Third International Conference on Applications of Mathematics to Nonlinear Sciences,
Electronic Journal of Differential Equations, Conference 27 (2024), pp. 1–12.
ISSN: 1072-6691. URL: https://ejde.math.txstate.edu, https://ejde.math.unt.edu
DOI: 10.58997/ejde.conf.27.g1

RESPIRATORY ILLNESS CLINICAL TRIAL MODELING

DAVID GERBERRY, HEM JOSHI, MAC PELOQUIN, SONIA VARGAS

Abstract. Respiratory illnesses pose a significant burden on public health, causing numerous fatalities annually. Using the classical SEIR framework, we model a general respiratory infection to investigate the interaction between the disease's epidemiological dynamics and the dynamics of a vaccine clinical trial. We develop a system to describe clinical trials for a vaccine targeting a new respiratory infection. We model the interplay between epidemiological dynamics and clinical trials, establishing the relationship between these two systems.

We also explore the impact of vaccines becoming available to adults and children at different times by dividing each epidemiological compartment into two age-based categories: adults and children. We calculate the basic reproductive number for the epidemiological model for each transmission category (adults and children) and then determine an overall reproductive number for the entire population. Additionally, we conduct numerical simulations under various assumptions and present our findings.

1. Introduction

Mathematical modeling is a powerful tool used for understanding complex systems including the spread of infectious diseases. Doing so involves creating mathematical equations and simulations that capture the dynamics of disease transmission and their impact on populations. By incorporating factors such as population size, contact rates, disease parameters, and intervention strategies, mathematical modeling can investigate potential scenarios to help inform public health decisions. These models can estimate the future course of an outbreak, evaluate the effectiveness of various interventions, and assess the potential impact of policy measures. They allow researchers and policymakers to explore different strategies and make evidence-based decisions to control and mitigate the spread of infectious diseases, ultimately helping to save lives and reduce the burden on health care systems [1].

Respiratory illnesses are a significant burden to modern life and a large cause of human death and suffering each year. The COVID-19 pandemic proved that these types of illnesses can change the way a society functions. To stop the spread and deaths caused by these diseases, efforts to quickly design vaccines for these respiratory illnesses are paramount. As shown during the response to the COVID-19

2020 *Mathematics Subject Classification.* 34-11, 00A71, 92-10.
Key words and phrases. Modeling; clinical trials; vaccine efficacy; reproductive number.

Published August 20, 2024.

pandemic, the emergence of mRNA technology allows for vaccines to be formulated much faster than ever before [2, 3, 4, 5, 6]. With the new found ability to develop vaccines so quickly, the time it takes to test new vaccines (i.e. clinical trials) represents the major limitation to the speed with which society can begin to immunize its population and ultimately change the course of the next pandemic [7, 8, 9, 10].

Of course, it is important to note that vaccine clinical trials do not occur in a vacuum but rather involve individuals (both in the control and treatment arms of the clinical trial) interacting with the general population under the current conditions of the epidemic. Therefore, the conditions of the epidemic will always impact the clinical trial. For example, a clinical trial will require a longer period to demonstrate a statistically significant protective effect if conditions are such that disease incidence is very low in the general population. If a clinical trial is conducted while disease incidence is very high, a shorter period of time will be needed to establish protection. Complicating matters further, vaccination is typically not tested and rolled out for the entire population at the same time. With COVID vaccines for example, clinical trials for adults were conducted first followed by children. Therefore, the clinical trial for vaccines in children occurred at the same time that vaccination was available to adults in the general population [11, 12].

In this modeling work, our goal is to examine the interaction between the epidemiological dynamics of a disease and the dynamics of a vaccine clinical trial. While motivated by the COVID-19 pandemic, our work generalizes to study a pandemic of a general respiratory disease; as respiratory infections (other corona viruses, avian influenza, H1N5, SARS, etc.) share many characteristics and all have the potential for causing future pandemics.

2. Epidemiological model

We use the classical SEIR framework to model a general respiratory infection, where individuals progress from being susceptible (S), exposed (E) in which individuals have contracted the disease but are not yet able to transmit it, infectious (I), and recovered (R). For simplicity, we assume permanent immunity after recovery. As we look to examine the effect of vaccines being available to adults and children at different times, we separate each epidemiological compartment into two classes based on age (A for adults, K for children or "kids"). Therefore, the model consists of the state variables S_A, E_A, I_A, and R_A for susceptible, exposed, infectious, and recovered adults; S_K, E_K, I_K, and R_K for susceptible, exposed, infectious, and recovered kids; and is given by the equations

$$S_A' = -S_A\Big(p\beta_{AA}\frac{I_A}{N_A} + p\beta_{KA}\frac{I_K}{N_k}\Big), \tag{2.1}$$

$$E_A' = S_A\Big(p\beta_{AA}\frac{I_A}{N_A} + p\beta_{KA}\frac{I_K}{N_k}\Big) - \gamma_1 E_A, \tag{2.2}$$

$$I_A' = \gamma_1 E_A - \rho_1 I_A - \delta_1 I_A, \tag{2.3}$$

$$R_A' = \rho_1 I_A, \tag{2.4}$$

$$S_K' = -S_K\Big(p\beta_{KK}\frac{I_K}{N_k} + p\beta_{AK}\frac{I_A}{N_A}\Big), \tag{2.5}$$

$$E_K' = S_K\Big(p\beta_{KK}\frac{I_K}{N_k} + p\beta_{AK}\frac{I_A}{N_A}\Big) - \gamma_2 E_K, \tag{2.6}$$

$$I_K' = \gamma_2 E_K - \rho_2 I_K - \delta_2 I_K, \tag{2.7}$$

$$R_K' = \rho_2 I_K, \tag{2.8}$$

where $N_A = S_A + E_A + I_A + R_A$ is the total population of adults and $N_K = S_K + E_K + I_K + R_K$ is the total population of kids. Exposed adults and kids progress to become infectious at rates γ_1 and γ_2, respectively, and recover from infection at rates ρ_1 and ρ_2, respectively. Disease-induced mortality occurs at rates δ_1 and δ_2 for adults and children, respectively. As we are modeling respiratory diseases with fast epidemiological dynamics (on the order of weeks or months), we ignore demographics and assume a fixed population. In other words, we do not consider birth/recruitment rates into the population or background mortality rates.

Transmission occurs both within and outside age groups at contact rates of β_{AA} between infected adults and susceptible adults, β_{KA} between infected kids and susceptible adults, β_{KK} between infected kids and susceptible kids, and β_{AK} between infected adults and susceptible kids. For consistency with [13], we consider these as contact rates sufficient to pass the disease and multiply by the probability p of infection actually being transmitted in such contacts.

2.1. **Basic reproductive number for epidemiological model.** In disease modeling, the basic reproductive number is defined as the number of new infections caused by a single infected person introduced into a completely susceptible population. Thus a reproductive number greater than one means that the disease will continue to grow and spread with time, while a reproductive number less than one means the disease will dwindle and eventually die out [14].

First, we calculated a reproductive number for each transmission category. These calculations are as follows:

$$\mathcal{R}_0^{AA} = \frac{B_{AA}}{\delta_1 + \rho_1}, \quad \mathcal{R}_0^{AK} = \frac{B_{AK}}{\delta_1 + \rho_1},$$
$$\mathcal{R}_0^{KA} = \frac{B_{KA}}{\delta_2 + \rho_2}, \quad \mathcal{R}_0^{KK} = \frac{B_{KK}}{\delta_2 + \rho_2}.$$

We then used these individual reproductive numbers to find an overall reproductive number for the entire population. This was found by finding the next-generation matrix and evaluating its eigenvalues at the disease-free equilibrium. The overall reproductive number is

$$\mathcal{R}_0 = \frac{\left(\frac{B_{AA}}{\delta_1+\rho_1} + \frac{B_{KK}}{\delta_2+\rho_2} + \sqrt{(\frac{B_{AA}}{\delta_1+\rho_1} + \frac{B_{KK}}{\delta_2+\rho_2})^2 - 4(\frac{B_{AA}}{\delta_1+\rho_1}\frac{B_{KK}}{\delta_2+\rho_2} - \frac{B_{AK}}{\delta_1+\rho_1}\frac{B_{KA}}{\delta_2+\rho_2})}\right)}{2}.$$

3. Clinical trial modeling

With the epidemiological model complete, we proceed to establish the system to describe clinical trials for a vaccine for a new respiratory infection. At this point, it is important to express the principal aspects of the clinical trial process that our model will consider and those it does not.

Clinical trials for new vaccines typically involve three separate phases. Phase 1 involves a small group of healthy volunteers to study dosage, safety, and immune response. Phase 2 trials expand the study population and further evaluate safety and immunogenicity while also exploring factors like age and underlying health conditions. Phase 3 trials, the largest phase, involve thousands of participants and assess vaccine efficacy by comparing vaccinated individuals to a control group receiving a placebo or alternative. These trials closely monitor participants for the

given respiratory infection, aiming to determine if the vaccine prevents or reduces the severity of the disease. Importantly, given the logistical challenge and size of Phase 3 trials, trial participants are not monitored for infection continuously but rather a fixed periods (e.g. weekly, biweekly, etc.).

The end of a Phase 3 trial can be determined in a few different ways. First, statistical significance can be used to indicate the successful completion of a trial. This occurs when the vaccine's performance is statistically significant enough to support the vaccine's approval. The analysis must determine whether the observed results are due to the effectiveness of the vaccine and not random chance [15]. In another method, clinical trials follow a predetermined protocol that outlines specific endpoints and goals, and the trials need to collect enough data to reach these goals. The extensive and complicated details of clinical trial design, execution, and regulation are beyond the scope of this modeling work [16], so we focus on the central characteristics related to epidemiological dynamics.

One last feature of clinical trials that is central to our modeling work is that clinical trials of new vaccines are typically conducted for adults before subsequent clinical trials for the vaccine in kids. This occurs for multiple reasons [17]. First, it is obvious that adults are in the workforce, and interact with others much more than children. Thus, curbing the spread starts with them since they come in contact with both adults and children alike. Children are often only in contact with other children, and their parents, whom they rely on for basic needs. Furthermore, it is important to test adults first to verify safety and will not have adverse effects that could affect their development. Overall, parents are also very weary of giving something to their kids that has not been proven safe [17].

For our mathematical model, we focus only on Phase 3, the large-scale trial that happens at the end of the testing process. We use a discrete-time model (i.e. difference equation) to track the number of infections in the control and treatment arms due to the fact that trial participants are monitored for new infection a fixed time periods (e.g. weekly, biweekly, etc.). The clinical trial model tracks the number of cumulative infections in the control arms, C, and treatment or vaccinated arms, V, of the clinical trial and e is the vaccine efficacy. Subscripts u and i refer to the numbers of uninfected and infected individuals in each clinical trial arm, respectively.

The equations for the clinical trial model are as follows:

$$V_i[j+1] = V_i[j] + V_u[j](1-e)(\text{probability of infection for time step } j+1), \quad (3.1)$$

$$V_u[j+1] = V_u[j] - V_u[j](1-e)(\text{probability of infection for time step } j+1), \quad (3.2)$$

$$C_i[j+1] = C_i[j] + C_u[j](\text{probability of infection for time step } j+1), \quad (3.3)$$

$$C_u[j+1] = C_u[j] - C_u[j](\text{probability of infection for time step } j+1). \quad (3.4)$$

Importantly, the probability of infection in a given time step (e.g. 2 weeks) is determined by the rate of new infections over that period in the general population which, in our modeling framework, is governed by the solution to the epidemiological component of the model.

3.1. **Coupling the epidemiological and clinical trial models.** As our goal is to model the interplay between epidemiological dynamics and clinical trials for new vaccines, it is essential to formulate the relationship between the two systems. Fortunately, the relatively small size of a clinical trial population compared to

the much larger size of the general population simplifies the process. While the dynamics of the ongoing epidemic certainly affect infection rates experienced by the clinical trial population, we can ignore any impact that the clinical trial population will have on the trajectory of the epidemic in the overall population. Clinical trials can be large and include thousands of individuals. However, the protective effect experienced by those individuals will not change the experience of the millions of individuals in the general population.

To couple the two models, we must express the probability of infection for a given time step in the discrete model in terms of the disease incidence resulting from the continuous epidemiological model. We do so using the formula

$$\begin{aligned}&\text{probability of infection for time step}\\ &= \frac{\text{new infections for time step}}{\text{number of uninfectious individuals at the beginning of the time step}}\\ &= \frac{\int_{t_0}^{t_0+\Delta t} \gamma E(t)\,dt}{S(t_0)+E(t_0)+R(t_0)},\end{aligned}$$

where the time step $j+1$ in the clinical trial model corresponds to the interval $(t_0, t_0+\Delta t)$ in the epidemiological model. In all of our simulations, we use a clinical trial timestep of $\Delta t = 14$ days.

With the linked epidemiological and clinical trial models, we can state the plan for our general simulation as illustrated in Figure 1.

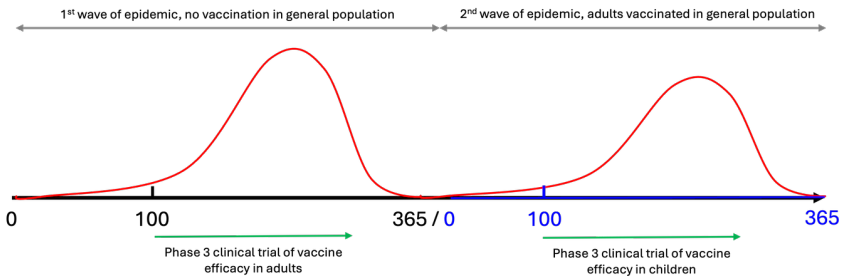


FIGURE 1. General simulation linking epidemiological dynamics to those of vaccine clinical trials in adults and children.

For simplicity, we assume that the respiratory infection of interest is transmitted in waves (as was true with COVID and for seasonal respiratory infections). For a clear comparison, we will also assume that these waves occur a year apart and are identical except for the aspects that are the focal point of this study.

We assume that a Phase 3 vaccine clinical trial begins on the 100^{th} day of the first wave of the epidemic. This first clinical trial is conducted to measure vaccine efficacy in adults and infection rates of the clinical trial population (both experimental and control groups) are governed by the state of the ongoing epidemic in the general population at large. These infection rates in the adult clinical trial are tracked by the model in Equations 3.1-3.4. We assume that the vaccine is approved for use in adults and that a certain level of vaccine coverage has been achieved by the beginning of the second wave of the epidemic. For simplicity, this second wave begins exactly one year after the first wave. Also for simplicity, the clinical trial

for vaccination in children begins 100 days into this second wave of the epidemic. The only difference between the first and second waves is the effect of adults being vaccinated in the population at large during the second wave.

4. Simulation results

In this work, our goal is to examine the interplay between background epidemiological dynamics and the outcomes of clinical trials for a new vaccine. More specifically, we are interested in the situation where a vaccine is tested and approved for adults before a clinical trial for the vaccine in children begins. To do so, we proceed to numerical simulations. First, we will examine this interplay when no heterogeneity between adults and children is assumed in population size, contact rates, and disease outcomes. We then conduct the same analyses when heterogeneity is incorporated.

Importantly, the epidemiological model stated in Section 2 does not include vaccination. For the second wave of the epidemic, we assume that a vaccine coverage of c in the adult population because the vaccine was tested and approved for adults during the first wave. To account for this most clearly, we adapt the first two equations for susceptible and exposed adults to become

$$S_A' = \Big(\frac{cS_A(1-e)+(1-c)S_A}{N_A}\Big)p(\beta_{AA}I_A+\beta_{KA}I_K), \tag{4.1}$$

$$E_A' = \Big(\frac{cS_A(1-e)+(1-c)S_A}{N_A}\Big)p(\beta_{AA}I_A+\beta_{KA}I_K)-\gamma_1 E_A, \tag{4.2}$$

where c is the vaccine coverage in the adult population during the second wave of the epidemic and e is the protective efficacy of the vaccine.

4.1. Results assuming homogeneous populations.

As mentioned above, our model represents a general respiratory infection for which a new vaccine is developed. We assume parameter values relevant to such infections but not for a specific disease. We begin the simulation of each wave of the epidemic using the initial values in Table 1. Note that we assume there are an equal number of adults and children in the population and seed the epidemic with equal numbers of exposed and infectious individuals.

Table 1. Initial values of state variables used at the beginning of both the first and second wave of the epidemic when assuming homogeneous populations.

Variable	Description	Initial Value
S_A	Susceptible adults	50,000
S_K	Susceptible children	50,000
E_A	Exposed adults	50
E_K	Exposed children	50
I_A	Infected adults	2
I_K	Infected children	2
R_A	Recovered adults	0
R_K	Recovered children	0

For the simulation carried out under the homogeneity assumption, we use the model parameters summarized in Table 2. Importantly, we note that identical

contact rates are used between the age groups in the population. Moreover, disease progression, mortality and recovery rates for adults and children are identical.

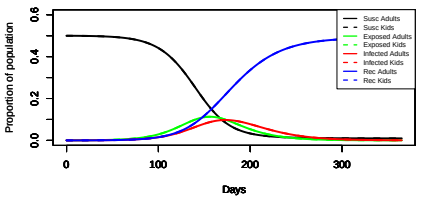
TABLE 2. Parameter values for simulations when assuming homogeneous populations. †,‡ Values used for first and second waves of epidemic respectively. * Value adapted from [13] by averaging age-specific contact rates.

Parameter	**Description**	**Value**
c	Vaccine coverage in adults	$0^{\dagger}$, $0.80^{\ddagger}$
e	Vaccine efficacy	$0^{\dagger}$, $0.80^{\ddagger}$
p	Probability of transmission	0.10
$\beta_{AA}, \beta_{KA}, \beta_{KK}, \beta_{AK}$	Contact coefficient	0.974^{*}
γ_1	Adult progression rate	1/21
γ_2	Child progression rate	1/21
ρ_1	Adult recovery rate	1/21
ρ_2	Child recovery rate	1/21
δ_1	Adult disease death rate	0.001
δ_2	Child disease death rate	0.001
Δt	Days between disease monitoring in CT	14 days

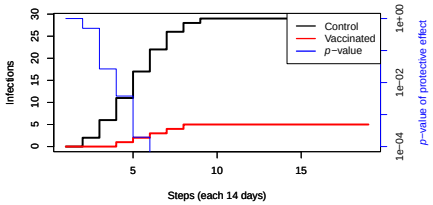
For illustration, we assume each vaccine clinical trial consists of 100 participants; 50 randomly assigned to the treatment (i.e. vaccination) arm and 50 randomly assigned to the control group. The number of infections in the two groups is tracked using the clinical trial model of Equations 3.1-3.4. Through the course of the clinical trial simulation, we track the p-value of the different infection rates using the Fisher exact test; a test for determining whether the proportions of data described by two or more categorical variables are random. While our modeling work is deterministic with no random effects, the p-value quantifies the probability of our observed infection rates if the vaccine had no efficacy at all. In a true clinical trial, many details and considerations can go into deciding when a clinical trial will stop. Even in the most basic plans, researchers would want statistical evidence that the vaccine efficacy was greater than a certain value (e.g. 50%, 70%, etc.). Our simplified estimates looks simply for evidence that the vaccine is showing any positive efficacy at all, regardless of how small. While clinical trials would continue longer to achieve more rigorous results, our simplification illustrates the effects that would most likely be amplified with more-detailed stopping conditions.

The results of our numerical experiment are illustrated in Figure 2. In Figure 2a, we see the first wave of the epidemic through an entirely unvaccinated population. Notably, the figure illustrates curve for both adults and children, but the dashed curves for children are entirely obscured by the curves for adults. This is to be expected as we are assuming complete homogeneity between adults and kids. Therefore, with identical initial conditions and parameters, the epidemic plays out the same for both sub populations. In Figure 2b, we see the results of the vaccine clinical trial in adults which starts 100 days into the first wave. The black line tracks the cumulative number of infections in the control group and the red line tracks those in the vaccine group. In blue, we calculate the p-value of the protective efficacy of the vaccine on a logarithmic scale. Using our simplified approach, we see

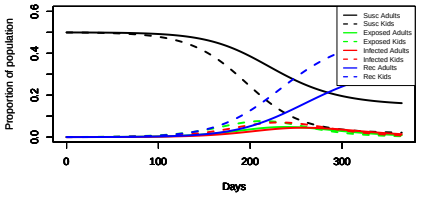
that a p-value of 10^{-4} is achieved after 6 steps of the clinical trials (i.e. 12 weeks, 84 days).



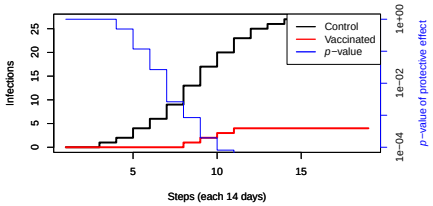
(a) First wave of epidemic; no one vaccinated



(b) Clinical trial for adults that begins on Day 100 of the first wave



(c) Second wave of epidemic; 80% of adults are vaccinated



(d) Clinical trial for kids that begins on Day 100 of the second wave

FIGURE 2. Simulation results when assuming population homogeneity between adults and kids (i.e. equal size populations and random mixing between populations) and a vaccine efficacy of $e = 0.80$.

In Figure 2(c), the simulation moves to the second wave of the epidemic where we assume that 80% of the adult population is vaccinated with the 80% effective vaccine. We see this protective effect as the second wave moves more slowly through the adult population than in children. In Figure 2(d), we see the results of the vaccine clinical trial for kids. Infections in the clinical trial for kids accumulate more slowly than in the adult clinical trial. As these simulations assume complete homogeneity between adults and kids, we know that this difference is caused entirely by the vaccine protection in adults during the second wave (and consequently fewer infections in the population overall). While fewer infections during the second wave is clearly a desirable outcome, we do see that the clinical trial for children must continue for a longer time period to achieve the same p-value as the adult clinical trial. Specifically, to get to the same 10^{-4} level of significance, the clinical trial in kids would need to run 10 steps (i.e. 20 weeks, 140 days).

4.2. **Results assuming differences between adults and children.** In the previous section, we saw that a vaccine clinical trial in children can be affected by vaccination among adults in the general population. More specifically, the clinical trial would need to run longer to establish statistically significant protection. However, this behavior was exhibited under an assumption of identical populations of adults and children. For some respiratory infections, such an assumption does not hold.

In this section, we investigate the same ideas when assuming heterogeneity (both in population size and epidemiological characteristics) among adults in children. In Table 3, we see the initial values for our simulations. Notably, we assume that there are significantly more adults than children (70% vs. 30%).

TABLE 3. Initial values of state variables used at the beginning of both the first and second wave of the epidemic when assuming heterogeneous populations.

Variable	**Description**	**Initial Value**
S_A	Susceptible adults	70,000
S_K	Susceptible children	30,000
E_A	Exposed adults	50
E_K	Exposed children	50
I_A	Infected adults	2
I_K	Infected children	2
R_A	Recovered adults	0
R_K	Recovered children	0

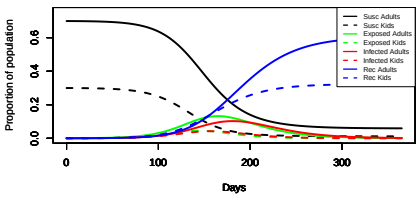
In Table 4, we now use age-specific contact rates to estimate mixing patterns between children and adults. To establish these parameters, we use the results of Del Valle, et al. [13] who built a detailed agent-based model from data on daily interactions between different age groups. More specifically, we used the averages of the age-structured contact rates in [13, Table 2] for adults and children to establish our values for $\beta_{AA}, \beta_{KA}, \beta_{KK}$, and β_{AK} in Table 4.

TABLE 4. Parameter values for simulations when assuming heterogeneous populations. †,‡ Values used for the first and second waves of epidemic respectively. * Value adapted from [13] by averaging age-specific contact rates.

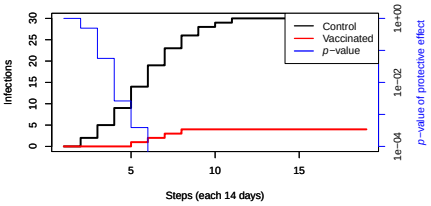
Parameter	**Description**	**Value**
c	Vaccine coverage in adults	$0^{\dagger}$, $0.80^{\ddagger}$
e	Vaccine efficacy	$0^{\dagger}$, $0.80^{\ddagger}$
p	Probability of transmission	0.10
β_{AA}	Adult-to-adult contact coefficient	1.15
β_{KA}	Child-to-adult contact coefficient	0.438
β_{KK}	Child-to-child contact coefficient	1.61
β_{AK}	Adult-to-child contact coefficient	0.697
γ_1	Adult progression rate	1/21
γ_2	Child progression rate	1/14
ρ_1	Adult recovery rate	1/21
ρ_2	Child recovery rate	1/14
δ_1	Adult disease death rate	0.01
δ_2	Child disease death rate	0.001
Δt	Days between disease monitoring in CT	14 days

In line with several respiratory infections, we include additional heterogeneity by assuming faster disease dynamics in children (i.e. $\rho_2 = \gamma_2 = \frac{1}{14}$) and higher disease-induced mortality in children (i.e. $\mu_1 = 0.01$).

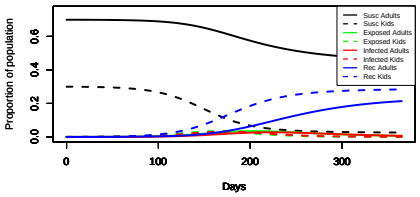
The results of this simulation are illustrated in Figure 3. In Figure 3a, we see disease dynamics in the first wave that differ for adults and children. In addition to different population sizes, we see the epidemic peaks slightly earlier in children. In Figure 3(b), the clinical trial in adults follows an almost indistinguishable pattern from that of Figure 2(b), with the clinical trial reaching a p-value of 10^{-4} in 6 steps (i.e. 12 weeks, 84 days). Figure 3(c) shows the second wave of the epidemic with 80% of adults vaccinated and receiving 80% efficacy from the vaccine. The most notable results are illustrated in the clinical trial in children shown in Figure 3(d). With heterogeneity included, we see that the clinical trial in children would reach a p-value of 10^{-4} in roughly the same number of steps as the adult clinical trial; specifically 7 steps (i.e. 14 weeks, 98 days). Therefore, we see that the result of vaccine clinical trials taking longer in children than in the adult population can be largely erased due to epidemiological differences between adults and children.



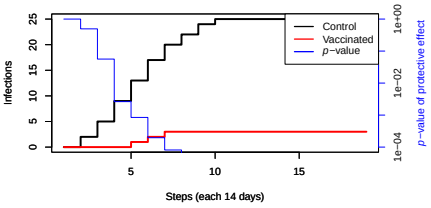
(a) First wave of epidemic; no one vaccinated



(b) Clinical trial for adults that begins on Day 100 of the first wave



(c) Second wave of epidemic; 80% of adults are vaccinated



(d) Clinical trial for kids that begins on Day 100 of the second wave

FIGURE 3. Simulation results when assuming population heterogeneity between adults and kids (i.e. population is 70% adult and 30% kids, and age-based mixing patterns adapted from [13]) and a vaccine efficacy of $e = 0.80$.

5. Conclusions and Further Research

Our objective was to model the interaction between epidemiological dynamics and clinical trials for a new vaccine targeting a general respiratory infection. The clinical trial for children was initiated only after the completion of the adult trials, utilizing the data from the adult trials to inform the children's trials. A key finding

was that the timeline for children's clinical trials is affected by adult vaccination rates and the resultant herd immunity.

Although the timing of another pandemic event similar to COVID-19 is unpredictable, preparedness is crucial. Our model simulates a general scenario and could be valuable for future pandemic preparedness. Further refinement of our results using more precise parameters is an area for future research.

Acknowledgements. This research wass partially supported by Xavier University's Summer Undergraduate Research funding during Summer 2023.

References

[1] P. White, M. Enright; *Mathematicals Models in Infectious Disease Epidemiology*, Infectious Diseases. 2010: 70–75.

[2] *Infection Exposure Questions.* Seattle Children's Hospital, 30 Dec. 2022, www.seattlechildrens.org/conditions/a-z/infection-exposure-questions/.

[3] Y. Li, J. Tan, S. Tan, et al.; *Infection Rate and Factors Affecting Close Contacts of COVID-19 Cases: A Systematic Review.* Journal of Evidence-Based Medicine, U.S. National Library of Medicine, Dec. 2022, www.ncbi.nlm.nih.gov/pmc/articles/PMC9877962/.

[4] V. Racaniello; *The Incubation Period of a Viral Infection*, 8 Oct. 2014, virology.ws/2014/10/08/the-incubation-period-of-a-viral-infection/.

[5] T. Tsang, L. Lau,S. Cauchemez, et al.; *Household Transmission of Influenza Virus.* Trends in Microbiology, 2016, Vol. 24, No. 2 http://dx.doi.org/10.1016/j.tim.2015.10.012

[6] Hosseinzadeh, Pouya, et al.; *Social Consequences of the COVID-19 Pandemic. A Systematic Review.* U.S. National Library of Medicine, Mar. 2022

[7] *About Our Landmark Trial*, Pfizer, www.pfizer.com/science/coronavirus/vaccine/about-our-landmark-trial.

[8] *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. Food and Drug Administration, 24 November 2017, www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

[9] *COVID Vaccine Testing and Approval*, University of Maryland Medical System, www.umms.org/coronavirus/covid-vaccine/testing.

[10] *Pfizer and BioNTech Provide Update on Ongoing Studies of COVID-19 Vaccine.* Pfizer, www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-ongoing-studies-covid-19.

[11] V. Piechotta, S. Waldemar, T. Iris, et al.; *Safety and Effectiveness of Vaccines against COVID-19 in Children Aged 5-11 Years: A Systematic Review and Meta-Analysis*, The Lancet Child & Adolescent Health Volume 7, Issue 6, June 2023, Pages 379-391.

[12] M. Thompson, Matthew, V. Talley, P. Blair, et al.; *Duration of Symptoms of Respiratory Tract Infections in Children: Systematic Review.*BMJ 2013; 347:f7027 doi: doi.org/10.1136/bmj.f7027

[13] S. Del Valle, J. Hyman, H. Hethcote; *Mixing Patterns between Age Groups in Social Networks.* www.researchgate.net/publication/228649013-Mixing-patterns-between-age-groups-in-social-networks.

[14] P. van den Driessche; *Reproduction numbers of infectious disease models.* Infectious Disease Modelling, 2017, Volume 2, Issue 3, pages 288-303

[15] S. Dahlberg, E. Korn, J. Le-Rademacher et al.; *Clinical Versus Statistical Significance in Studies of Thoracic Malignancies*, Journal of Thoracic Oncology, Vol. 15 No. 9: 1406–8.

[16] *Guiding Principles for Ethical Research.* National Institutes of Health, www.nih.gov/health-information/nih-clinical-research-trials-you/guiding-principles-ethical-research.

[17] A. Paturel. *Understanding Covid-19 Vaccine Trials in Children Cedars-Sinai*, 13 July 2021, www.cedars-sinai.org/blog/covid-19-vaccine-trials-children.html.

[18] Lasch, Florian; *The Impact of COVID-19 on the Initiation of Clinical Trials in Europe and the United States.* ASCPT, ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2534. 28 Jan. 2022.

David Gerberry
Department of Mathematics, Xavier University, Cincinnati, OH 45207, USA
Email address: david.gerberry@xavier.edu

Hem Joshi
Department of Mathematics, Xavier University, Cincinnati, OH 45207, USA
Email address: joshi@xavier.edu

Mac Peloquin
Department of Mathematics, Xavier University, Cincinnati, OH 45207, USA
Email address: peloquinj@xavier.edu

Sonia Vargas
Department of Mathematics, Xavier University, Cincinnati, OH 45207, USA
Email address: vargass2@xavier.edu