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B.S.

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Rollins School of Public Health of Emory University

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Abstract

Estimating and modeling the number of children susceptible to measles in light of COVID-19

By Ashley Gambrell

Measles elimination hinges on vaccination levels remaining above certain thresholds. The current global pandemic has resulted in a decline of childhood vaccinations, including measles vaccinations. This study's goal is to estimate the number of children aged 0-18 susceptible to measles currently and model potential susceptibility rates in decreased vaccination scenarios, utilizing survey responses from the CDC's national NIS-Teen survey.

Participants were respondents to the survey conducted by the CDC between the years 2008-2017 that also had provider-verified vaccination documentation. The exposure of interest was vaccination with a measles-containing vaccine, and the age at which they were vaccinated for all doses given. Using the age at vaccination, age-based probabilities of vaccination were compiled and used to model population levels of immunization and immunity vs susceptibility.

Currently 9,136,434 children (12.9%) are estimated to be susceptible to measles, with 61,642,824 (87.1%) children immune. With conditions mimicking pandemic-level vaccination rates, 15,121,801 children (21.4%) would be susceptible to measles if no attempt at catch-up is made, or 9,448,396 children (13.3%) if a mild attempt is made. Models based on increased vaccine hesitancy also show increased susceptibility at national levels, with a 10% increase in hesitancy nationally resulting in 14,697,783 children (21%) susceptible to measles, irrespective of pandemic vaccination levels.

Current levels of immunity, nationally, remain slightly below herd immunity thresholds based on data. If rates continue to remain depressed at current levels, our models indicate population-level immunity to measles will continue to move further from herd immunity thresholds.

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Measles Virus Review: Illness, Vaccinations, and COVID-19 Disruption

Introduction

The Measles virus (MeV) is the causative agent of the childhood illness, Measles. From the family Paramyxoviridae and the genus *Morbillivirus*, MeV is a single stranded, nonsegmented, negative-sense RNA virus, pleomorphic in shape and utilizing an envelope from host cell membrane surrounding it. The genome codes for eight functional proteins, with 6 as major structural players and two with as yet unknown functions [1]. Host-virus interactions occur when the H and F proteins interact with the principal host cell receptors, CD46 and signaling lymphocytic activation molecule (SLAM/CD150) [2]. The MeV has 24 distinct genotypes based on structure of the surface proteins, with only one serotype [1].

Measles is a respiratory disease of childhood, with varying severities of clinical presentations. Generally, symptoms include fever, coryza, cough, and generalized malaise followed by the characteristic erythematous maculopapular rash beginning at the head and extending down the trunk and extremities. Measles can also result in whitish plaques on the interior of the mouth – usually the insides of the cheeks – called Koplik spots. Often appearing immediately prior to development of the skin rash, these spots are so common they are often used in diagnostic criteria. A case of measles is considered infectious from 4 days prior to rash onset, until 4 days after the rash has emerged. In that time, Measles can be spread via large respiratory droplets, droplet nuclei, and fomites. With a basic reproduction number often quoted at 18, Measles represents one of the most infectious illnesses known to humanity [1].

Measles has an incubation period of 7-14 days, though conservative guidelines typically set it closer to 7-21 days for sensitive case definitions and surveillance efforts. Prior to any concerted, large-scale vaccination efforts, Measles was very common, so much so in fact that approximately

90-95% of the population contracted it prior to 15 years of age. Most common in the late winter and throughout spring, MeV also showed larger scale outbreaks on a 2–3-year cycle. Over half of cases occurred in children aged 5-9, with highest complication and fatality rates in very young children under 12 months of age. Symptoms typically lasted about 10 days, though complications could extend beyond the acute disease presentation, and typically affected more than one organ system [1]. The most common immediate complications and secondary issues post-Measles are otitis media, secondary bacterial pneumonia or giant-cell pneumonia, and diarrhea, occurring in up to 30% of reported cases [3]. More severe complications tend to occur in those younger patients, or in immune naïve adults who contract the virus. Complications can range in presentation but have been known to affect many different organ systems including hematologic, cardiovascular, gastrointestinal, dermatological, respiratory, or neurologic [4].

In addition, long-term effects of MeV can also include wiping out up to 70% of a patient's prior immune memory acquired throughout childhood, an issue that can persist years after acute infection. One of the most serious long-term complications is a rare, though devastating, degenerative neurological condition called Subacute Sclerosing Panencephalitis (SSPE). A persistent infection in the patient's central nervous system (CNS), SSPE can often present almost a decade after initial illness. It is characterized by progressive cognitive decline beginning with behavioral changes and motor skill deterioration, and ending with seizures, intellectual deterioration, comas, and finally death over the span of 1-3 years. Although it is rare, research indicates it might not be as rare as once was thought. Initial estimates put the incidence at 1 in 100,000 cases, though recent global data could show the incidence anywhere from 22 in 100,000 to 1 in 2,000 due to the slow and nonspecific progression of the symptoms [1].

In the pre-vaccine era of the US, approximately 500,000 cases of measles were reported annually. Given its infectiousness and relative ubiquity, however, it is much more accurate to assume that a large percentage of each successive birth generation was infected. Amongst the 500,000 reported cases, there were 500 deaths along with a slew of other reported complications. In the early 1960's among children most affected by measles, those aged 5 – 9 years, incidence rates were about 1,200 cases in 100,000 children. After vaccines were introduced, those numbers fell in the same group to 1.8 cases per 100,000 in just 20 years [1]. As of 2006 case numbers have declined by 99.9% in the US [5].

The Measles virus first infected humans likely sometime around the 4th century BCE after the Neolithic Revolution and the dawn of humanity's agricultural pursuits led them to congregate in larger and larger populations in cities [6, 7]. First described by a Persian physician and scholar, MeV's presentation was initially often confused with smallpox virus given the relatively similar rashes produced. By the later 18th century physicians were just beginning to understand its infectiousness and ability to spread between people, as well as reliably diagnosing it apart from smallpox [1].

Measles Vaccine

Measles vaccine development began, first, with viral isolation in tissue culture in 1954. Researchers were able to isolate a sample taken from a young patient, and the strain was given the boy's surname, Edmonston. Once the virus was isolated, work on vaccines began, and by 1963 two candidates were up for licensure for use and distribution in the United States. One candidate was a killed, purified vaccine, though its success was short lived, as its immunogenicity was much weaker when compared with the other candidate. It was used for several years but given the rate at which the public had to have booster doses, meant that it was retired in favor of the other candidate. The live, attenuated vaccine derived from the Edmonston strain performed well in terms of immunogenicity, however it was known to cause unpleasant side effects in up to half of those vaccinated, most commonly fever and/or a rash. By the later 1960’s, several other live, attenuated vaccine candidates had been produced. Of those, the most successful and only remaining licensed vaccine today in the US is the Moraten vaccine [1].

In 1971, the Measles, Mumps, and Rubella (MMR) vaccine was created as the first iteration of a trivalent vaccine to cover vaccination against three childhood illnesses at once. The second iteration, the MMR II, had a change in the Rubella vaccine component, however the Moraten vaccine remained as the Measles vaccination strain [1]. The vaccine was, and continues to be, recommended by the Centers for Disease Control and Prevention (CDC) as a series of two doses, the first occurring at age 12-15 months with the second following at 4-5 years old. The CDC recommends that children who have not received any doses of MMR be vaccinated with both doses, at least 4 weeks apart. A similar schedule is recommended for older teens and adults considered higher risk (ex. Communal living, post-secondary education, healthcare workers, etc.), also with two doses in series, 4 weeks apart [8].

Vaccine coverage for MMR steadily rose, nationally, from approximately 60% of 2-year-olds, until it peaked in 2006 with 92.4% of children aged 19-35 months. From there, it declined to approximately 91.6% by just 10 years later in 2016, though it maintained consistently at 91% – 92% [9]. Unfortunately, national immunity levels can often mask harmful trends at the state level, with state immunity levels masking community problems as well. In California, a state whose MMR vaccine coverage for 2015 was 92.6%, researchers still found over 20 individual communities with statistically significant levels of under immunization [10]. On the state level there was a similar decline in 28 states from 2009 to 2019, with a median decrease of 0.6% [11].

With estimates of young people under the age of 18 in each state being around 20%, a 0.6% is a noticeable decline, especially in populous states where population numbers can stretch into the millions [12]. Although this decline in vaccinations is relatively recent, rates remained high enough that by 2000, the WHO was able to declare endemic measles eradicated in the United States [13].

COVID-19 and Vaccination Rates

With already declining vaccination rates coupled with increasing hesitancy towards vaccines, public health professionals were expressing concern, though this issue became much more complicated with the emergence of the newest coronavirus, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) in early 2020. Although the virus likely emerged in humans in late 2019, it was not until reports of growing outbreaks in 2020 that the spread of this virus was fully recognized. By March 11, 2020, the WHO had declared a pandemic, and by the end of that March, the United States had declared a federal state of emergency and individual states began releasing statements urging the public to remain at home as much as feasible, though with varying levels of urgency and compulsion. Following swiftly was guidance from the CDC reminding parents that childhood vaccinations remained vital, and that they should continue to make every effort to ensure their children were immunized. The Vaccines for Children (VFC) Program, a federally funded body responsible for almost half of all vaccinations for US children, began monitoring vaccination levels. After only one week, they began reporting noticeable declines in doses of MCV ordered, compared to levels in January 2020. In addition, the Vaccine Safety Datalink, managed by the CDC, reported less than half the amount of doses from the preceding weeks, were delivered the week after the emergency declaration, a gap that, though it has narrowed, has not returned to its baseline prior to the pandemic [14].

In an effort to understand the scope of the problem, several entities, including pediatric primary care networks and large insurance companies began analyzing vaccination rates. The Nationwide Children's Hospital network, based in Ohio, cares for over 90,000 pediatric patients. They reported that while vaccination rates among 16-month-olds were at 72% prior to March 2020, a number stable since early 2017, the rates declined to 62.4% by August 2020, and showed no signs of rebounding at the time of reporting [15]. Corroborating this, BlueCross BlueShield released a report in November 2020 that reported as much as a 26% decrease in MCV's compared with the previous year, with predictions of a staggering 9 million missed doses by 2021 [16]. With such rapid and large declines in immunization activities, experts warn that after social distancing restrictions are lifted, new measles outbreaks will not be a question of "if", but "when" [17].

The fastest vaccine development in the history of the US was, until recently, held by the Mumps vaccine. The entire process of developing and testing the vaccine took place over only 4 years. This record was shattered by the vaccine development against SARS-CoV-2, with isolation, genetic sequencing, manufacturing, and all stages of clinical trialing occurring within 12 months [18]. This success, however, was darkened by troubling statistics regarding hesitancy towards the new vaccine, with approximately 23% of US adults still reluctant to get a vaccine as of February 2021. Similar findings from the public in France were associated with a perception of decreased severity of COVID-19 and less vaccination uptake in the past as well [19]. Among a large survey partnering researchers at Carnegie Mellon with Facebook, the most common reason for refusal was a concern of side effects, with 45% of people refusing vaccines citing this as a reason. There are, however, a smaller portion, around 27-29% citing mistrust of the US government and/or the vaccine itself, with another 20% simply believing that the vaccine candidates are ineffective [20]. Misinformation has marred the rollout of vaccine options and has been a growing problem as the pandemic has gone on, until finally in February of 2021 Facebook banned its users from actively sharing misinformation through its platform, an attempt to stem the flow [21]. With an already growing generally vaccine hesitant movement, often coined “Antivax”, these added concerns could potentially compound the already deleterious effects of vaccine misinformation and hesitancy [22].

Conclusion

Despite vaccine hesitant individuals and the spread of misinformation, the vaccination campaign for the US has begun to recover from its shaky beginnings, and in early March 2021, President Biden reported that efforts were “on track” to have all US adults eligible for vaccination by May 1, 2021 [23]. Following large scale vaccination attempts, the US should begin to see a return to a degree of normalcy as the year goes on, with the CDC already reporting that vaccinated individuals can socialize without masks in small indoor gatherings, or with unvaccinated individuals provided they are from the same household [24]. With increased socialization, travel, and commerce will inevitably come resurgences in measles cases. Due to decreased coverage with MMR vaccinations, however, the results of these outbreaks could become much more dire and long lasting. Prior to the pandemic and the initial wave of stay-at-home orders, the US retained its measles elimination status by a very thin margin, with vaccination rates greater than what we currently see today [25]. Robust and multipronged efforts, focused not just on vaccination rates but on hesitancy as well, will be needed to identify children who have fallen behind and catch up on vaccinations. Ensuring measles vaccination rates remain above the herd immunity threshold will be vital to the future of measles elimination status in the US.

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Estimating and modeling the number of children susceptible to measles in light of COVID-19

Introduction

In 2000, the World Health Organization declared that measles had been eliminated from the United States (US) [1], recognizing a lack of endemic measles transmission that has persisted for over two decades. Measles vaccine coverage in the US is high: as of 2017, 91.5% of children aged 19-35 months had received at least one measles, mumps, and rubella (MMR) vaccine [2].

Despite high MMR vaccine coverage in the US, transmission from international travel to areas with endemic measles still poses a risk of cases and outbreaks in the US. High US vaccination coverage has, to date, prevented large-scale measles outbreaks [3,4].The US Centers for Disease Control and Prevention (CDC) reported that in 2019 the US experienced its highest number of measles cases since 1992 - 1,249 cases documented between January and September 2019 [5]. Of those cases, 86% were associated with tight knit communities previously known to have low rates of vaccine acceptance. These clusters of under-vaccinated – individuals who have only partially completed the recommended vaccination series, and unvaccinated individuals illustrate that while national vaccine coverage remains high, sustained transmission can still occur in communities with low vaccination coverage, either due to vaccine hesitance or outright refusal [6, 7]. This issue is compounded by cases among under- and unvaccinated children due to a lack of resources including lack of health insurance and poverty [8,9].

Due to the COVID-19 pandemic, routine childhood vaccination coverage has dropped nationally [10-12]. Reports of missed well-child visits that normally involve routine childhood vaccinations have grown larger than their pre-pandemic numbers, with one prominent insurance company's internal audit reporting a 26% decrease in most childhood vaccinations, including measles-containing vaccines (MCV) [13]. Given the highly contagious nature of measles, coupled with the additive nature of each birth cohort’s unimmunized children adding to the susceptible pool without intervention, larger clusters of measles-susceptible children could reignite endemic transmission in the US [14].

A 2016 modeling study estimated that 1 in 8 US children and adolescents under the age of 18 are potentially susceptible to measles, but this does not account for the impact of the COVID-19 pandemic-related drops in childhood vaccination on measles susceptibility in the US [14]. To address this gap, we updated that prior modeling study, accounting for drops and potential recovery of childhood measles vaccination in the US during the COVID-19 pandemic.

Methods

Data sets

All analyses used publicly available NIS-Teen datasets. Briefly, NIS-Teen is a nationally representative survey of parents of adolescents aged 13-17 living in the United States at the time of data collection. In addition to coverage of routine adolescent vaccinations (i.e. tetanus, diphtheria, acellular pertussis (Tdap); human papillomavirus (HPV); and quadrivalent meningococcal conjugate vaccine (MCV4)), NIS-Teen also collects data on coverage of measles containing vaccines (MCV) among these adolescents. The survey is carried out by the Centers for Disease Control and Prevention (CDC) using household, and more recently, exclusively cell phone surveys for the general public and mailed surveys for medical providers to verify their patients' vaccinations [15]. This survey contains responses from household phone surveys as well as provider verification for vaccination receipt for vaccinations among children aged 13-17. As part of the provider verification process, age at receipt of each MCV dose is assessed [16].

Data analysis

All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), using PROC SURVEYFREQ appropriate weighting for complex survey analysis [16 – 18]. Only children with provider-verified immunization data were included in this analysis. These provider-verified data were used to compute age- and dose-specific probabilities of receipt of MCV.

Baseline model assumptions and estimates

The methods for the data analysis and modeling conducted here is based on prior estimates of measles susceptibility in the US [14]. Estimates of measles-containing vaccine coverage, for both first and second dose of the recommended two-dose series, were generated by taking the probabilities of the first and second dose administrations at each individual age, from 0 – 17 years. These age- and dose-specific data were aggregated and birth cohorts representing the years that the surveyed children were born (2000-2017) were gathered from the National Center for Health Statistics [19]. To allow for both the most conservative estimate of the total number of susceptible children and to keep consistency with prior calculations, the smallest birth cohort size (2017; n = 3,855,500) was used for all years to calculate the most conservative number of un- and under-vaccinated children [19].

This aggregated data was used to generate conditional probabilities for each age receiving both the first and second MCV doses. First dose probabilities were incorporated into the model directly, while second dose probabilities were summed across the remaining ages after the first dose. For example, a child aged 5 years old could only receive a second dose at age 5 or older. These summed second dose probabilities were then added to the model as the probability of a second dose, given the first was received. Measles, mumps, and rubella vaccine (MMR), the most commonly given MCV, has an estimated effectiveness against measles infection of 93% for a single dose, and 97% for two doses [20]; these values were incorporated into the model to account for children who had received the vaccine but remained susceptible.

We assumed passive protection from maternally-transferred anti-measles antibodies, lasting approximately 6 months after birth [20-22]. Because this model is measured in years, we assumed that half of all children under 1 year of age were immune due to transferred maternal antibodies.

Some cancer treatments have been shown to remove functional immunity in children by decreasing antibody titers below those that would confer immunity. Current literature indicates that this can occur in approximately 25% of the children undergoing therapies [23, 24]. We used American Cancer Society estimates that 1 in 285 children under 19 years old will contract cancer [25], prorated this estimate across the ages under study, and assumed that 50% of children would undergo therapies, and 25% of those children would lose functional immunity.

Sensitivity analysis assumptions and estimates

Three sensitivity analyses were performed to simulate sustained current pandemic conditions, conditions 5 years post-pandemic, and conditions related to increased vaccine hesitancy that may arise following the implementation of the COVID-19 vaccination program given uncertainties about COVID-19 vaccine acceptance and the long-term impact on overall vaccine confidence. Each analysis was then plotted, as with the baseline model, as age (from 0 to 17 years) against the percentage immune of the population.

Well-child visit rates have dropped substantially due to COVID-19 in Spring 2020 [9-12], with related decreases in administration of MMR vaccines to half of the documented rates in the same month of the prior year [9, 11]. The impact of COVID-19 on routine childhood vaccination varies around the country, though recently a major health insurance company indicates that a 26% reduction in routine immunizations, including MMR and MCVs, remains and is expected to worsen as the outbreak continues [12]. To model this decrease conservatively, we decreased the probabilities of receiving either the first or second dose at each age, based on the baseline model, proportionally, assuming that parents of younger children would be more hesitant than those of older children to expose their children to healthcare settings [27]. For ages

0-5 we estimated a 10% decrease in vaccination, relative to current percentages, with a 7% and 5% decrease for ages 6-10 and 11-17, respectively.

To model continuing impacts over the next five years after the pandemic, we assumed that those children born within that five-year window would not have decreased vaccination rates (i.e., vaccination probability among 0–5-year-olds would return to pre-pandemic levels, while assuming continued impacts on older ages) and assumed a 7% decrease for ages 6-10 and 5% decrease for ages 11-17.

We assumed vaccine hesitancy (VH) for MCVs to already be accounted for by the baseline model, in a category that indicates how many children missed doses, for any reason. We then assumed that 30% of the population would express hesitancy related to COVID-19 vaccines [28]. To account for possible increased VH towards MCVs as a result of increased hesitancy related to COVID-19 and any vaccines to follow it, we modeled proportional decreases in select age groups. We again assumed that parents of younger children are more vaccine hesitant than those with older children, decreasing vaccination probabilities by age (10%, 7%, 5%, and 3% decreases for ages 0-2, 3-6, 7-13, and 14-17 years, respectively).

Immunological calculations

For each age we used the probabilities for vaccination combined with the estimates of vaccine effectiveness, cancer treatment, and maternal antibodies to obtain the percentage of children who were functionally immune or susceptible to measles and computed the number of immune and susceptible children based on birth cohort-level calculations. We compared these estimates to a herd immunity threshold of 92%.

Results

Baseline model results

Among birth cohorts 2000-2017 for ages 0-17, we estimated that approximately 9,085,181 children (13.1%) are susceptible to measles, with the remaining 60,313,819 (86.9%) of children immune to measles. Age-specific immunity increases as the age groups increase, from 52.6% of children less than one year old, to 91.0% of children aged 17 years (Figure 1).

Sensitivity analyses results

With assumptions simulating the current pandemic without sufficient recovery in MCV uptake, we estimate that the number of susceptible children would rise to 15,066,022 (21.7%) children, with declines in all age-specific immunity levels compared to the baseline model. Age-specific immunity also showed a decrease from age 1 year onwards in comparison to the baseline. Percent immunity for any age group did not reach 80% until 6-year-olds only reaching a high of 81.9% by 15 years of age, where in the baseline model at least 80% immunity was achieved by 1-year olds (Figure 2).

In the model assuming at least partial recovery in MCV uptake several years removed from the pandemic, we estimated 9,392, 579 children (13.5%) would be susceptible to measles. Age-specific immunity for ages 6 to 17-years old was lower than in the baseline model. Immunity for ages 13 to 17-years old exceeded 90%, though the highest age-specific immunity (90.6% for ages 14 and 15) did not meet the herd immunity threshold (Figure 3).

With the baseline model and assumptions for increased vaccine hesitancy based around COVID-19 vaccine hesitancy spillover, we estimated that 14,827,860 (21.4%) children would be susceptible. Age-specific immunity again did not exceed 90%, and did not surpass 80% until age 6 (Figure 4).

Discussion

Baseline Model

This model updates prior estimates of measles susceptibility in the US, using a larger aggregated set of data to better approximate the true population average with respect to measles immunity [14]. We found that children in birth cohorts from 2000 - 2017 failed to meet the herd immunity threshold for measles immunity of 92% [32]. This coverage estimate is based on a wide variety of child characteristics, including maternal antibody levels and cancer prevalence, and can be treated as a sentinel with regards to national coverage for MCVs, indicating when vaccination rates are at acceptable levels and warning when those levels might be declining in some areas. Due to the previous successes of US vaccination programs, outbreaks in recent years have largely been confined to locations with international travel and under-vaccinated communities, resulting in no large-scale consequences for dipping below critical population immunity levels, yet. However, the 2019 measles outbreak, which had 1,282 cases between January 1, 2019 and October 1, 2019, nearly resulted in the US losing its measles elimination status. Given these estimates, recent outbreaks, and the highly infectious nature of measles, we can ill afford complacency with regard to vaccination rates.

Along with total cumulative population-level immunity, we also assessed age-specific immunity. No individual age group was estimated to meet the 92% herd immunity benchmark. These are national-level estimates, which may mask smaller clusters of unprotected children. As seen in the 2019 measles outbreak, pockets of unvaccinated children remain a source of measles transmission [7]. Given these communities and the decline of the national immunity levels, it is likely that they have grown in size, placing more susceptibility both in these communities as well as in surrounding areas that may have a higher vaccination coverage, but now also may have a higher exposure rate. This increases the risk not only of outbreaks centered in these under- and unvaccinated communities, but in the wider geographical area surrounding them as well.

While the percentage of children who have received at least one dose of MCV remains above 92%, those that are functionally immune against measles do not reach these same levels. This illustrates the multipronged problem of immunization vs. functional immunity, including factors such as vaccine effectiveness, number of doses, loss of immunity due to chemotherapies, and other factors not covered by this model. Thus, the number of children that need to be vaccinated to cover 92% of the population would be closer to 95% given the lack of a completely perfect vaccine [20]. When vaccination rates dip even slightly, it can result in gaps in functional immunity resulting in sporadic outbreaks.

Discussion of Sensitivity Analyses with Pandemic Implications

In addition to our updated baseline model, sensitivity analyses were based on reports of decreased well-child and immunization visits across the United States during the COVID-19 pandemic. Estimates of the approximate decrease in childhood vaccinations vary, with some indications that where approximately 65% of children were receiving vaccinations during pre-pandemic times, less than half of those same children, closer to 30% were receiving vaccinations after the declaration of the pandemic in the country in Spring 2020 [9-11]. A large health insurance company's internal data indicates an average decrease administration of MCV's of approximately 26% when compared with doses administered the previous year [11]. In an effort to generate the most conservative estimates, we chose to halve those percentages for the purposes of our models. While the estimates from these models are concerning with regard to reaching herd immunity, it is possible that an even larger portion of children could remain susceptible to measles than was indicated by these prospective models. These analyses do not indicate vaccine coverage at this exact moment; rather, they function as scenarios to evaluate and prepare for situations that may arise from pandemic-related decreases in vaccination.

These analyses and models re-emphasize the importance of high childhood vaccine coverage, and the reality that a decline in coverage of even a modest amount could result in the re-emergence of measles as an endemic virus in the US. Estimates generated in these analyses and models will help raise awareness of the need to increase childhood vaccination rates as we move forward from the pandemic. Small clusters of unvaccinated children have been the target of measles each time an internationally sourced outbreak occurs, and these outbreaks can range from a handful of children to upwards of 1,200, spread across the country [6]. These outbreaks occurred despite maintenance of the population immunity above the herd immunity threshold range of 92%-95%. With population immunity dipping below, that only increases the possibilities of larger, longer measles outbreaks within vulnerable populations. In 2019 the US very narrowly avoided having its measles elimination status revoked, so any increase in outbreak size or duration could push the US over this tipping point related to its elimination status moving forward [33].

Pandemic mitigation measures (e.g., physical distancing, shelter-in-place, travel restrictions) are likely responsible for the low level of measles in the US in 2020-21 [6]. However, now is the time to focus efforts on recovering from pandemic-related drops in routine vaccination coverage, to prevent large outbreaks once international travel again becomes routine.

The Current Pandemic Conditions model shows a potential future in which the decreased vaccination rates are not addressed in any fashion, and no attempt for “catch up” campaigns is made. A scenario in which no attempt is made to rectify declining vaccination rates is unlikely, but a model of such inaction serves to illustrate a “floor” from which these catch-up rates can be compared. If rates of vaccinations decrease across age groups even by a relatively modest 10%, the percent of children functionally immune against measles sharply declines to 78.3% (compared to the 86.9% immune in the baseline model). In addition to this population-level decrease, age-specific immunity also suffers, and no single age group reaches even 80% immunity until age 6. No age group reached greater than 82% immunity, with the highest levels of functional immunity in adolescents aged 14 and 15. These numbers are concerning because measles attack rates hover around 90% amongst people living in close contact, meaning the virus has a very high critical vaccination threshold required to interrupt transmission in potential outbreaks [29].

Our second analysis, Model 3: Pandemic Conditions, 5 years, posits one method that might result from a policy that ignores vaccination gaps that began during the pandemic, and instead focuses solely on ensuring that children born during and after the pandemic do not fall behind on the immunization schedule. Model 3: Pandemic Conditions, 5 years, reveals that while age-specific immunity for those children, now aged between 0 and 5 years returned to rates seen in the baseline model, age-specific rates for those children 6 and older remain decreased. This decrease is enough to result in 86.5% immunity at the population level, with only adolescents 13 – 17 reaching over 90% immunity. This model also fails to achieve the measles herd immunity threshold in all age groups and overall. The difference, however, between the first and second scenarios could be enough to result in a substantial number of measles cases being prevented. This method of attempting to close the gap, however, still falls shy of correcting the problem fully. By not addressing the vaccination gap in those children missing milestones during the pandemic, clusters of school aged children will remain unprotected and at risk for propagating outbreaks imported into the community.

Discussion of Vaccine Hesitancy Implications

The last analysis, Model 4: Vaccine Hesitancy Conditions, was based on increased vaccine hesitancy and a subsequent decline in numbers of children vaccinated with MCV. According to Pew Research Center, by December 2020, approximately 30% of US citizens would not, or would likely not, receive the COVID-19 vaccine once available [28]. Hesitancy surrounding the vaccine stems from conspiracy stories in some cases, or from a distrust of the medical community and its dark legacy [30, 31]. Another survey from Gallup shows that approximately 11% of adults in the USA think that vaccines are more dangerous than helpful, with most support coming from those with lower education levels, adults older than 50, and parents under the age of 18 [34]. With this model, we illustrate the potential deadliness of vaccine hesitancy, including possibilities of spillover hesitancy related to the current COVID-19 pandemic and concerns about the development of the COVID-19 vaccine.

The hesitancy towards COVID-19 vaccines does not exist in a vacuum, and as such, conceivably has the potential to cause hesitancy towards other, more routine, vaccinations. This model explores what might happen if generally increased hesitancy towards vaccinations were to increase hesitancy towards MCVs. Increased vaccine hesitancy that results in 10% or less of each age group abstaining from the vaccine results in numbers similar to those that resulted from the lockdowns and the pandemic. We see the percentage of children immunized fall below 90%, and the percentage of children immune unable to even break 80%. Age specific immunity also suffered, and even the adolescents failed to exceed 83% immunity.

Limitations

This study has some limitations. First, the aggregated data used to record the age at first and subsequent doses for MCVs was based on the compiled responses of survey data via the NIS-Teen Survey done by the CDC annually. Given the fact that it is deidentified data that was aggregated without respect to geographical area, there will be variations across the country in terms of vaccination rates and age-specific vaccination probabilities. The CDC's School Year Vaccination Coverage Reports highlight the differences in vaccine coverage for kindergarten-aged children based on location. Estimates of population level immunity do not directly correlate with sustained transmission of measles in the US, but they can serve as warnings that sustained transmission would be more likely.

Maternal antibodies transferred via the placenta can provide a transient period of immunity for infants, however the exact age at which this immunity is rendered inert is unclear and may occur as early as 6 months or as late as 12 months. Given the variability, we chose to model the effects of maternal antibodies as a percentage of children under one year of age that were functionally immune. If maternal antibodies provide increased immunity beyond 6 months, then the number of functionally immune children would increase in the 0 to 1 year old age group and might help to bridge the gap between maternal antibodies and initial vaccine doses. Conversely, however, if maternal antibodies last much longer, they could reduce the effectiveness (through reduced immunogenicity) of the first immunization with MCV.

Diagnoses of cancer and subsequent immunity loss from suppressive therapies were based on percentages given by the American Cancer Society and were not based in actual incidence for each study year. This could result in more or less children with cancer, and as a result, more or less children having undergone chemotherapies that cause their vaccine conferred immunity to dip below protective titer values. Though the numbers for those treated with chemotherapies and those that then lost immunity were based on assumptions, given how small a proportion children with cancer make up, estimates of immunity for the population would not really be altered if those numbers fluctuated a great deal.

Finally, though lost immunity due to cancer and immunosuppressive therapies was added into the model to give a better representation of functional immunity at a population level, there is evidence to suggest that immunity conferred by MCV's, specifically MMR vaccines, can wane over a lifespan, potentially leaving more adults vulnerable or even older children depending on the degree of decline [35]. More research is needed to assess how waning immunity functions within the scope of outbreak prevention and functional population immunity for those that age out of pediatric vaccination schedules.

Conclusions

As previously mentioned, there were 1,282 cases of measles in the US in the year 2019 alone. Measles, with its high infectivity, acts as the proverbial canary in the coal mine. Where vaccination rates in children dip, measles will often be the first to re-emerge in noticeable quantities. The number of measles cases in 2019 were the highest the United States has seen since 1992. In 2020, there were 13 cases for the entire year, and as of February, there have been no measles cases in 2021 [5]. The COVID-19 pandemic has resulted in levels of social distancing and isolation that has not been seen yet in many of our lifetimes, and somehow also a very unique opportunity to stem the tide of measles transmission across the country. Society will not, however, remain in this stasis forever. We have reached a crossroads in vaccinations and public health, a chance to strengthen our vaccination policies, practices, and condemnation of misinformation.

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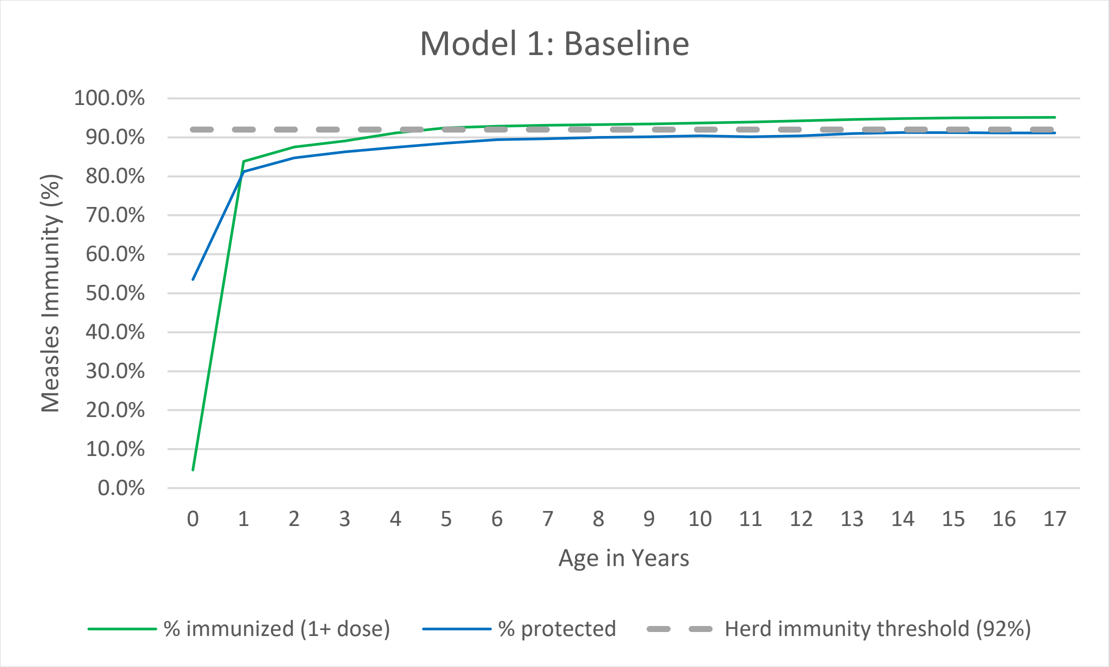

Figure 1. Percent of Children Immunized and Protected from Measles

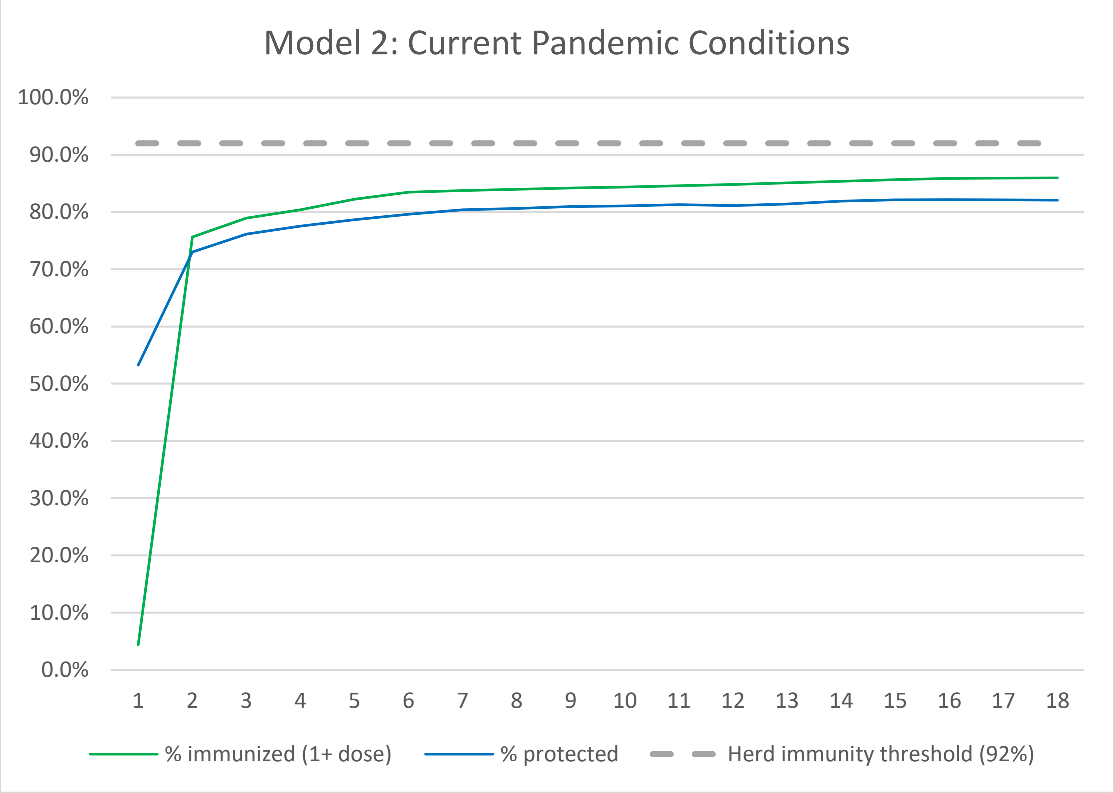

Figure 2. Percent of Children Immunized and Protected from Measles Based On Current Vaccination Rates

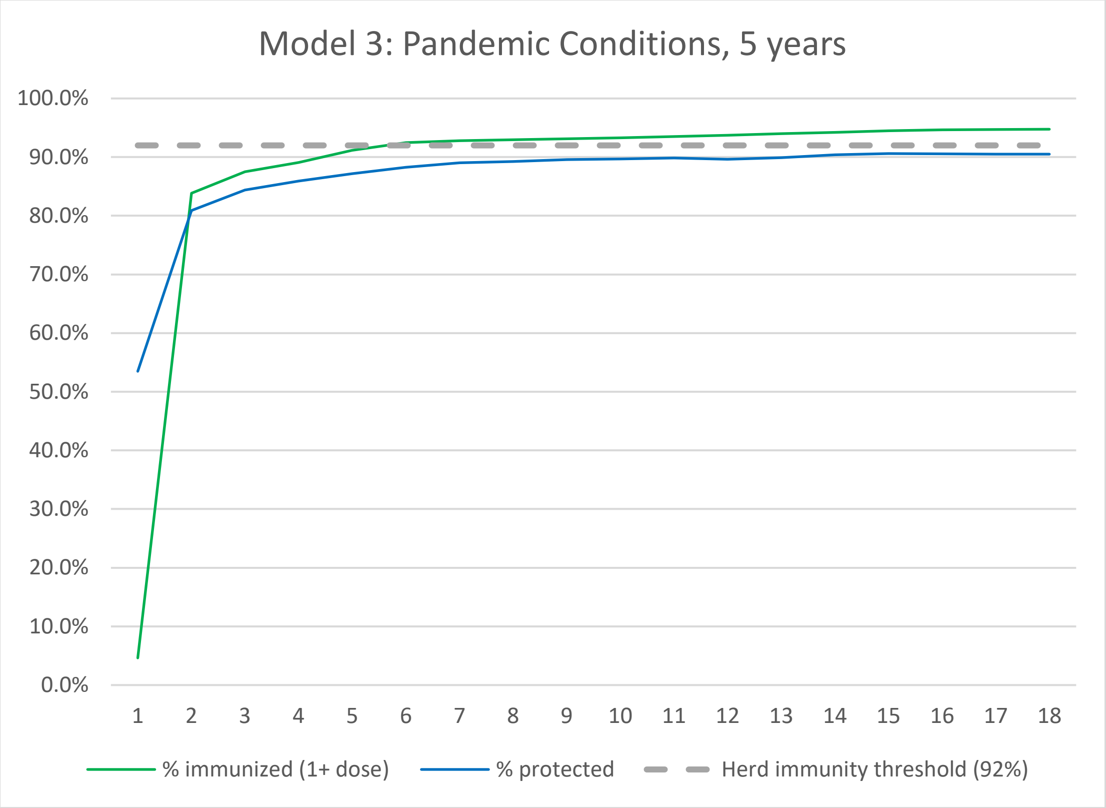

Figure 3. Percent of Children Immunized and Protected from Measles, 5 Years Post-Pandemic

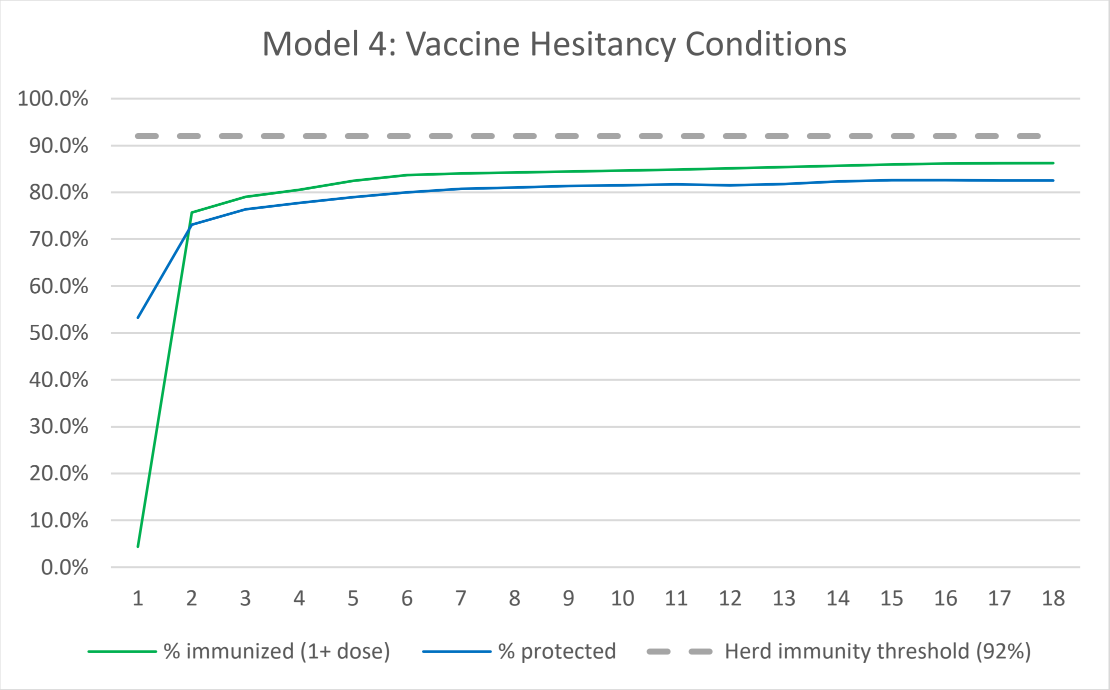

Figure 4. Percent of Children Immunized and Protected from Measles with Increased Vaccine Hesitancy