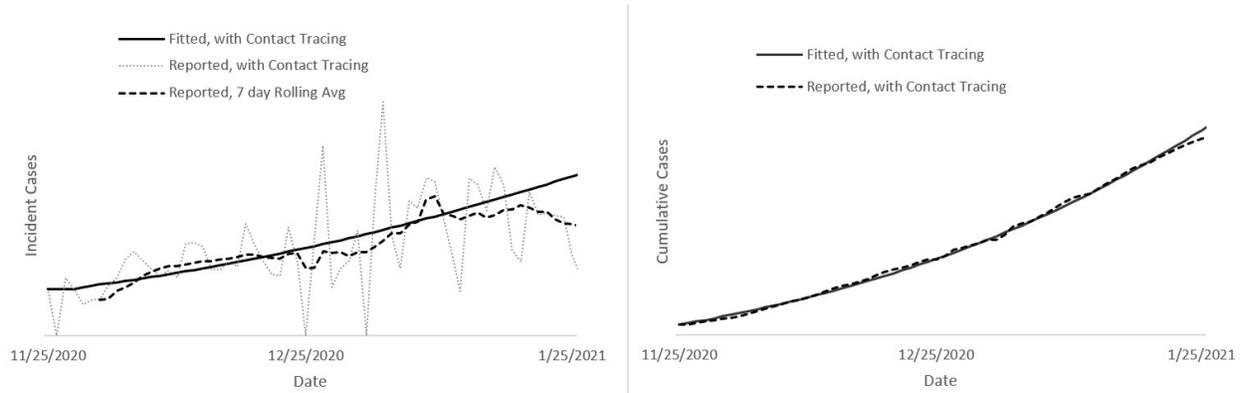
Jurisdiction 7

Fits Using Cumulative Cases

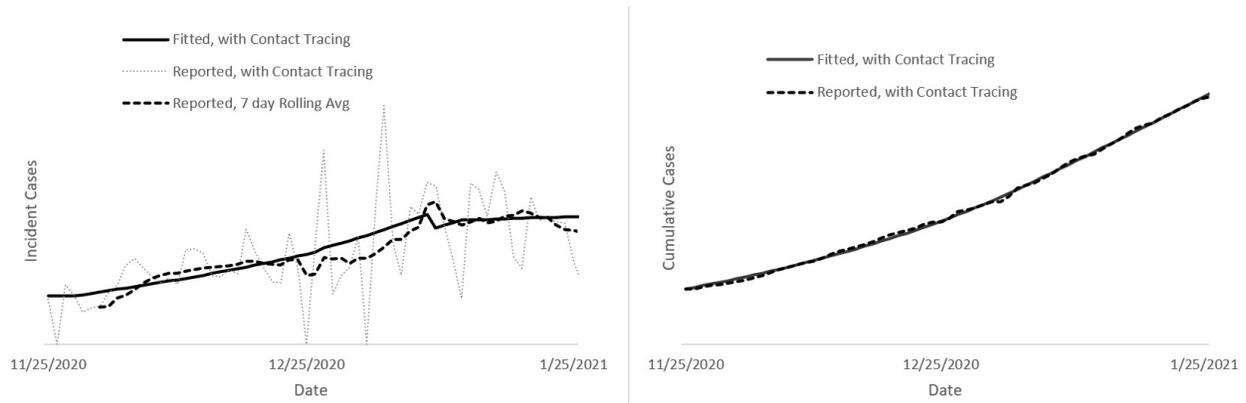**Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods***

* Two fitting periods maximized fit for this jurisdiction.
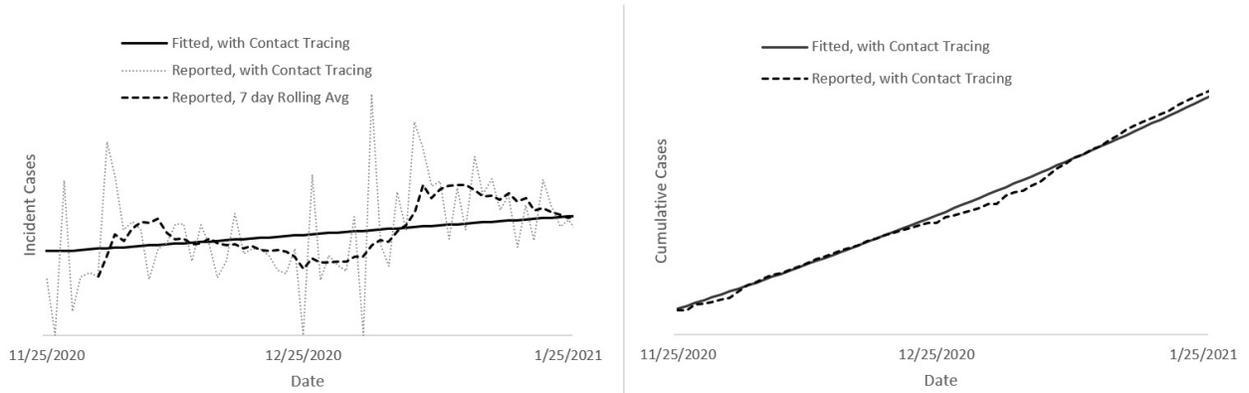
Jurisdiction 12

Fits Using Cumulative Cases

Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods
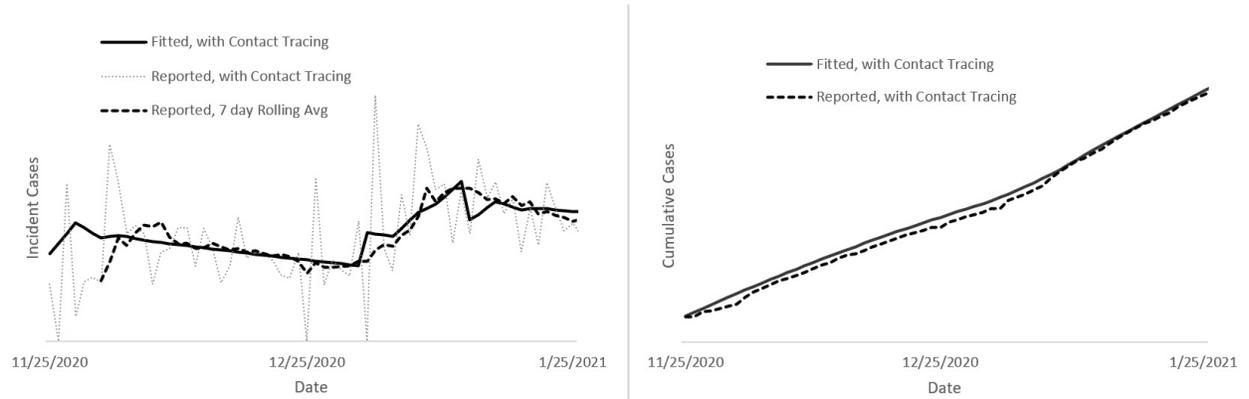
Jurisdiction 20

Fits Using Cumulative Cases

Fits Using Incident Cases' 7-day Moving Average and Multiple Fitting Periods

Isolation/Quarantine Compliance Scenarios: *Sources and Details*

A review of multiple cross-sectional population surveys in the UK suggests 40-45% of people who had COVID-like symptoms self-reported fully complying with isolation guidance during their infectious periods.[11] Another survey in the US found that 85% of respondents who had COVID-like symptoms or tested positive stayed home (according to CDC guidelines) except to get medical care.[12] And a third survey, also in the US, found that 93% of adults said they would definitely (73%) or probably (20%) quarantine themselves for at least 14 days if told to do so by a public health official because they had the coronavirus (*i.e.,* they were confirmed cases; not just exposed contacts).[13]

APPENDIX 4 - Instructions for using COVIDTracer Advanced Special Edition

This appendix provides the step-by-step instructions for using the COVIDTracer model to repeat the analysis described in Study 3 to estimate COVID-19 cases averted by case investigation and contact tracing activities. The Special Edition version of COVIDTracer Advanced is a modification of the publicly available tool on CDC's website that enables users to assess the impact of CICT before vaccine was widely available. Additional modifications would be required if you intend to explicitly account for vaccinated individuals (*e.g.,* decreasing susceptible population over time, decreased risk of hospitalization among vaccinated individuals, etc).

Readers seeking basic information about the model, data elements, and definitions should refer the COVIDTracer Advanced User Manual. However, some statements in the web manual are not applicable to the Special Edition version used in this analysis. https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/COVIDTracerTools.html

COVIDTracer Advanced uses the Windows operating system (Microsoft Windows 2010 or higher) and Excel (Microsoft Office 2013 or higher).

Before starting, complete the following:
1) Determine your 60-day study period. The first day of your study period is your "model start date." This "model start date" will be referenced later in these instructions. For example, if you are interested in estimating cases and hospitalizations averted by CICT during the 60-day period from January 1-March 1, 2021, your "model start date" is January 1, 2021.

2) Obtain these data for the jurisdiction of interest:
    a. Total population
    b. Total cases as of the day before the model start date (In the example study period above, this is the total cases reported as of December 31, 2020.)
    c. Cases reported during the past 14 days (In the example study period above, this is the sum of cases reported from December 18 to 31, 2020.)
    d. The case trend during the past 14 days (*e.g.,* increasing, plateaued, decreasing)
    e. Daily (*i.e.,* incident) case counts for the 60-day study period
    f. The following case investigation and contact tracing program metrics. These metrics are meant to be representative of the 60-day study period. If you don't have such data for the entire study period, you may base these metrics on a shorter period (*e.g.,* 30 days or 4-weeks) from the model start date (and assume they are representative of the full 60 days):

> i. Number of days from exposure to case isolation and contact quarantine
>
> ii. Percent (%) of all cases successfully isolated and contacts quarantined
>
> 3) Open the COVIDTracer Advanced_SpecialEdition tool (Supplement 2)
>
> a. When opening the spreadsheet file, click the "Enable Macros" button for full functionality of the tool.
>
> b. Enable Excel "Solver Add-In." **Instructions**: in Excel, click on File → Options → Add-ins → select "Analysis ToolPak" → click "Go" (not the "Ok" button) → select checkbox for "Solver Add-In" and click "Ok."
>
> The Solver button, ?→ Solver will appear in the "Data" menu.

In worksheet, "A. Outbreak Details"

Step 1: Enter the population for the jurisdiction of interest.

Enter the population of your jurisdiction

Total Population	1,000,000	persons

Step 2: Enter the model start date, the total number of COVID-19 cases in the jurisdiction until the day before the model start date, and the number of cases reported in the last 14 days within the jurisdiction.

Enter information about case counts in your jurisdiction

Start Date	1/1/2021	
Total Cases as of 12/31/2020	35,000	cases
Cases in the last 14 days (from 12/18/2020 to 12/31/2020)	5,000	cases

Note: These data inputs will only create curves for the purpose of calculating resources needs. They are not intended as, nor should be intepreted as, forecasts of future cases

Step 3: Set the pattern of daily cases over the past 14-day period selected in Step 3.

The default is "Daily case counts are slowly increasing." However, if daily case counts have been changing rapidly, remaining constant, or decreasing over the last 14 days, select from the pull-down menu the pattern that best matches the jurisdiction's data.

The selection of the case trend in the past 14 days determines how reported cases are distributed over the 14 days prior to the model's initiation date. Visually inspect the case trend and choose the most appropriate option. You can also run the model with different case trend patterns and pick one that yields the "best fit" (by repeating steps 3 to 6).

Enter estimates about the effectiveness of community interventions implemented through the present date

Are community interventions currently in place?	Yes	
Pattern of change in daily case counts over the last 14 days	Daily case counts are slowly increasing	How to choose?

In worksheet, "Case Counts"

Step 4: Paste the jurisdiction's daily case counts (*i.e.,* incident cases) for the 60-day study period into the "Daily" column (column AH)

Cover	**Case Counts**	A. Outbreak Details	B. Impact of contact tracing
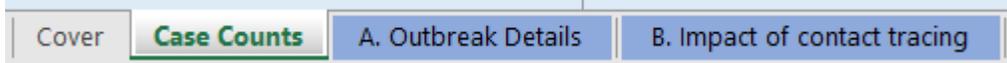
In Worksheet, "B. Impact of Contact Tracing"

Step 5: Using your representative CICT program data, enter values for:

- Number of days after infection that case is isolated
- % of all cases successfully isolated and contacts traced and monitored

Set up the scenarios for contact tracing strategies

Contact Tracing Strategy Input	No Contact Tracing	Continued Contact Tracing	Strategy 3 (Optional)
Number of days after infection that case is isolated	15	9	
% of all cases successfully isolated and contacts traced and monitored	0%	20.0%	
Strategy Trigger	Symptoms	Contact ID	
Contacts are identified and listed?	No	Yes	
Contacts follow-up occurs?	No	Yes	

*Successfully traced = the strategy worked as assumed and transmission to the next generation was prevented

Step 6: Estimate the % reduction in transmission due to community interventions (shown in cell G28) by fitting COVIDTracer Advanced's simulated curve to your observed case curve. You will use the Solver Add-in to do this: The Solver Add-in finds an optimal solution for the % reduction in transmission due to community intervention by minimizing the mean squared error (a mathematical value describing the differences between both curves; shown in cell O32).

Instructions for using the Solver:

From the Excel menu tab, click "Data" and the "Solver" button, then follow the instructions described here to set up the parameters in the pop-up dialogue box (see screen shot below):
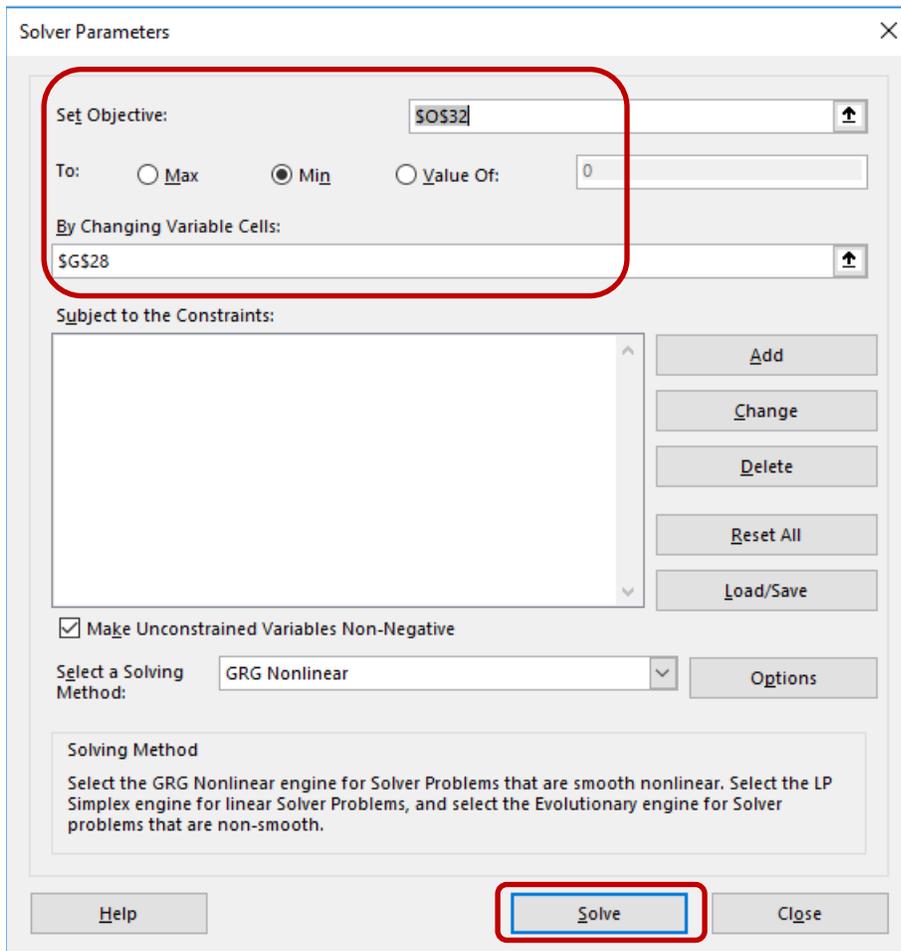
Set Objective: Set objective to cell "O32", which is the mean squared error.

To: Select "Min".
By Changing Variable Cells: Enter G28 (This cell refers the Solver to the "Estimated % reduction in transmission due to continued community interventions.")

Select a Solving Method: For simplicity, we recommend selecting "GRG Nonlinear" from the drop-down menu.

Click "Solve" button.

Then the Excel Solver function will automatically find the optimal value (estimated % reduction in transmission due to continued community intervention) and populate the value in cell G28. The figure below shows a fitted curve (solid line) generated by

COVIDTracer Advanced after Step 6, that minimizes deviation from the reported case counts (dashed line).

Example Figure: Fitted curve using COVIDTracer Advanced
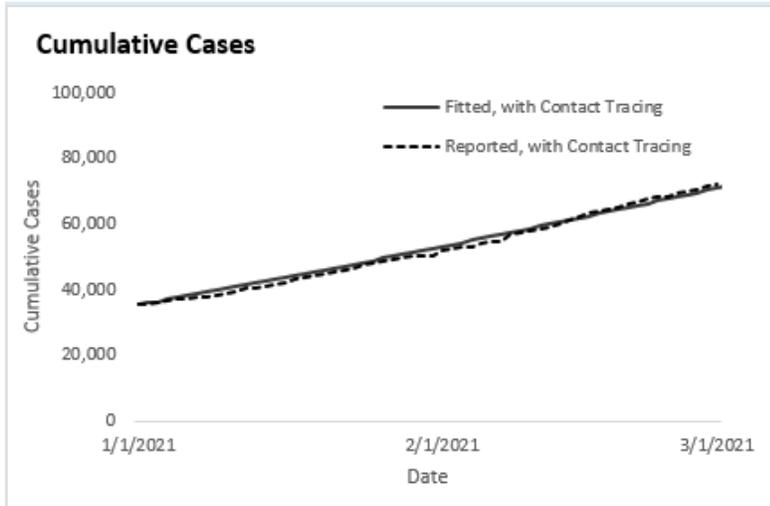
In Worksheet, "Results – Cases Averted"

Step 7. Users can find the % reduction in transmission due to CICT, and those that are attributable to all other interventions. The estimated number of cases and hospitalizations averted by CICT are also provided on this page.

Transmission Fraction

Transmission Reduction from Contact Tracing	4.5%
Transmission Reduction from All Other Interventions	54.7%
Remaining Transmission*	43.3%

*Calculated as follows: (1-reduction from CT) * (1-reduction from other interventions)

Cases Averted, 60 days

Cases Averted by Contact Tracing	8,937
Cases Averted per 100,000 population	894
% of Additional Cases Averted by Contact Tracing**	19.7%

**Additional cases averted by contact tracing out of every 100 remaining cases after accounting for the impact of all other interventions (e.g., vaccination, facemask policies, social distancing).

Hospitalizations Averted, 60 days

Hospitalizations Averted by Contact Tracing	220
Hospitalizations averted per 100,000 population	22
% of Additional Hospitalizations Averted by Contact Tracing***	19.7%

***Additional hospitalizations averted by contact tracing out of every 100 remaining hospitalizations after accounting for the impact of all other interventions.

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