The Epidemiology of Varicella Under a Two-Dose Vaccination Strategy: Results of a Mathematical Transmission Model With a Novel Strategy of Sensitivity Analysis

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Abstract

In 1995 the United States implemented a single-dose strategy of varicella vaccination in infants. Varicella incidence, morbidity, and mortality declined dramatically, though outbreaks continued, even in highly vaccinated populations, and the incidence of varicella began rising in 2003. These events prompted the recommendation of a two-dose vaccination strategy in 2005. In part one of this dissertation, a deterministic, age-structured transmission model of the two-dose strategy is used and predicts a large epidemic of varicella in the near future, even with high second-dose coverage rates. In the long-term, incidence rates under a two-dose regime will be 10% or less of the pre-vaccination rates, compared with up to 50% with a continued one-dose strategy. Varicella cases will consist mostly of mild, breakthrough disease in previously vaccinated individuals.

A full sensitivity analysis should be performed on all models of disease transmission. The sensitivity analysis is used to determine the sensitivity of the model output to the values of input parameters, and to the structure of the model itself. In part two of this dissertation, we present a simple, systematic method to perform deterministic sensitivity analysis on a mathematical model of infection transmission, and apply it to the varicella transmission model of part one. The methods are general, and should be applicable to any qualitative transmission model.
Dedication

To my beautiful wife and daughter, Katie and Lily. Their love transcends everything that I do.
Acknowledgements

This dissertation was only possible with the enormous amount of time, teaching, and encouragement of my family, committee, the UNC faculty, and friends. The support of my parents, Ray and Tyra, who knew I could accomplish this even when I was not as sure, was wind in my sometimes sagging sails. My wife’s parents, Bill and Ginger, maintained an unwavering belief in my abilities that gave me confidence, and their support allowed me the time and freedom to finish this project. My wife’s brothers, Billy and Jimmy, were invaluable as intellectual and creative outlets; they could always put things in a different perspective that opened up new insight. I will never be able to repay my wife, who was a light in dark times, for her patience, love, and understanding as I navigated the highs and lows of this project. She was a perfect partner. There are no words for me to express the amazement, joy, and unconditional love that was given to and received from my daughter Lily, who came along at the perfect time, and framed all aspects of my life in the proper context.

I owe a tremendous debt of gratitude to my advisors, Annelies Van Rie and Alun Lloyd. They gave me the intellectual freedom and motivation that drove me to succeed. The amount of time and effort that they put into this project was phenomenal (I do not know how they had time for the other 50 projects they were working on), and made its completion possible, and they fostered my development as a scientist as well as a student. They will always stand as role models as I progress in my career.
My committee of Steve Meshnick, Vic Schoenbach, and David Weber gave me invaluable guidance and insight. Their genuine curiosity about this project helped me realize that this was all worthwhile. They asked me difficult questions at the right times that pushed me to constantly improve my work. I especially want to thank Vic Schoenbach for teaching me how to teach. Everything that I do in the classroom during my career will be influenced by him, and my students will receive a better education because of it.

I am deeply grateful to the entire Department of Epidemiology at UNC for their commitment to excellence. They fueled my enthusiasm for epidemiology, an analytical mindset, and my desire to ease suffering in this world through the use of our unique skills. The faculty of the North Carolina State University College of Veterinary Medicine and the University of Georgia College of Veterinary Medicine, especially Dr. Corrie Brown, helped me realize that the concept of “one medicine” can change the world.

I am also grateful to the Wu-Tang Clan, for always bringing the ruckus.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ARU</td>
<td>Attack Rate Unvaccinated</td>
</tr>
<tr>
<td>ARV</td>
<td>Attack Rate Vaccinated</td>
</tr>
<tr>
<td>BRFSS</td>
<td>Behavioral Risk Factor Surveillance Survey</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>FAMA</td>
<td>Fluorescent Antibody to Membrane Antigen</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titer</td>
</tr>
<tr>
<td>gpELISA</td>
<td>glycoprotein Enzyme Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HZ</td>
<td>Herpes Zoster</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>LHS</td>
<td>Latin Hypercube Sampling</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>MMRV</td>
<td>Measles Mumps Rubella Vaccine</td>
</tr>
<tr>
<td>SEIR</td>
<td>Susceptible, Infected, Infectious, Immune</td>
</tr>
<tr>
<td>NIS</td>
<td>National Immunization Survey</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>pdfs</td>
<td>probability density functions</td>
</tr>
<tr>
<td>PRCC</td>
<td>Partial Rank Correlation Coefficient</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<td>-------------</td>
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<tr>
<td>Ro</td>
<td>Basic Reproductive Number</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>SI</td>
<td>Stimulation Index</td>
</tr>
<tr>
<td>SIR</td>
<td>Susceptible, Infectious, Immune</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>u</td>
<td>units</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VEm</td>
<td>Vaccinated with mild latent infection</td>
</tr>
<tr>
<td>VEs</td>
<td>Vaccinated with severe latent infection</td>
</tr>
<tr>
<td>VIm</td>
<td>Vaccinated and infectious with mild disease</td>
</tr>
<tr>
<td>VIs</td>
<td>Vaccinated and infectious with severe disease</td>
</tr>
<tr>
<td>VP</td>
<td>Vaccinated and complete protected</td>
</tr>
<tr>
<td>VRm</td>
<td>Vaccinated and recovered from mild illness</td>
</tr>
<tr>
<td>VRs</td>
<td>Vaccinated and recovered from severe illness</td>
</tr>
<tr>
<td>VS</td>
<td>Vaccinated Susceptible</td>
</tr>
<tr>
<td>VV</td>
<td>Vaccinated and Permanently Immune</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella Zoster Virus</td>
</tr>
<tr>
<td>WAIFW</td>
<td>Who Acquires Infection From Whom</td>
</tr>
<tr>
<td>wt</td>
<td>waiting time</td>
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</table>
I. Introduction

A. The Epidemiology of Chickenpox

Varicella Zoster Virus (VZV) is the etiologic agent of the diseases varicella, or chickenpox, and Herpes Zoster, or shingles. It is an α-Herpes Virus, and like all Herpes viruses, infection is lifelong, and reactivation of latent virus can cause disease long after the initial infection. Varicella is typically a childhood disease, whereas zoster, which is reactivation of latent VZV, is a disease of older adults. In temperate, developed countries without vaccination, VZV infects more than 95% of the population before reaching adulthood. Chickenpox is commonly perceived as a relatively minor disease of childhood. Before vaccination the incidence of hospitalization was 2 per 100,000 person-years in children less than 15 years old, with a case-fatality rate of 2 per 100,000 cases. Infection after age 15 is much more severe, with 18 hospitalizations, 15 cases of encephalitis, and 50 deaths per 100,000 person-years. A more common serious manifestation of adult infection is congenital varicella syndrome.

Varicella also causes a financial burden. A 1986 study estimated the annual economic impact of varicella at $400 million. Most of that cost was attributed to parents missing work to care for their sick child.

A modified live virus vaccine against varicella was developed in Japan in the 1970s. In 1995, following the results of several randomized controlled vaccine trials, the US began mass vaccination of infants between 12 and 15 months. Currently, vaccination coverage is high (~88% nationally). Within 10 years, vaccination had reduced the
incidence of chickenpox by roughly 80%, with hospitalizations and mortality falling by a similar amount. However, since 2003 incidence rates have stabilized and even started to increase in some areas.

Surveillance data suggest that the effectiveness of the vaccine in a population setting has been less than what efficacy trials predicted. Breakthrough disease, defined as infection in a previously vaccinated individual, continues to occur. Several well-publicized outbreaks have occurred in schools and day care centers, with attack rates in vaccinated children ranging from 12% to roughly 50%. Breakthrough disease tends to be much milder, indicating that the vaccine is effective against serious morbidity despite a low effectiveness in preventing infection. Due to the occurrence of breakthrough disease, a second dose of vaccine is now recommended for all children at age 4-6 years in an effort to stop breakthrough disease. The first dose of vaccine is still recommended between 12 and 15 months of age.

Several models have explored the epidemiology of varicella following the introduction of a routine single dose vaccination strategy and predicted a resurgence of incidence within several years of the introduction of the vaccine. This is not surprising as many models, as well as observed data for diseases other than varicella, show that there is often a resurgence of incidence within several years of the start of a mass vaccination campaign. While a two-dose program will almost certainly decrease the incidence of chickenpox, the extent to which this will happen has not been thoroughly evaluated yet. Additionally, vaccination causes the average age of infection to increase and a second dose will increase the age further. This may problematic given the increase in morbidity that results from infection at an older age, as well as an possible increased
risk of congenital varicella syndrome as infection moves into older age groups.

B. Statement of Purpose

This dissertation will describe the immediate and long-term epidemiologic effects of a two-dose vaccine campaign on the epidemiology of chickenpox. Close attention will be paid to the epidemiology of chickenpox in the next 20 years. This will be accomplished with the use of age structured, deterministic, compartmental mathematical transmission models. These will be specified in such a way as to make general predictions about future trends in the incidence of varicella including breakthrough varicella. The model is thus qualitative by nature. A specific prediction about incidence rates or total numbers infected is not a goal of the model. The model will explore the long-term epidemiology of varicella, comparing a continued single dose campaign with several variations of a two-dose regimen. The long-term epidemiology of two-dose regimens will be compared to what would have happened if a one-dose recommendation had persisted.

A thorough sensitivity analysis will be performed to assess the range of outcomes that are possible given uncertainty about the input values into the model. Sensitivity analyses are crucial for validating models, and determining their generalizability to different settings. Too often, sensitivity analyses are incomplete, and no single standard method is utilized throughout the transmission modeling literature. A systematic, step-by-step method for sensitivity analysis will be described.

These analyses will aid in public health planning for the future control of varicella. These results could help policy makers determine the best strategies for two-
dose vaccination. Additionally, it will show the expected trends in varicella incidence over the next two decades, when a resurgent epidemic could be expected. Such qualitative predictions are important for planning public health interventions aimed at preparing for and controlling for such an epidemic, if it is expected. The sensitivity analysis will present a picture of possible alternative scenarios that could affect the likelihood of a resurgent epidemic, as well as the range of long-term epidemiologic effects of two-dose vaccination given some degree of uncertainty about the values for input parameters. From a methodological standpoint, the description of a recommended strategy for assessing the sensitivity and uncertainty present in models will aid future modelers in their efforts, and increase the generalizability across different models in different populations.
C. References


II. Review of the Literature

A. The Epidemiology of Varicella Zoster Virus

1. VZV Infection

Chickenpox is perceived as a minor childhood disease, yet its public health impact is substantial. Varicella-Zoster Virus (VZV) is the etiologic agent that causes both chickenpox (varicella), a disease that occurs in childhood, and Herpes Zoster (HZ, zoster, or shingles), a disease that occurs predominantly in adults and immunocompromized individuals. VZV is a herpes virus, and like all herpes viruses results in life-long infection.

The virus is transmitted via infectious droplets originating from vesicular fluid or respiratory secretions from infectious hosts. Infection occurs when these droplets contact mucosal surfaces in a susceptible person. Typically this occurs via inhalation. After roughly four days of replication at the site of infection, a viremia occurs as virus spreads to lymph nodes. After about 1 week of replication in lymph nodes a second, more severe viremia occurs as T-cells transport the virus to epidermal cells.\textsuperscript{1,2} Replication at the skin surface results in a process called ballooning degeneration where multinucleate giant cells are formed and quickly die. The characteristic vesicular rash occurs as an exudate forms between living and dead cells.\textsuperscript{3} The incubation period (from infection to rash) lasts around 14 days. Infected individuals become infectious during the last two days of the incubation period, typically via respiratory secretions.\textsuperscript{4}
The clinical course of chickenpox in an individual typically consists of fever and a maculopapular-vesicular rash that lasts about one week.\textsuperscript{5} Other constitutional symptoms include headache, sore throat and fatigue in a prodromal period 1-2 days before the onset of the rash. The most serious complications include central nervous system involvement, pneumonia, severe bacterial superinfections, and occasionally death.\textsuperscript{4}

The vast majority of those infected recover within 5 to 7 days, with no sequelae. The virus then becomes latent in dorsal root ganglia and ganglia of the trigeminal nerve. Virus associated DNA can be found in these nerve cells, as well as in associated cells such as glial cells and satellite cells.\textsuperscript{6} Re-infection is rare, but reactivation causes herpes zoster, or shingles. Herpes Zoster is a significant cause of morbidity in older adults, and its incidence plays a role in VZV epidemiology. Herpes Zoster is currently the focus of much research. The main focus of the research for this dissertation, however, will be on chickenpox.

2. VZV Impact

In developed countries with a temperate climate and without a routine VZV vaccination program, VZV infects more than 95\% of the population before reaching adulthood.\textsuperscript{7} Prior to vaccination, the annual incidence rate in the United States was 15-16 cases per 1,000, resulting in roughly 4 million cases annually.\textsuperscript{8} The incidence is highly age-dependent, with 90\% of children infected by age 12. In the pre-vaccine era, peak incidence varicella occurred in 3-6 year olds, with estimated incidence rates of up to 120 cases per 1,000 person-years.\textsuperscript{9}
The nearly 4 million annual cases in the US lead to approximately 9,300 hospitalizations and 100 deaths.\textsuperscript{10, 11} Hospitalization rates ranged from 2 to 6 cases per 100,000 population.\textsuperscript{12, 13} and case-fatality rates ranged from 2-4 per 100,000 varicella cases.\textsuperscript{10, 14} These summary statistics obscure an important facet of the epidemiology of varicella morbidity and mortality, namely its severity in adults and infants. The hospitalization rate for varicella in adults aged 20 and older is 13 times that of children in the 5 to 9 year age group.\textsuperscript{12} Among infants <1 year, the hospitalization rate is 6 times that of the 5-9 year age group.\textsuperscript{12} The case fatality rate in adults ranges from 21.3 to 50 deaths per 100,000 cases, compared with 2-4 per 100,000 varicella cases in children.\textsuperscript{15, 16} Furthermore, it is estimated that 75\% of varicella associated deaths in adults occur in healthy individuals without pre-existing conditions.\textsuperscript{17}

In addition to the direct effects of morbidity and mortality, varicella in the pre-vaccination era was associated with a significant financial burden. A 1986 study estimated the annual economic impact of varicella in the US at $400 million. Most of that cost was attributed to parents missing work to care for their sick child.\textsuperscript{14} An Australian study estimated a mean of 5.5 days of missed school or day-care for infected children. While medical costs for each infected child were relatively low ($33 per child), the total cost per infected child including work and school absenteeism was estimated at $393 to $578 per child.\textsuperscript{18} In a German study, savings of 4 to 8 Euros were anticipated for each euro invested in vaccination.\textsuperscript{19} A follow-up study estimated that with 85\% vaccine coverage, the break-even point financially occurs at three years.\textsuperscript{20} Recent studies in the US have estimated that prevention of varicella through vaccination can result in a total annual savings of $1.3 billion in direct and indirect costs.\textsuperscript{15}
B. Varicella Vaccination

1. The VZV Vaccine

All VZV vaccines are derived from the same original seed strain. The Oka strain of VZV was isolated from a Japanese child in the early 1970s and attenuated via cell-culture passage. Japan licensed the first Oka vaccine in 1987 followed by Korea in 1988. In 1995, an Oka strain vaccine, VARIVAX® (Merck & Co., Inc., Whitehouse Station, New Jersey), was licensed for use in the United States for children 12 months and older. It is the most commonly administered varicella vaccine. Another Oka vaccine, Varilix® (GlaxoSmithKline) is licensed for use in children 9 months of age and older. In 2005 a combined measles, mumps, rubella and varicella (MMRV) vaccine ProQuad®, was licensed for use in children 12 months to 12 years.

Vaccination is recommended for all children at 12 months of age, with catch-up vaccination for susceptible children up to 12 years of age, and for susceptible adults likely to have contact with infectious persons such as parents with young children, schoolteachers, and health care workers. Vaccination is also recommended before school entry, for outbreak control, and for children with HIV. A single dose was recommended at 12 months, and 2 doses at least 3 months apart for anyone older than 12 years old. A 2-dose regimen for all children has been recommended since 2005. The current recommended timing is one dose at 12 months, and a second dose between 4-6 years of age. Currently, vaccination coverage is 88% nationally, with a range of 69% to 96% depending on region.
2. Immune Response to Immunization

The pathogenesis of infection with the VZV vaccine (Oka strain) is similar to that with wild-type virus, but usually without the vesicular rash or constitutional symptoms. Some children may develop a rash within 42 days of vaccination, but the illness is typically quite mild. More serious reactions including anaphylaxis, encephalitis, thrombocytopenia and pneumonia have been reported rarely. There have been a few cases of transmission of the vaccine strain, likely via respiratory spread.

Several studies have evaluated the nature and persistence of the immune response to VZV vaccination. Natural infection and vaccination both stimulate a humoral reaction against glycoproteins present on the surface of the virion. A glycoprotein ELISA (gpELISA) measures antibodies against these glycoproteins. A titer $\geq 5$ units/ml is a reliable indicator of immunity. At least 85% to greater than 90% of children will achieve such a protective titer after one dose of vaccine. A large retrospective analysis of 5 multi-center clinical trials examined 3,771 children aged 12 to 23 months who had pre and post-vaccination VZV antibody titers measured. Following immunization with 1-dose of Varivax® vaccine, greater than 90% of children achieved a 6-week post vaccination geometric mean titer (GMT) of 13.1 or greater as measured by the gpELISA. According to studies examining the persistence of anti-VZV antibodies, humoral persistence lasts for at least 10 years.

By 12 months of age most children mount an effective cellular immune response to vaccine and wild-type VZV. Markers of cellular response such as the stimulation index (SI) demonstrate a proliferative T-cell response to vaccination. Cytokine stimulation also occurs. The cellular response elicited by vaccination persists for several years.
Some vaccinated children fail to mount a humoral response to vaccination, and can be subsequently infected (breakthrough infection). A decreased duration and severity of breakthrough disease demonstrates a cellular response to vaccination.\textsuperscript{44, 45}

3. Efficacy trials of the VZV vaccine

Vaccine efficacy is a function of the proportion of vaccinated individuals who acquire any protection, the degree of protection, and the duration of protection. It is measured by the relative risk of infection in vaccinees compared with the unvaccinated.\textsuperscript{46} Efficacy is a term typically reserved for the performance of the vaccine under ideal conditions, such as clinical trials. The performance of the vaccine under field conditions, or vaccination in the community, is usually referred to as effectiveness.

Pre-licensure clinical trials and post-licensure surveillance studies have demonstrated the efficacy of this vaccine. Estimates for protection from any (mild and severe) disease are 70\% to 100\% over 7-10 years when administered at 12 months.\textsuperscript{34} Efficacy against severe disease has been measured at 95\%, also over 7-10 years when administered at 12 months.\textsuperscript{36, 37, 47}

Two double blind, randomized, placebo controlled, clinical trials in healthy children were conducted before licensure of VZV vaccine in the US.\textsuperscript{48, 49} In a trial in the US, vaccine was randomly assigned to 956 one to 14 year old children. The efficacy was 100\% in over 9 months of follow-up, and 98\% after 2 years of follow-up.\textsuperscript{48} A subset of vaccinated children was followed for an additional 3 to 7 years. The study was no longer blinded at this point. After 7 years the efficacy was 95.7\%.\textsuperscript{34} In a European trial, 513 children aged 10-30 months were followed for 29 months. Vaccine efficacy was 88.2\%
Another clinical trial studied 3,303 vaccinees. A subset of 1,463 subjects was randomized to one of 5 production lots of vaccine. This trial was not placebo controlled. Questionnaires regarding illness and blood samples were taken at 6 weeks and 1 year following vaccination. The immunogenicity of the vaccine was similar to that found in other studies. The 6-week seroconversion rate was 96%. Seropositivity was measured by the gpELISA and defined as a 3 standard deviation increase in post-vaccination optical density. After 1 year, 99% of the subjects had positive titers, with a geometric mean titer (GMT) between 10 and 15 units/mL, well above the 5 units/mL threshold that is correlated with protection. The efficacy of the vaccine was 86% after 1 year.\textsuperscript{22}

4. Post-licensure Surveillance

The post-licensure effectiveness of the Varivax® vaccine, as measured by household contact, case-control, and retrospective cohort studies, averaged 80% to 85% against any disease, and 95% against severe disease, estimates consistent with the pre-licensure data.\textsuperscript{4, 30}

The largest and most complete household contact study was conducted between 1997 and 2001 in Antelope Valley, California. Active surveillance identified 1,602 primary cases of varicella and 5,912 household contacts. The attack rate in vaccinated contacts of unvaccinated cases was 15.1%. This is contrasted with a secondary attack rate of 71.5% when both the case and the contact were unvaccinated. Vaccine effectiveness (%) is calculated by the cohort method:\textsuperscript{50}:

\[
\frac{(ARU - ARV)}{ARU} \times 100
\]
where ARU and ARV stand for the secondary attack rate in unvaccinated and vaccinated contacts respectively. In this study the effectiveness of varicella vaccination against any disease was estimated at 79%. It is important to note that household exposures are more intense and occur for a longer duration than the typical community exposure.\textsuperscript{51}

The success of the single-dose varicella vaccination campaign has also been measured by changes in varicella incidence, hospitalization and case fatality rates. Within 10 years, the incidence of chickenpox has fallen by roughly 80% in most areas, with hospitalizations and mortality decreasing by a similar amount. Data from three sites with active varicella surveillance have been instrumental in documenting this trend.

In the previously referenced site in California, the annual incidence was 10.3 per 1,000 population in 1995, just before vaccination began. Age-specific data were consistent with other studies, with rates of 48.8/1,000 for 1-4 year old children, and 54.9/1,000 among 5-9 year olds. Seroprevalence data indicated that 93% of the population was infected by age 15.\textsuperscript{52} In 2000, five years after the implementation of routine varicella vaccination, and with a vaccine coverage rate of 82.1%, the overall varicella incidence rate at the California site was 2.5 cases per 1,000 population, a drop of roughly 95%, with significant declines in all age groups. The highest rates continued to occur in the 1-4 and 5-9 year age groups, with rates of 7.5 and 20.5 cases per 1,000 population respectively. Hospitalization rates also declined ranging from 2.7-4.2 cases per 100,000 population in 1995 to 0.6-1.5 per 100,000 population by 2000. Similar coverage rates and declines were seen in the two other surveillance sites (West Philadelphia, PA, and Travis County, Texas).\textsuperscript{52}

A national survey of hospitalization data from 1993 to 2001 revealed a similar
decline in varicella related hospitalizations. At the start of vaccination in 1995, the hospitalization rate was 5 per 100,000 US population. It decreased to 2.5 per 100,000 by 1999, and further fell to 1.3 per 100,000 in 2001. The mortality rate attributable to varicella decreased from 0.41 per million population at the beginning of vaccination, to 0.14 per million population by 2001.

5. Vaccination and the average age of infection

A well-known consequence of vaccination is an increase in the average age of infection. As the incidence rate of an infectious disease increases, the average age at infection decreases. Simply put, if the incidence of varicella is high, individuals spend less time susceptible to infection before becoming infected. This can also be expressed in terms of waiting time (wt), where the rate of moving from a susceptible to infected state is 1/wt. With vaccination, incidence rates decrease, and the average age of infection increases.

This has important implications for VZV vaccination programs. Recall that morbidity and mortality increases substantially when infection occurs after age 15. While vaccination will decrease the overall incidence of disease, an shift in the average age of infection could lead to a net loss of public health. This concern was widely discussed before widespread vaccination started. These changes have also occurred with rubella, a disease with potentially serious consequences in adolescents compared with younger children.

In the absence of vaccination, peak infection rates in temperate, industrialized countries occurred in 1-4 year olds, with upwards of 95% of the population infected by
In Canada and the UK, highest rates were seen between ages 5 to 11 years. However, in the years just preceding the beginning of vaccination, rates increased in children aged 2-4 years, presumably as a result of increased day care utilization, and thus more contacts in this age group. This pre-vaccination shift has occurred elsewhere, with the highest incidence shifting from 5-11 year olds to 1-4 year olds in the US.

Modeling studies were utilized to predict the shift in the average age of infection that would occur with vaccination. Models by Halloran et al. predicted more cases in individuals 30 years and older after vaccination than before vaccination. However, when infection occurred in individuals partially protected by prior vaccination, the severity of disease is likely to be less than infection in completely susceptible individuals. Another model predicted that after vaccination, 81% of cases would occur in children 12 years of age and younger, compared with 86% before vaccination. However, this model also predicted that with different assumptions about vaccine coverage and population mixing, up to 50% of cases could occur in those aged 19 years and older. The absolute number of cases drops in all age groups, so a net loss in public health was not predicted.

With over 10 years of widespread vaccination in the US, data are now available on the shift in the age distribution of VZV infection. The most complete data come from active surveillance conducted in Antelope Valley, California, Philadelphia, Pennsylvania, and Travis County, Texas. In these communities, the peak infection rates have shifted from 3-6 years of age before vaccination to 9-11 years of age 10 years after vaccination started. The increase in the age distribution has thus not yet caused the peak incidence to shift into age groups where infection is more dangerous, and incidence, morbidity and mortality have fallen in all age groups.
C. Breakthrough Varicella

While the routine vaccination campaign has been highly successful in reducing varicella morbidity and mortality in the US\textsuperscript{17, 52, 53}, the issue of “breakthrough varicella” surfaced. Breakthrough varicella is defined as chickenpox in a vaccinated individual, at least 42 days after vaccination (which differentiates it from symptoms of pre-vaccine incubating infection, or symptoms caused by vaccination).\textsuperscript{5, 52}

1. Morbidity of breakthrough varicella

Breakthrough disease tends to be milder than chickenpox in an unvaccinated individual. Afflicted individuals typically have fewer vesicles (<50 is a usual cutoff for mild disease), a lower incidence of fever, a shorter duration of disease, and are less contagious.\textsuperscript{4, 5} Breakthrough disease is mild in roughly 75\% of breakthrough cases. The remaining 25\% of breakthrough cases are severe, have >50 vesicles, and are prone to the full effects of chickenpox infection, including contagiousness similar to natural infection.\textsuperscript{15, 62-64}

A matched case control study identified 202 PCR positive cases and 339 matched controls. Out of 122 previously vaccinated cases, 87\% had mild disease with <50 lesions. Only 98 (45\%) of the unvaccinated cases had mild disease. The rash in unvaccinated cases was also more severe than in vaccinated cases.\textsuperscript{65, 66}

One study examined the effect of time since vaccination on the severity of breakthrough varicella. Severe disease was defined as chickenpox with >50 lesions. Among unvaccinated children, severity of disease increased as the age of disease onset increased. Compared with children infected before 1 year of age, those infected at 8-12
years were 1.53 (CI 1.26-1.85) times as likely to have severe disease, and those infected at 13 years or greater were 2.2 (CI 1.76-2.24) as likely to have severe disease. 67

2. Incidence of breakthrough varicella

The annual incidence of breakthrough varicella is currently estimated to be 2%-3% per year. 22, 46 A large randomized trial compared children receiving 1-dose of Varivax® with children receiving 2-doses, 3 months apart. 30 The trial enrolled 2,216 one to twelve year old children between 1991-1993 and followed them for 10 years. The yearly incidence proportion in the single dose group ranged from 0.2% to 2.3% with the highest incidence occurring 2 to 5 years after vaccination. The 10-year cumulative incidence was 7.3% (95% CI 5.5, 9.0). The majority (77.2%) of breakthrough cases were mild, with <50 vesicles. Roughly 23% had more than 50 vesicles, with disease similar to natural varicella. Overall, one dose of vaccine was 94% against any disease. The efficacy was 98.3% in the two-dose group, with a 10-year cumulative incidence of 2.2% (95% CI, 1.2, 3.2). Breakthrough disease was mild in 81% of cases. It is unclear why the incidence was highest in the period 2-5 after vaccination. As wide-scale vaccination started in 1995, 2 to 4 years after enrollment, it is possible that exposure to wild-type virus was limited during this 2-5 year period. The increased incidence could have resulted from a lack of exogenous boosting (exposure to wild-type VZV) rather than decreased vaccine effectiveness.
3. Infectiousness of breakthrough cases

In a household contact study, the transmission potential of VZV from individuals with breakthrough disease to vaccinated and unvaccinated contacts was evaluated.\textsuperscript{51} Attack rates were calculated for transmission from vaccinated and unvaccinated cases to vaccinated and unvaccinated contacts. The transmission rate from unvaccinated cases to unvaccinated contacts was 71.5\%, consistent with other studies.\textsuperscript{68} Transmission from breakthrough varicella cases to unvaccinated contacts was highly dependent on the number of vesicles. Only 23.4\% of unvaccinated contacts of breakthrough cases with <50 vesicles became infected, whereas 65.2\% became infected when there were >50 lesions.\textsuperscript{51} This study confirmed prior observation that children with fewer than 50 vesicles have milder disease and are less infectious, whereas children with more than 50 vesicles tend to have more severe disease and a transmission potential similar to that seen in unvaccinated individuals.\textsuperscript{29, 32, 69}

4. Outbreaks of breakthrough varicella

Because the duration and intensity of exposure is higher in households than in the community at large, estimates of attack rates in households may overestimate the secondary attack rates typically seen in the community.\textsuperscript{51} Several reports have documented outbreaks of breakthrough varicella that occurred in schools and day care centers, with attack rates in vaccinated children ranging from 12\% to 50\%.\textsuperscript{62-64, 70-75}

In a large case-control study conducted between 1997 and 2003 in Connecticut, 202 PCR positive cases were compared with 339 matched controls. Vaccine effectiveness against any disease was 87\%, and this estimate was unchanged after adjusting for
covariates including sex, race, and location of day care, corticosteroid use, asthma, and MMR vaccination within 28 days of varicella vaccination. The effectiveness of the vaccine against severe disease was 99%.65

One outbreak occurred in a daycare facility in New Hampshire in 2000.63 The index case appeared to be a previously vaccinated four-year old boy with severe breakthrough varicella (fever and >150 lesions). Varicella developed in 25 out of 88 at risk. Seventeen of the cases had been previously vaccinated, 8 were not. The 63 children who escaped infection included 10 (15.9%) unvaccinated, 32 (50.8%) vaccinated, 16 (25.4%) with previous infection, and 1 with an unknown history. The secondary attack rates in vaccinated and unvaccinated children were 34.6% and 44.41% respectively. Vaccinated children experienced milder disease with a shorter duration than unvaccinated children. In this population the vaccine effectiveness against any disease was 44% (95% CI 6.9,66.3), and 86% (95% CI 38.7,96.8) effective against severe disease.76

In 2002, another outbreak occurred in an elementary school in Minnesota. The investigation identified 49 infected students who did not have a previous history of chickenpox. The case definition for infection classification was the acute onset of a macropapular rash, with no other apparent cause, between July of 2002 and January of 2003. Morbidity was defined as mild when <50 lesions were present, moderate at 51-100 lesions, and severe if >100 lesions were present. Breakthrough disease was defined as varicella illness in a child vaccinated >42 days before symptom onset. Vaccine coverage among the 49 infected was 59% (29 total), 41% (20 total) were not vaccinated. Overall there were 36 unvaccinated children at the school, and 118 vaccinated children. The attack rates were 25% (29/118) in the vaccinated, and 56% (20/36) in the unvaccinated.
The vaccine effectiveness against was thus 55% against any disease. Breakthrough disease was mild in 76% (23/28) of 28 breakthrough cases, and moderate among the rest. In the unvaccinated students, only 20% had mild disease (4/20), with the rest suffering moderate disease. No severe illness was noted. The vaccine effectiveness was thus 90% against moderate illness.\textsuperscript{62}

Another elementary school was reported in Utah. Cases occurred from October 2002 until February 2003. The index case was a vaccinated child who developed chickenpox with severe complications. A total of 74 cases (26 vaccinated children and 48 unvaccinated) were identified at the index case’s school and one other elementary school in the community. The vaccine effectiveness against any disease was 87%, which is well within the range predicted in pre and post-licensure studies. Even though the attack rate in vaccinated children was low (4% in one school and 5% in another) parents in this small community were left with the perception that the vaccine was ineffective. The fact that 35% of the cases were vaccinated fueled this perception. Additionally, 12 parents mistakenly assumed that their children were vaccinated against varicella, but were in fact not.\textsuperscript{72}

The publicity associated with these outbreaks, combined with a general perception of chickenpox as a mild illness, may threaten the continued success of the vaccination campaign. Even when the vaccine performs well, parents may misjudge the effectiveness.\textsuperscript{72} The varicella vaccine is already refused by more parents than any other recommended childhood vaccine.\textsuperscript{77, 78}
D. Factors Associated with Breakthrough Disease

Several factors associated with vaccine failure and breakthrough disease in some studies include a history of respiratory syncytial virus infection, pneumonia, asthma, corticosteroid use, and vaccination within 30 days of receiving the MMR vaccine. 79-81

Two factors associated with breakthrough disease have received the most attention. First, many studies uncovered an association between younger ages (<15 months) at vaccination and future breakthrough disease. 64, 65, 71, 72, 79 The second association is time since vaccination, with longer time periods associated with an increased risk of breakthrough varicella and severity of breakthrough disease. 63-65, 67, 72, 79, 82, 83 It is important to note that these two findings are not consistently present in every study. It is thus worthwhile to consider the type of study design, outbreak vs. specifically designed study, when interpreting such results. The following sections will examine the evidence for and against these the associations with age at vaccination and time since vaccination.

1. Time since vaccination and age at vaccination

Several outbreak studies have assessed the associations between breakthrough disease, time since vaccination, and age at vaccination. In the 2000 chickenpox outbreak at a New Hampshire day care center, both age at vaccination and time since vaccination were associated with the incidence of breakthrough disease. Children vaccinated 3 or more years before the outbreak were 2.6 (95% CI 1.3,5.3) times as likely to develop breakthrough disease as children vaccinated less than 3 years prior. The median age of vaccination was 18.4 months for children with breakthrough disease, and 24.7 months for children who remained healthy. 76
Similarly, an outbreak in elementary schools in Illinois found that vaccination before 15 months of age was associated with a 3.7 (1.1 to 13.1) times increased risk of breakthrough disease compared with vaccination after 15 months. No other associations were noted.\textsuperscript{73}

In the Minnesota elementary school outbreak, receipt of vaccination before 16 months doubled the risk of breakthrough disease (RR 2.1, 95% CI 1.1,4.1). Additionally, receipt of vaccination 5 or more years before the outbreak led to a risk for breakthrough disease 2.6 (1.3-5.4) times as high as vaccination less than 5 years prior to the outbreak. The authors also found that children who experience chronic ear infections were twice as likely to have breakthrough disease (RR 1.9, CI 1.0-3.5).\textsuperscript{79}

The investigation of the Utah elementary school outbreak also revealed an increasing risk of breakthrough infection with decreasing age of vaccination, with vaccination at or before 18 months associated with an incidence of breakthrough disease 2.6 times (95% CI 1.2,5.6) as high as for children vaccinated after 18 months. Similar to the Minnesota outbreak, children vaccinated 5 or more years before the outbreak were 3 (95% CI 1.4,6.4) times as likely to develop varicella as children vaccinated less than 5 years before the outbreak. An additional risk factor identified in this study was the incidence of eczema. Children with a history of eczema were 3.8 (1.8-7.1) times as likely as children without eczema to have breakthrough disease. To assess the effect of age at vaccination independently of time since vaccination, the investigators restricted their analysis to children vaccinated 5 years or more before the outbreak. The resulting relative risk of 9.3 (1.3-68.9) times for vaccination at or before 18 months vs. after 18 months is interesting, but the width of the confidence interval shows how imprecise this
estimate is. Of the 65 children vaccinated after 18 months in this sub-group, only 1 had breakthrough disease.\textsuperscript{72}

An outbreak investigation at a school in Oregon showed that vaccination 5 or more years before the outbreak was associated with breakthrough disease (RR 6.7, CI 2.2-22.9). The attack rate in children vaccinated at 15 months or younger was 14%, essentially identical to the attack rate of 11% in children vaccinated after 15 months.\textsuperscript{74}

In a daycare center outbreak in Pennsylvania in 2000, children vaccinated before 14 months of age were 3.0 (95% CI 0.9-9.9) times as likely as children vaccinated at 14 months or later to develop breakthrough varicella. No other risk factors were noted.\textsuperscript{84}

These results from these outbreak investigations certainly raise the possibility that age at vaccination, or time since vaccination may play a role with breakthrough disease incidence. It is important to note that outbreak studies are small, and thus their estimates are imprecise. Their small size decreases the statistical power for multivariate assessment of risk factors.\textsuperscript{15} Age at vaccination and time since vaccination are necessarily correlated with each other. Most of these outbreaks occurred in the first 5 years after universal vaccination, thus children vaccinated at the longest time before an outbreak were likely to be younger at vaccination than their similarly aged peers who were vaccinated more recently. Thus these variables confound each other, highlighting the necessity for studies designed to undertake multivariate analysis.

Non-outbreak studies that aimed to examine multiple risk factors for breakthrough varicella, especially the effects of age and timing of vaccination, include case-control, follow-up, retrospective cohort, and laboratory studies.

A large case-control study conducted in Connecticut between 1997 and 2003
examined potential risk factors for breakthrough disease. The analysis was restricted to 202 PCR confirmed cases and 389 matched controls. The vaccine was 85% (CI 78-90) effective against any disease, and 97% (93-99) against moderate to severe disease, similar to other studies. In their investigation of risk factors associated with breakthrough disease, they found that overall effectiveness was 97% (95% CI 91,99) in the first year following vaccination and decreased significantly to a range of 81% to 86% in years 2 through 8 post-vaccination. Age at vaccination was associated with effectiveness in the first year after vaccination. In the first year following vaccination, the effectiveness of the vaccine was 73% in children who received the vaccine before 15 months of age in the first year following vaccination, and 99% in those vaccinated at 15 months of age or older. Age at vaccination was not statistically significantly related to vaccine effectiveness for years 2 through 8 following vaccination, with effectiveness estimates of 81% and 85% among children vaccinated before and after 15 months respectively. A possible explanation for the association of age at vaccination and risk of breakthrough disease occurring only in the first year post-vaccination could be the possibility that in the first year, most children with poor vaccine response became infected. Children who were vaccinated before 15 months but escaped infection in the first year could have had a similar immune response to children vaccinated after 15 months. The overall decrease in effectiveness after year one could indicate that waning immunity increases the risk of breakthrough disease over time. However, the differences in effectiveness were not statistically significantly different for years two through eight. It is important to note that this study looked at cases from 1997 to 2003. Over that time period, vaccine coverage in active surveillance sites described previously rose from <20% to >70%. Thus, in each
year after vaccination, vaccinated individuals had less exposure to wild VZV and therefore a lower risk of developing breakthrough disease. Even if substantial waning of immunity was taking place, the increasing risk from waning immunity could have been balanced by the decreased exposure.

Chavez et al. performed active surveillance in California between 1995 and 2004. Multivariate analysis was performed to examine the risk of breakthrough disease, accounting for the independent effects of age at vaccination and time since vaccination. One analysis was performed on a subset of children aged 8-12 years, to account for the collinearity of age of onset, age at vaccination, and time since vaccination with regards to disease severity. The adjusted odds ratio for the effect of vaccination 5 or more years in the past compared with less than 5 years was 2.6 (CI 1.2-5.8). The rates of breakthrough disease increased as time since vaccination increased. At 1-year post-vaccination, the incidence rate was 1.6 (1.2-2.0) per 1,000 person years, increasing to 9.0 (6.9-11.7) per 1,000 person years at 5 years, 20.4 (14.1-29.6) per 1,000 person years at 8 years, and 58.2 (36.0-94.0) per 1,000 person years at 9 years. This study provides evidence for an effect of time since vaccination on the risk of breakthrough disease. The authors conclude that there is waning of immunity over time, but also point out that increasing vaccine coverage might have decreased opportunities for exogenous boosting, leading to a reduction in vaccine effectiveness over time. Unfortunately, the investigators did not include vaccine coverage as a covariate in their regression model. Additionally, age at vaccination was examined as a categorical variable, and it was not possible to examine an independent effect of age at vaccination.

Risk factors for breakthrough disease were also identified in a retrospective cohort
study at two sites that followed children born after 1993 until 1999. In an adjusted model, the relative risk for developing breakthrough disease among children vaccinated before 15 months of age vs. vaccination at or after 15 months was 1.2 (95% CI 0.8,1.9) to 1.4 (95% CI 1.1,1.9). Children who received the varicella vaccine within 28 days of receiving the MMR vaccine were 2.1 (95% CI 0.3,16.3) to 3.1 (95% CI 1.5,6.4) times as likely to develop breakthrough disease. Their model adjusted for the effect of time since vaccination. Children who had taken oral steroids were 2.4 (95% CI 1.3,4.4) to 2.8 (95% CI 1.0,7.8) times as likely to develop breakthrough disease in the following 3 months as children who did not take oral steroids. Previous studies have demonstrated an increased risk of severe varicella among unvaccinated children receiving steroids, as well as in children with severe immunosuppression. The authors point out that children who use steroids may have more severe breakthrough disease and thus may be more likely to be seen at their health maintenance organization, leading to an overestimate of an increase in breakthrough incidence in such children.

Li et al. performed a prospective cohort study that followed 1,164 children vaccinated with a single dose of vaccine between 1991 and 1993, with subsequent follow-up for seven years. Children vaccinated between 1-2 years of age had a 7-year cumulative incidence of breakthrough disease of approximately 11%, compared with a 5% cumulative incidence in children vaccinated between 3 and 5 years of age. Unfortunately, the 1-2 year age group was not split into subgroups that would allow the analysis of vaccination at 12-15 months of age vs. after 15 months.

The observed association between time since vaccination and breakthrough disease can be attributed to several biologically plausible pathways, including waning of vaccine-
induced immunity, maternal antibody interference with vaccination, immunological immaturity, and sub-optimal immune response to vaccination.

2. Waning of vaccine-induced immunity

Humoral immunity is important for protection against VZV infection. Antibody titers <=8u/mL 6 weeks post-vaccination as measured by the fluorescent antibody to membrane antigen test (FAMA) led to a 300% increase in breakthrough disease incidence compared with a 6-week titer >=64u/mL. Similarly, a 6-week gpELISA <5 u/mL was associated with a 250% increase in risk. Over time, antibody levels may drop or cellular immunity could wane. Sufficient numbers of T and B-cells may be stimulated such that the immune system is primed for an anamnestic response upon revaccination or natural exposure. However, in the absence of such exposure, populations of virus-specific cells decline as a part of normal immune system regulation. After a single dose of vaccine, the number of helper T-cells and memory B-cells may be insufficient to provide long-term protection.

3. Interference from maternal antibodies and immunological immaturity

Antibodies passively transferred transplacentally from mother to fetus can bind to vaccine virus, preventing it from being presented to the infant’s immune system. Maternal antibody interference led to increasing the recommended age at vaccination for measles from 9 months at licensure, to 15 months. The age was then decreased to 12 months in 1994 as levels of circulating maternal antibody had decreased after 31 years of vaccination. This effect has also been described after vaccination against pertussis,
influenza, polio, measles, mumps, *Haemophilus influenzae b*, and many more viral, bacterial and protozoan agents.\textsuperscript{91} In addition to maternal antibody interference, the infant immune system may not be sufficiently developed to mount an effective humoral or cellular response.

4. Sub-optimal immune response to vaccination

A recent population-based study utilized the fluorescent membrane antigen (FAMA) test, which is much more sensitive and specific than the widely used glycoprotein ELISA (gpELISA), and found that only 76\% of vaccinees seroconverted, indicating that primary failure or suboptimal vaccine response due to a weak humoral response may be more frequent than previously believed based on studies using the gpELISA assay.\textsuperscript{92, 120}

A review of a large randomized control trial lasting 2 years with an additional 7 years of follow-up after the trial ended measured antibody persistence in children receiving either one or two doses of Varivax\textsuperscript{®}.\textsuperscript{34, 48} Antibody persistence over time was measured using a glycoprotein ELISA (gpELISA). A titer $\geq$5 units/ml is strongly correlated with protection against infection.\textsuperscript{28, 29} The percentage of vaccinees with a gpELISA $\geq$5 units/ml increased from 85.7\% to 95.5\% by year 5. The increase in seroprevalence could be explained by exogenous boosting from exposure to circulating virus, or from endogenous reactivation of the vaccine virus.\textsuperscript{30} The persistence of anti-VZV antibody remained stable in years 4 through 10 of follow-up, which corresponds to the implementation of universal vaccination. Vaccine coverage increased from 26\% to 76\% during this 6-year period. If the increasing titers in the first 5 years resulted from
exogenous boosting, then the decreasing levels of circulating virus as vaccination coverage increased could explain the steady seroprevalence between years 4 and 10. While it is difficult to draw definitive conclusions from these results, this study does not lend support to the idea that humoral immunity wanes over time.\textsuperscript{30}

Another study looked at the persistence of immunity in healthy adults who were vaccinated during vaccine trials between 1979 and 1999. As time since vaccination increased, there was no change in the severity or incidence of breakthrough disease. Among vaccinees who did not seroconvert, or had lost detectable antibody, breakthrough disease was still mild. This indicates an important and persistent effect of cell-mediated immunity.\textsuperscript{45}

Health care workers were vaccinated and followed for an average of 4.6 years (1 month to 20.6 years). There was no increase in breakthrough incidence or severity over time. The FAMA test, considered the gold standard for antibody detection, was used to measure antibody titers. Five people did not seroconvert after vaccination, three of whom became infected. Of the remaining 115 who did seroconvert after vaccination, only 9 (8\%) had breakthrough disease. Thirty-six of the 115 (31\%) who did seroconvert lost detectable antibody over 1 to 11 years. Six of these 36 (17\%) developed breakthrough disease. Titers were also measured over time to examine antibody persistence. These measurements occurred at \textless 6 months, 6-48 months, and \textgreater 49 months after vaccination. The proportions with measurable antibody were 93\%, 75\%, and 86\% respectively. Because this study was carried out between 1979 and 1998, it is difficult to conclude that humoral immunity was persistent or if exogenous boosting from circulating wild VZV was occurring. The increased breakthrough incidence in seroconverters who
became negative over time could indicate waning of immunity.\textsuperscript{92}

In a 7-year follow-up study of children who were vaccinated between 1991 and 1993, nearly 100% seroconverted (\(\geq 0.6\) u/mL from gpELISA), and the geometric mean titer (GMT) increased from an average of 20.3 u/mL (95\% CI 18.2, 22.6) after 1 year to 47.4 u/mL (95\% CI 41.2, 55.2) after 6 years. In addition, breakthrough disease was mild and did not change in severity over time.\textsuperscript{32}

Taken together, these studies do not indicate that humoral or cellular immunity wanes over time. However, the studies that specifically examined persistence of immunity were primarily conducted before there was universal vaccination. Since there was considerable circulating VZV during this period, it is difficult to determine if immunity was truly persistent or if there was a boosting effect from exposure to wild VZV. The outbreak studies that demonstrated an association between time since vaccination and breakthrough disease incidence occurred in the era of universal vaccination, when exposure to wild VZV was decreasing. These results demonstrate that it is difficult to conclude if the increased breakthrough incidence observed as the time since vaccination increases is a result of a protective response that wanes over time, or a sub-optimal response to a single dose of vaccine that increases susceptibility when boosting does not occur.

The following studies examine aspects of infant immunity that could explain the relationship between age of infection and breakthrough disease incidence. Results from the measles literature are illustrative of the effect of maternal antibody presence and vaccination. A German study found a slightly decreased immune response to measles vaccine (measured by prevalence of a humoral response) in 9-11 months olds (84\%), vs.
older ages (100%). A study by Gans et al. was able to evaluate humoral and cell-mediated immune responses to measles vaccine in the first year of life. One striking finding was that cell-mediated immunity, measured by T-cell proliferation and IFN-gamma concentrations, did not differ in children vaccinated at 6, 9, or 12 months. This finding did not differ between children who still had passive antibodies vs. those who did not. This would suggest that, at least for measles, immaturity of the cellular immune response is not a problem, even at very young ages, and that maternal antibodies do not interfere with the cellular immune response. The humoral response was mitigated in the presence of maternal antibodies. Nine-month olds with measureable maternal antibodies did not mount an effective humoral response to measles immunization. However, 9-month olds without passive immunity mounted an equally vigorous response as older children who also were free of passive antibodies. Thus the barrier to vaccination, at least in 9-month olds, was not a result of cell-mediated immaturity, but simply the presence of maternal antibodies. In 6-months olds, there was evidence of an undeveloped B-cell induced humoral response. Six-month olds were not able to mount a humoral immune response to the measles or mumps vaccine, regardless of their passive antibody titers.

Maternal antibody interference with varicella vaccination has been investigated. Before widespread vaccination, most infants were born with maternal antibodies against VZV. One study found anti-VZV antibodies in more than 96% of cord blood samples. This value is similar to the seroprevalence of anti-VZV antibodies among adults. Passive antibody transfer of anti-VZV antibodies to infants via breast feeding does not occur.
Maternal antibodies against VZV have been measured in children up to 15-months of age. \textsuperscript{28} A Swiss study examined the seroprevalence of anti-VZV antibodies in hospitalized infants up to 16 months of age. Ninety percent of 0-3 month olds, 38\% of 3-6 month olds, and 0\% of 6-12 months olds had measurable passive antibody titers. The seroprevalence in children 12-16 months of age was 7\%, presumably from exposure to circulating virus.\textsuperscript{101} The same investigators documented a similar decline in maternal antibody persistence to varicella, measles, mumps and rubella in a study of pre-term vs. full-term infants.\textsuperscript{102}

In a large, retrospective analysis of 5 multi-center clinical trials, Silber et al. provide evidence against maternal antibody interference with vaccination.\textsuperscript{31} Their analysis included 3,771 children aged 12 to 23 months who had pre and post vaccination VZV antibody titers measured. Seropositivity at 12 months was 27.5\%, dropping to 12.4\% at 15 months. Following immunization with 1-dose of Varivax® vaccine, greater than 90\% of children achieved a 6-week post vaccination geometric mean titer (GMT) of 13.1 or greater. These titers were determined with the gpELISA. This average result was similar to age-stratified results with strata of 12-14, 15-17, and 18-23 months. The authors also looked at immune reactivity in strata defined by pre-vaccination serostatus at age 12-14 months. Among 2,388 children seronegative at this age, 93.6\% (92.5-94.5) had a gpELISA titer $\geq$ 5, with a GMT of 15.2 (95\% CI 14.7,15.7) 6-weeks after vaccination. For 558 children with low titers (<1.25) of passive antibody at 12-14 months, 95\% (95\% CI 92.8,96.6) had a 6-week titer $\geq$ 5, with a GMT of 14.2 (95\% CI 13.3,15.2). Finally, for 187 children with pre-vaccination, passive titers $>$1.25, 93.6\% (95\% CI 89.1,96.6) seroconverted by 6-weeks after vaccination, with a GMT 16.5 (95\%
These results suggest, similar to what has been observed with measles, that maternal antibody interference is not a factor in children vaccinated after 12 months of age. They provide evidence that maternal antibody presence is minimal at this age, and that even when present, does not inhibit the humoral response to the vaccine. Studies of cellular immunity reveal that by 12 months of age the cellular immune response is well developed, and that vaccination yields a long-term cellular response.

E. Two-Dose Vaccination

Regardless of the precise mechanism that leads to susceptibility for breakthrough infection, a second dose of vaccine is now recommended for all children between 4 and 6 years old. A second dose of vaccine should cover those who are susceptible to breakthrough infection, including those not vaccinated at 1 year, those who had primary vaccine failure or sub-optimal vaccine response, and those in whom vaccine induced immunity may have waned. It is thus hoped that a second dose will prevent further outbreaks in highly vaccinated elementary school populations.

1. Immunologic response to a second dose

Several investigations have documented the immunological response to a second dose of varicella vaccine. Humoral and cellular immunity are both greatly enhanced after a second dose of vaccine is administered. Studies that have evaluated cellular immunity via the stimulation index (SI) have shown a significant effect after a second dose of vaccine. A clinical trial in the early 1990s assessed the immune response to two
doses of varicella vaccine. Four hundred and nineteen children who had been vaccinated 4-6 years previously were given a second dose of vaccine. Before the second dose, 99% of the children were seropositive, the GMT from the gpELISA was 25.7, and the stimulation index (SI), a measure of T-cell function, was 40.3. Three months after the second dose, all of the 358 children had antibodies against VZV, with a GMT of 119.0, and a SI of 61.4. This demonstrates the ability for a strong anamnestic response in previously vaccinated children.38,42 A limitation to the study is that children eligible to receive the booster dose were those who did not develop breakthrough disease between their first dose and 4-6 years later. Thus, this was a subset of children who had mounted a protective response to the first dose of vaccine.

A randomized control trial with 10 years of additional post-trial follow-up examined 1,029 children randomized to receive two doses given 3-months apart. All of the children developed gpELISA titers >5 u/mL. The GMT in 2-dose recipients at 6-weeks post immunization was 142.6 vs. 12.5 for the 1-dose vaccinees. It should be noted that during the 10 years of follow-up, the GMT in the 1-dose group increased to 57.8 u/mL. In the two dose group, the GMT dropped to a low of 24.6 u/mL 2 years after vaccination, and then rose to 61.0 u/mL by the end of follow-up.30

2. Second dose efficacy

In the randomized control trial just described, individuals receiving one dose were 3.3 times as likely as those getting two doses to develop breakthrough disease, despite similar antibody titers in the two groups. The cumulative incidence was 2.4% in the two-dose group compared with 7.3% among the single dose vaccinees. The estimated
effectiveness was 94.4% (95% CI 92.9,95.7) for one dose, and 98.3% (95% CI 97.3,99) for two doses. Among laboratory confirmed cases, the single dose efficacy was 97.8% (95% CI 96.7,98.5), with a two-dose efficacy of 99.4% (95% CI 98.7,99.8). Two doses were 100% effective against severe disease.30

F. Infectious Disease Modeling

1. Modeling basics

Mathematical models are useful tools for forming hypotheses about how various host, population, environmental, and agent specific factors interact to affect infection transmission. They are used to predict outcomes of epidemics, and to assess the likely impact of different control measures. Strengths of the modeling approach are the transparent presentation of the model structure, parameter estimation, and various assumptions about factors important to infection transmission.

The simplest types of models are deterministic compartmental models. These models account for the states of the population that are relevant to transmission dynamics. For instance the compartments could represent Susceptibles, Infectious, and Recovered and permanently immune (SIR). Within each compartment, the population is treated as a continuous quantity. The transition, or flow, between compartments is modeled using ordinary differential equations that incorporate various epidemiologically significant parameters. The movement from $S \rightarrow I$ is governed by the “force of infection”($\lambda$). The force of infection is an instantaneous rate at which susceptible individuals become infected. It depends on the rate of contact between an $S$ and $I$ individual, multiplied by the probability of transmission when such contact occurs. The Greek letter $\beta$ represents the transmission contact and transmission rate. $\lambda$ is calculated
as \( \beta I/N \) where \( N \) is the population size. The incidence rate of infection in the population is therefore \( \lambda S \). Movement from \( I \) \( \rightarrow \) \( R \) can be expressed as the reciprocal of the infectious period, which gives the per-time unit rate of recovery. The state and dynamics of the model can be completely described by a set of differential equations\(^{56}\)

An important concept in modeling is represented by the basic reproductive number, \( R_0 \). \( R_0 \) is simply the number of new infections that occur if a single infectious individual is introduced into a completely susceptible population. This measure defines a threshold value for the occurrence of epidemics. When \( R_0 > 1 \), an epidemic will occur, if \( < 1 \), the infection will go extinct, and at 1 the disease will remain endemic. In the SIR model described above, \( R_0 \) is calculated as \( \beta/\gamma \), where \( \gamma \) is the recovery rate.\(^{56}\)

A notable assumption in these simple models is that the population is well mixed or homogenously mixed. A mass action law, derived from the mass action principle that describes the rate of chemical reactions in a well-mixed flask, characterizes the incidence rate. Contact is equally likely between any two people in the population. The probability that a susceptible individual has contact with an infectious individual is equal to the proportion of infectious individuals in the population. This assumption is clearly not realistic, however for some infectious processes, adding complexity obscures the methods without having a meaningful impact on the results.\(^{56}\)

Many infectious disease models require some amount of heterogeneity in the population mixing patterns. In the case of varicella, mixing rates between different age groups have a large impact on the transmission dynamics. So an age-structured model should be used. Within each age group the model may look like a simple, homogenously mixed SIR type model, but there is age dependent mixing between groups. This
heterogeneous age mixing can be accounted for in the force of infection by setting different contact rates between different age groups.\textsuperscript{55, 56, 103}

A matrix can be constructed showing the contact probabilities between the age groups. This is known as a who acquires infection from whom (WAIFW) matrix. Different sorts of mixing assumptions can be made. In assortative mixing, the majority of contacts occur within age groups. So an infectious 5-year old has the highest probability of contacting and infecting another 5-year old. Disassortative mixing assumes that higher contact rates occur between age groups. In this case the 5 year old may infect a 25 year old with a higher probability than any other age group. With proportionate mixing, transmission between groups is proportional to the numbers of susceptibles and infectious in each age group.\textsuperscript{56}

These matrices can be constructed by observing actual contact rates in a population. Or, the age specific incidence rates can be measured, and maximum likelihood techniques can describe matrices that would produce such rates. Such data can yield several equally likely matrices. Thus, subject matter knowledge, and analysis of the sensitivity of the output to small changes in the matrix, is needed to choose the best matrix.\textsuperscript{56, 61}

2. Modeling the transmission of VZV

Several studies have modeled VZV transmission. Most of these studies are concerned with the effect of vaccination on the long-term epidemiology. Factors such as changes in the age distribution of infection, reduction in case numbers, reductions in morbidity and mortality, and the economic effects of vaccination have all been investigated. The effect of vaccination on herpes zoster (HZ) incidence has also
generated substantial interest from the modeling community.

Garnett and Grenfell introduced a quantitative model with the aim of describing VZV transmission dynamics as well as HZ. Their model is a simple compartmental, deterministic model. Infants enter the model into a class with maternal antibodies (M), become susceptible (S), then exposed (E), infectious (I), and finally recover with permanent immunity (R). In the terminology presented above, this is an MSEIR model. The parameters that describe the flow from one compartment to the next are estimated from observed data. Age structure and the rate of zoster occurrence among the recovered add complexity to the model. The effect of age is accounted for by including age-specific forces of infection calculated with WAIFW matrix. Their results concern rates of viral reactivation, which causes HZ in previously infected and recovered individuals. They find that an age-dependent reactivation rate approximates real data better than a constant reactivation rate.\textsuperscript{104}

The above study was not intended to study the effect of vaccination on varicella epidemiology. It is useful to this discussion however, to see how such a simple model is used. Only seven compartments and six partial differential equations were needed to describe the infection dynamics in a population. Despite the simplicity, the authors were able to fit a model that produced estimates of HZ incidence that matched real world data.

Ferguson et al. used a stochastic, age-structured model to measure transmission dynamics following vaccination. The stochastic model utilizes parameter distributions rather than fixed values for the parameters. Random values from these distributions are determined for each run of the model. The average behavior of the model over repeat runs approaches the results of the deterministic model. By varying parameter values it is
possible to quantify a range of possible epidemiologic outcomes. This study was mostly concerned with the technical aspects of their model, rather than a study for an audience of epidemiologists. However, they made important findings. They conclude that after vaccination there will be a marked decrease in incidence of VZV, followed years later with a large epidemic as the susceptible population accumulates. \textsuperscript{105}

Two transmission models published by Halloran in 1996 were the first to study the impact of vaccination on breakthrough disease and varicella epidemiology. One purpose of the model was to study the direct effects of vaccination, meaning the effect of vaccination in the vaccinated. Another purpose was to measure the indirect effects, i.e. the effect of vaccination in the unvaccinated. As mentioned previously, vaccination will increase the average age of infection. This occurs in the vaccinated and unvaccinated. A major concern is a marked increase in varicella infection in adults, who are much more susceptible to major complications and mortality. The model was a deterministic, age-structured, compartmental, model. Vaccinated children either become completely (but not permanently) protected, partially protected (and thus susceptible to breakthrough infection) or they stay completely susceptible (primary vaccine failure). Immunity from vaccination wanes at a fixed rate. If exposed to wild type VZV, the completely protected and partially protected can become permanently immune (exogenous boosting). Breakthrough disease is another potential outcome when partially protected individuals are exposed. They are infectious but to a lesser degree than unvaccinated infectious individuals. A WAIFW matrix was used to determine contact rates between age classes.

Using published values for infectiousness, duration of infection, probability of breakthrough disease, and infectiousness of breakthrough cases, the model was
parameterized. Various vaccination assumptions were tested. These concerned the effectiveness of the vaccine, waning of immunity, the amount of protection conferred by the vaccine, and vaccine coverage. For values that were not previously estimated in other studies, a panel of 6 experts was used to provide reasonable upper and lower bounds for these parameters.

The results of the study showed a marked decrease in cases and hospitalizations, and a shift towards older age of infection. Breakthrough disease occurred, but never to levels comparable to pre-vaccination varicella incidence. The age shift did not push the average age so high as to increase overall morbidity. These results were robust to a broad range of parameter values. The important point is made that trends and qualitative results of the model are more important than the actual numerical output. This model, including parameter values and age structure has been used by many other investigators to predict the effect of vaccination in different countries and under different scenarios.

After 5 years of routine vaccination, enough data on vaccine effectiveness was available to update the model. Brisson et al. observed data on breakthrough disease incidence to describe new parameters. Under their scheme, most individuals move into a “vaccinated protected” (VP) class, and some to a “vaccinated susceptible” (VS) class following one dose of vaccination. Upon exposure to wild VZV, most VP become permanently immune (R), whereas most VS become infected (breakthrough disease) with the remainder moving to VP. Finally, in the absence of exposure, VP moves so VS at a constant rate representing waning immunity. Their analysis of available data showed that previous models underestimated the rate of breakthrough disease significantly. This
model was important in that it updated the values of the parameters determining vaccine effectiveness, but was limited as they made the simplifying assumption of homogenous mixing and used a model without age structure.46

In a later study, this same group used an age-structured model and assessed different vaccination strategies.61 The age structure is represented in a WAIFW matrix consisting of contact rates estimated by maximum likelihood techniques from data on age-specific incidence of natural VZV infection in Canada. Eight age groups represent typical ages for infants, day care users, elementary school children, adolescents, young adults, adults, middle age, and elderly. They also estimate the effect of vaccination on HZ incidence. In one of their models, the contribution of HZ cases to the force of infection in susceptibles is constant. In a second model, they explicitly modeled the number of HZ cases, their contact with susceptibles of all ages, and the probability that they transmit infection with such contact. This more complex model did not produce significantly different outcomes than the simpler model, so this discussion will be limited to the simpler model. To model demographics, there was a constant birth rate into a class protected by maternal antibodies for 6 months who then become susceptible. The maternal antibody class has no relationship with vaccine effectiveness. Mortality occurs only in the 65 years of age and older group. A constant death rate leads to a life expectancy of 75 years, and births balance deaths.61 The infectiousness of breakthrough cases was determined from a household contact study.51

Their base model assumes 90% vaccine coverage of 12 month olds, a waning rate of 0.031 per year (32 year average duration of immunity), with 93% of vaccinees moving into VP, 91% of whom become permanently immune with exposure, 73% of VS
becoming breakthrough cases with exposure, and breakthrough cases are half as infectious as natural cases. The output of this model shows a 70% drop in varicella in the first 5 years after vaccination, somewhat less than the observed 80% decline. Their model predicts an outbreak 5 years after the start of vaccination, constant breakthrough rates, and further predicts that incidence rates will fall to less than 5% of pre-vaccination rates after this “post honeymoon” outbreak. It is important to note that not all of their models predicted the post honeymoon outbreaks, and this was usually dependent on the mixing matrix. Their output next shows a large increase in incidence from about 12 to 18 years following vaccination, after which the incidence settles close to an endemic equilibrium with rates roughly 15% of what they were before vaccination. These incidence rates include both breakthrough and natural varicella.

It is 13 years since universal vaccination started. Currently, there are no modeling studies predicting the outcome of a second dose for varicella vaccination. Additionally, thorough sensitivity analyses have not been performed in prior studies. This dissertation will attempt to address such questions.

G. Sensitivity Analysis

An important part of any model of infectious disease transmission is the sensitivity analysis. Sensitivity analysis provides information about how uncertainty in model structure, assumptions and parameter values affect the outcome. It allows readers to assess the generalizability of the results, which may be limited as parameters are often chosen from specific populations. Even if a modeler has estimated and specified the model with a great degree of certainty, the non-linearity that is a hallmark of most
transmission models can make predetermination of how parameter variability will affect the outcome of interest.

Uncertainty may arise for different reasons. There could be uncertainty about the value of inputs, there may be inconsistency about the value or distributional form of a parameter in the literature, there could be statistical uncertainty resulting from sampling variability, or estimates may have been drawn from different populations. Uncertainty may be present in the model structure, or the model parameters. Uncertainty in the model structure includes doubt about how parameters should be combined to define processes in the model. Additionally, decisions are made about what factors should or should not be included in the model. Uncertainty about the parameters typically reflects unknown estimates, variance, or distribution of values for a parameter. Relationships between parameters, such as whether the effects are additive or multiplicative provides another source of uncertainty about the form of the model. Another useful description of the sources and issues related to uncertainty come from Briggs et al., who invoke four broad types of uncertainty, (1) sampling variability when estimating parameters; (2) methodology of estimation; (3) increasing uncertainty about the reliability of parameter values over time; and (4) the generalizability of results between populations.

The sensitivity analysis should include those parameters for which there is considerable uncertainty, or parameters that have been estimated with some certainty but have a large influence on the outcome of interest. Parameters may also have been estimated similarly across different studies, but have a wide variance.

There is no standard method to conduct sensitivity analyses in transmission modeling studies. Methods can be qualitative or quantitative, deterministic or
probabilistic, and univariate or multivariate. The purpose of the transmission model should dictate whether qualitative or quantitative sensitivity analysis techniques are used. Models that make general predictions or analyze trends are well served by qualitative sensitivity analysis, whereas models intended to make precise quantitative predictions call for a quantitative sensitivity analysis.

The simplest and most common type of sensitivity analysis is a one-way, or univariate analysis. In such an analysis, the values of a single parameter are varied from some base case; the change in the outcome measure from the base case is calculated, and the sensitivity of the output to this single parameter change is investigated. Typically, this is a deterministic method for sensitivity analysis; the modeler directly chooses the values for the alternate cases. In contrast, values are chosen from parameter distributions with various sampling schemes in a probabilistic analysis.

A recent infection model investigated the differences in mortality from Anthrax infection (the model outcome measure) as parameters in the model were varied. Each parameter was changed in isolation, and the percent reduction in mortality for this change in the parameter value was measured. This process was repeated for each parameter in the model. They found that the model was most sensitive to antibiotic efficacy, and was only marginally sensitive to antibiotic adherence. More importantly, the authors were able to determine which parameters needed to be specified with greater accuracy and precision for future studies.\textsuperscript{113}

A model evaluating the effect of recommending an earlier age for influenza vaccine among adults used a deterministic, univariate analysis to determine the parameters that lead to the greatest uncertainty in the model outcome, which was the cost associated with
a vaccination policy where all vaccinees were reimbursed, vs. the current policy where only high risk adults are reimbursed for vaccination. The study determined that the choice of policies was not as important as the incidence rate of influenza, proportion of the population at high risk, and the mortality rate.\textsuperscript{114}

These simple sensitivity analyses provide important insights into the factors that affect the chosen outcome for a transmission model. They help determine which parameters need to be estimated with greater accuracy. The choice of parameter values for deterministic, univariate analysis is arrived at via a literature review that reveals a well-estimated range of values. In this case, the parameter value is varied because of a known amount of variability in the estimate.

A drawback of the univariate methods is the necessity of assuming that the estimate for each parameter is independent of the values for other parameters. Interactions between parameters that lead to non-linear or multiplicative relationships with the outcome will be overlooked when each parameter is varied independently of the others.\textsuperscript{109, 111, 112}

Multivariate sensitivity analysis involves simultaneously adjusting the values of two or more input parameters. Parameters that are not independent, for instance maternal antibody titers and protection afforded by vaccination for measles, can be varied together. Of course this assumes that relationships between parameters are known. As the number of parameters varied together increases, the sensitivity analysis becomes more difficult.\textsuperscript{109} To account for such complexity, the number of values for each parameter might be constrained to extreme values, for instance the highest and lowest reasonable values. Often this is considered a best and worst case analysis; the modeler \textit{a priori} assigns
values to parameters that are considered to cause the most favorable and unfavorable outcomes. Analysis of extremes can miss important relationships between the parameters. If the relationship between the input parameters and outcomes are non-linear, then the extreme parameter values may not actually represent a best and worst case. For instance, if a U-Shaped relationship exists between parameter values and the outcome, the a priori determined extreme values may not actually cover a best or worst case. Additionally, the extreme values could represent values from the tails of an unknown distribution, and thus be quite unlikely to occur in combination with each other.\textsuperscript{109, 112}

The most complicated type of multivariate, deterministic analysis is a full-factorial or n-way analysis.\textsuperscript{109, 115-117} Such an analysis investigates the outcome under every possible combination of parameter values. A set of parameter values used in a single run of the transmission model can be thought of as a vector, and there is a vector representing every possible parameter combination. The number of vectors scales a $k^N$, where $k$ is the number of parameters, and $N$ is the number of values for that parameter. Clearly this method is computationally taxing, since even a simple model can have thousands of vectors that need to be analyzed. A benefit of this method is that every possible outcome under a certain model structure and set of assumptions is calculated. The entire multi-dimensional parameter space is explored.\textsuperscript{116} This method does not require assumptions about the distributions that values of a parameter fall into, nor does it make assumptions about the independence of parameter values, or that there is a monotonic relationship between the values of a parameter and the values of the model output. When feasible, this method is highly valuable due to its thoroughness and lack of assumptions.\textsuperscript{115}
Probabilistic methods present more efficient means for performing multivariate sensitivity analysis. In this type of sensitivity analysis, the values for each parameter follow some distributional form. For instance, constant mortality rates will follow an exponential distribution, while the infectious period of an infection could be normally distributed. The distribution for each parameter is split into N intervals. The model is run N times, each time with a randomly chosen input vector. The uncertainty in each parameter is treated as a random variable. A form of this type of probabilistic sensitivity analysis was utilized in models of HIV and tuberculosis (TB) transmission. In these studies, a sampling technique known as Latin Hypercube Sampling (LHS) was used to randomly choose parameter vectors. Since a sampling scheme is used, and the distribution that the samples are drawn from is known, the resulting output can be analyzed with traditional statistical methods. The benefit of this method is its efficiency. Rather then requiring $k^N$ input vectors, only $N$ input vectors are needed, where N represents the number of values that will be drawn from the parameter distribution of each parameter.

In a model of HIV transmission among heterosexual, intravenous drug users, Blower et al. used the LHS design for the first time in a deterministic, infectious disease transmission model. Their model is explained by 34 ordinary differential equations with 20 total parameters. If five possible values were chosen for each parameter, there would be $3.2 \times 10^6$ input vectors under a full-factorial analysis. Thus the efficient sampling design of a probabilistic sensitivity analysis was ideal.

One of the first steps in such a probabilistic sensitivity analysis is choosing probability density functions (pdfs), or distributions, describing the values of each
parameter. Given that the results of this type of sensitivity analysis are analyzed statistically, determining these pdfs is a crucial component of the sensitivity analysis. Determination of these pdfs is based on direct calculation from primary data collection, secondary analysis of existing data, and reviews of the literature. Sometimes, the pdf of a parameter will have been directly measured by calculating the mean and variance of an estimate. In many cases, however, choices are based on best guesses given what data exist. An illustrative example of pdf selection from the Blower et al. model is the choice of distribution for the progression of HIV to AIDS in pediatric patients. At the time of the study, little data were available to directly measure the distributions. However, studies had shown that some children progressed to AIDS very quickly, measured by months, whereas other children took years to progress to AIDS. Thus a bimodal distribution was used, specifically a Weibull distribution with two peaks. The flexibility of this distribution, which ranges from a nearly exponential (early progression) to a nearly normal distribution (for the second peak) depending on the value of a shape parameter, is ideal for such a bimodal distribution. When estimates to support a given pdf are lacking, a uniform distribution is used. If every parameter were assigned a uniform distribution, the analysis would be no different than a full-factorial analysis since each value for a parameter is chosen with equal probability.

Partial rank correlation coefficients (PRCC) were calculated for each parameter. The PRCC assesses the strength of the linear relationship between a single parameter and the outcome, while controlling for the values of the rest of the parameters. The values of the statistic range from -1, which indicates a perfectly linear inverse relationship, and 1, which indicates a perfectly positive linear relationship. A value of 0 is calculated if there
is no linear relationship present. This statistic requires two assumptions; (1) there is a monotonic relationship between the parameter and the outcome (either increasing or decreasing), (2) there is no interdependence or interaction between parameters. There are methods to deal with covariance between parameters, but the techniques are difficult and the interaction must be identified in advance. If the assumptions are met, then the magnitude of the PRCC indicates how sensitive the model is to the parameter. It is important to realize that this type of analysis only quantifies the uncertainty of the chosen transmission model structure. Thus the results do not address generalizability to other settings.

There are clear advantages and disadvantages to the deterministic and probabilistic approaches to sensitivity analysis. The choice method relates to the motivation for the transmission modeling study. If the purpose of the study is to predict general trends over time, then deterministic, qualitative methods should suffice. When precise, quantitative estimates are required, such as in an analysis of the cost-effectiveness of a new therapy, then the quantitative techniques based on statistical methods are likely more apt. It is also important to keep in mind the assumptions that underlie each method. The full-factorial, deterministic analysis makes no assumptions about the probability density function that describes the values of a parameter or about the interrelationship between parameters in the model. It also makes no assumption regarding the linearity of the relationship between a parameter and the chosen outcome. When assumptions of independence and monotonicity are met, the probabilistic methods provide the most information in the most efficient fashion.
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III. Statement of Specific Aims

A. Aim 1

Aim: Measure the short and long-term incidence of natural and breakthrough varicella after introduction of a 2-dose vaccination program, paying special interest to the epidemiology in the next 20 years.

Rationale: The short and long-term effect of a 2-dose vaccination schedule is unknown. Of immediate concern is the magnitude of a post-vaccination resurgent epidemic that could occur in the next 10 to 20 years.

Hypothesis: A resurgent epidemic is unavoidable, even with the introduction of a two-dose vaccine program. A two-dose vaccine program will decrease both natural and breakthrough varicella rates relative to a single dose program.

B. Aim 2

Aim2: Demonstrate methods for a systematic sensitivity analysis for transmission models that can be applied to other settings, standardizing the methodology and increasing the generalizability of different models.

Rationale: Sensitivity analyses are often ignored or given superficial treatment in transmission models, limiting the assessment of model uncertainty and decreasing comparability between different models.

Hypothesis: A systematic method of sensitivity analysis will demonstrate a high degree of uncertainty in the current model, and will prove to be sufficiently general that it can be applied in a wide variety of model settings.
IV. Methods

A. Study Design

An age-structured, deterministic, compartmental model will be specified. The model consists of fourteen ordinary differential equations. The model structure and age-specific mixing patterns are adapted from a previously described model\(^1\), with updates to the structure and parameters reflecting the observed epidemiology of the last 13 years. The sensitivity analysis makes use of qualitative, deterministic techniques that measures the sensitivity of the model to every possible combination of input parameter values. Univariate and multivariate techniques are outlined. These methods provide a systematic method for performing a qualitative sensitivity analysis, which should be generalizable to other modeling studies in different settings.

B. The Varicella Transmission Model

The population is split into 66 age cohorts for 0 to 64 years, anyone 65 years and older are in the 66\(^{th}\) cohort. Births are added as partial susceptibles the 0 year age class, and all mortality will occur in the 65 years and older group. Birth and death rates, \(\mu\), are equal to maintain a constant population size. Births, aging, and mortality happen at the end of each year, thus maintaining discrete age cohorts. The mixing patterns and contact rates are described by what Brisson et al. described as the base-case and matrix 1 who acquires infection from whom (WAIFW) (figure 4.2).\(^1\) Discrete time steps of 0.1 days are
used, and the model runs from one year before the implementation of routine vaccination in 1995 until 2095.

The population is divided into mutually exclusive, epidemiologically relevant compartments (figure 4.1). Children are born into the susceptible class (S) at age 0. To account for maternal antibody protection, children in this age class are $\frac{1}{2}$ as infectious as a susceptible in any other age class. Effective contact with an infectious individual moves susceptibles into latent class (E) at the rate determined by the force of infection, $\lambda(a,t)$, where individuals are infected but not yet infectious, becoming infectious (I) at rate $\sigma$ (where $1/\sigma$ equals the duration of the latent period), before finally recovering with permanent immunity (R) at rate $\gamma$ ($1/\gamma$ equals the duration of the infectious period). Susceptibles are vaccinated at rate $c_1$, which is set to 90%, rounded up from the US average coverage rate of 88%.$^2$ Vaccination of susceptibles moves them into the vaccinated protected class (VP) with probability $(1-\varphi)$, which is the probability that a full immune response is mounted, or to a vaccinated susceptible class (VS) with probability $\varphi$, which is the probability of mounting a sub-optimal immune response. Members of VP are completely but temporarily protected against infection, while the VS class consists of individuals who are susceptible to infection, though less so than members of S. Infection of VS is deemed “breakthrough infection.”

Members of the VP class become permanently immune if they have effective contact with an infectious individual at rate $k\lambda(a,t)$, or if they receive a second dose of vaccine at coverage rate $c_2$. Either event moves them into a permanently immune class, VV. Exposure of the VS class to infectious individuals leads to breakthrough infection at rate $b\lambda(a,t)$, where $b$ represents the relative susceptibility of VS compared with S, or they
become permanently immune and move into the VV class at rate \((1-b)\lambda_{(a,t)}\). Members of VS also become permanently immune after a second dose of vaccine at rate \(c_2\).

Breakthrough infections are either mild (VEm and ViM) or severe (VEs and ViS). Movement to VEm vs. VEs is determined by the proportion of effective contacts that are breakthrough cases \((\pi_{a,t})\). Mild cases are assumed to be 30\% as infectious \((m)\) as a severe breakthrough or natural case based on a household contact study.\(^3\) From this same study, we assume that 90\% \((\alpha)\) of VS move to VEm if exposed to a breakthrough case, whereas 75\% \((\epsilon)\) of VS move to VEm if exposure is to a naturally infectious individual \((I)\), or to a severe, fully infectious breakthrough case \((VEs)\).\(^3\) Immunity following breakthrough infection is, similar to natural disease, considered to be lifelong; additionally breakthrough cases have the same latent and infectious periods as natural cases.\(^4\)

Rather than modeling the impact of herpes zoster directly, a constant is added to the force of infection to account for zoster related transmission.\(^1\) The parameters that define the transitions between compartments are assigned values based on relevant data from the literature review, and are presented in table 4.1.

The model runs by integrating a set of 14 ordinary differential equations (figure 4.2). A single dose vaccine program will be run for 10 years in the model, with the first dose of vaccine given to children as they turn 1 year of age; after 10 years second doses will be given to 2 or 5 year olds at various coverage rates. A comparison model is run that does not have a second dose. The simulations are run using newly written C++ code (developed by SV and AL). The incidence rates from 2005 to 2025 under one-dose and two-dose regimes where the second dose is given to either 2 or 5 year olds are calculated. This includes overall incidence rates, incidence rates in the unvaccinated, and
breakthrough incidence rates. Additionally, age-specific incidence rates are examined to determine the change in the average age of infection in a one vs. two-dose scheme. Incidence rates after 100 years are examined in the same way, to determine the long-term expected outcomes.

C. Sensitivity Analysis

1. Validation of baseline parameter values.

To validate the choices for a base set of parameter values, the results of models with presumed baseline values are compared against data of the observed annual varicella incidence rates since 1995, when vaccination started.

2. Definition of outcomes

The sensitivity of two different outcomes from the model is assessed against changes in the input parameter values. The first outcome is the post-vaccination epidemic peak incidence rate. This is the instantaneous, per-capita incidence of infection in the population. A second distinct but related outcome is the cumulative number of infections from 2005 to 2025, which covers the time period of the post-vaccination epidemic. These outcomes are chosen based on their epidemiologic relevance. The incidence rate provides an idea of the short term needs of public health planners, whereas the cumulative incidence determines the overall public health burden of the outbreak.
3. Design of the sensitivity analysis

A full factorial analysis is used. In such an analysis, the transmission model gets run using every possible combination of parameter values. Each combination can be thought of as an input vector, with a single value for each parameter. To create vectors, the continuous distribution of parameters was reduced to a series of discrete values close enough together as to not miss any possible departures from linearity in the relationship between the parameter and output. For parameters distributed between 0 and 1, we added or subtracted 0.05 from the base value to the upper and lower values of the range. The range of values is given in table 4.2.

Keeping with the qualitative nature of this sensitivity analysis, which is appropriate given the qualitative nature of the transmission model, univariate relationships are analyzed and displayed in spider plots. The relative change in the output from the baseline output is plotted against the relative change in parameter values from their baseline value. With this method it is possible to examine the relationship between changes in a single parameter value with changes in the output.

We use box plots to examine every possible output value across different values of a single parameter. The box plots are useful in determining the occurrence of parameter interactions, departure from linearity, and for examining the variability in the outcome associated with specific values of a parameter. This technique is not typically performed, but it provides much more information than spider plots or other univariate graphs.

Next, an analysis of two different scenarios is presented. Typically modelers will a priori determine “best” and “worst” case input vectors. In our case, the worst-case
vector assigns the following values: $\phi=0.4$, $b=0.9$, $m=0.8$, and $1/\omega=1$ year. The best-case scenario uses the opposite extremes where: $\phi=0.05$, $b=0.3$, $m=0.2$, and $\omega=0$. Examining only these extremes implicitly assumes a monotonic relationship between the best and worst case.$^7,9$

A benefit of the full factorial analysis is that every possible outcome can be examined.$^{10,11}$ Then outcomes that truly are the best or worst, where very low or high numbers are infected, can be examined and the vector that gave rise to such an outcome determined. These vectors may differ from what was a priori determined as a best or worst case vector, and such evidence of a non-monotonic relationship provides clues about the presence of interactions between parameters.

Finally we assess linearity of the each parameter with the number of cases using the partial correlation coefficient. This statistic gives a value of -1 to 1, which represents complete inverse and positive linearity, with 0 indicating the lack of a linear relationship. The coefficients for each parameter are controlled for every other parameter. It is essentially a quantification of the results of the spider and box plots. This is a useful technique, but it assumes independent relationships amongst the parameters. If there is no evidence of a linear relationship, this does not mean there is not another relationship.$^{12}$ The model is run with every possible parameter combination. The outcomes of this full-factorial analysis are compared, and the parameters leading to the largest changes in outcome measures are identified. Additionally, interactions are assessed in multivariate analysis where parameter-outcome relationships are examined under different values for a second-parameter. The extreme values for the outcome (highest and lowest peak incidence rate and total incidence) are singled out, and the parameter vectors that give
rise to these extreme values is determined. The results of this analysis are presented graphically, providing a qualitative determination of sensitivity and uncertainty in the model outcomes and parameters. The results of the simulations are analyzed with STATA version 9 (College Station, Texas). The simulations were created with handwritten C++ software.
Figure 4.1. The Base Model, compartments and flows. See table 4.1 for explanations of parameters that are numbered here.

S=Susceptible to infection; E=Infected but not yet infectious; I=Infectious; R=Recovered and permanently immune; VP=Vaccinated protected (full but temporary protection from infection after a single dose of vaccine); VS=Vaccinated susceptibles (sub-optimal response and thus somewhat susceptible to infection after a single dose); VE=vaccinated, infected but not yet infectious, VI=vaccinated infectious, e.g. a breakthrough case; VR=Recovered and permanently immune after breakthrough infection; the subscripts m and s refer to mild disease and severe disease respectively; VV=Permanently immune from either two doses of vaccine, or one dose of vaccine followed exogenous boosting of immunity without becoming infectious.
### Table 4.1. Description and values of parameters and flows between compartments.

<table>
<thead>
<tr>
<th>Flow</th>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Births</td>
<td>$B$</td>
<td>400,000</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>$\mu_a$</td>
<td>0 for $a&lt;65$, 0.1/year for $a\geq65$</td>
</tr>
<tr>
<td>2</td>
<td>$S \to E$</td>
<td>$\lambda_{a,t}$</td>
<td>Varies with time and age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\lambda_z$</td>
<td>0.00000274</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$z_a$</td>
<td>0.5 for $a=0$, 0 for $a\geq1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$m$</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$E \to I$</td>
<td>$\sigma$</td>
<td>0.0714/day</td>
</tr>
<tr>
<td>4</td>
<td>$I \to R$</td>
<td>$\gamma$</td>
<td>0.1429/day</td>
</tr>
<tr>
<td></td>
<td>$V_{Im} \to V_{Rm}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$V_{Is} \to V_{Is}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$S \to VP$</td>
<td>$c_1$</td>
<td>0 or 0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(1-\varphi)$</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>$S \to VS$</td>
<td>$\varphi$</td>
<td>0.25</td>
</tr>
<tr>
<td>7</td>
<td>$VP \to VS$</td>
<td>$\omega$</td>
<td>0.0333/year</td>
</tr>
<tr>
<td>8</td>
<td>$VP \to VV$</td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td>9</td>
<td>$VP \to VV$</td>
<td>$k$</td>
<td>0.91</td>
</tr>
<tr>
<td>10</td>
<td>$VS \to VV$</td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td>11</td>
<td>$VS \to VV$</td>
<td>$(1-b)$</td>
<td>0.25</td>
</tr>
<tr>
<td>12</td>
<td>$VS \to VEm$</td>
<td>$\alpha$</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\varepsilon$</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\pi_{a,t}$</td>
<td>Varies</td>
</tr>
<tr>
<td>13</td>
<td>$VS \to VEs$</td>
<td>$(1-\alpha)$</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(1-\varepsilon)$</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Table 2. Mathematical Representation of the Model (Numbers below terms link these equations with the pathways in figure 1.) Births, deaths, aging, and vaccination events are treated as discrete processes that occur at year-end. These terms, therefore, do not appear in the differential equations.

\[
\begin{align*}
\frac{dS_{a,t}}{dt} &= -z_a \lambda_{a,t} S_{a,t} \\
\frac{dE_{a,t}}{dt} &= z_a \lambda_{a,t} S_{a,t} - \sigma E_{a,t} \\
\frac{dI_{a,t}}{dt} &= \sigma E_{a,t} - \gamma I_{a,t} \\
\frac{dR_{a,t}}{dt} &= \gamma I_{a,t} \\
\frac{dVP_{a,t}}{dt} &= -(\omega + k \lambda_{a,t}) VP_{a,t} \\
\frac{dVS_{a,t}}{dt} &= \omega VP_{a,t} - \lambda_{a,t} VS_{a,t} \\
\frac{dVV_{a,t}}{dt} &= k \lambda_{a,t} VP_{a,t} + (1 - b) \lambda_{a,t} VS_{a,t} \\
\frac{dVEm_{a,t}}{dt} &= (\alpha \pi_{a,t} + \epsilon \{1 - \pi_{a,t}\}) b \lambda_{a,t} VS_{a,t} - \sigma VEm_{a,t} \\
\frac{dVIm_{a,t}}{dt} &= \sigma VEm_{a,t} - (\gamma + \mu_a) VIm_{a,t} \\
\frac{dVRm_{a,t}}{dt} &= \gamma VIm_{a,t} \\
\frac{dVES_{a,t}}{dt} &= \left(1 - \alpha\right) \pi_{a,t} + \epsilon \{1 - \pi_{a,t}\} b \lambda_{a,t} VS_{a,t} - \sigma VES_{a,t} \\
\frac{dVIS_{a,t}}{dt} &= \sigma VES_{a,t} - \gamma VIS_{a,t} \\
\frac{dVRS_{a,t}}{dt} &= \gamma VIS_{a,t}
\end{align*}
\]

\[
\lambda_{a,t} = \sum_{\mu = 0}^{65} \beta_{a,\mu} \left\{ \frac{I_{a,t}}{N_{a,t}} + \frac{VIS_{a,t}}{\lambda_{a,t}} \right\} + \lambda_Z
\]

\[
\pi_{a,t} = \sum_{\mu = 0}^{65} \beta_{a,\mu} \left\{ \frac{VIS_{a,t}}{\lambda_{a,t}} + m \frac{VIm_{a,t}}{N_{a,t}} \right\}
\]
Figure 4.2a Brisson et al. Base matrix. β values are contact and transmission rates per 100 days. The first row and column are the age groups.

<table>
<thead>
<tr>
<th></th>
<th>0–1</th>
<th>2–4</th>
<th>5–11</th>
<th>12–18</th>
<th>19–24</th>
<th>25–44</th>
<th>45–64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0.70</td>
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<td>0.70</td>
<td>0.70</td>
<td>0.85</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>2–4</td>
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<td>4.42</td>
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<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>5–11</td>
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<td>5.16</td>
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<td>0.85</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>12–18</td>
<td>0.70</td>
<td>1.20</td>
<td>1.20</td>
<td>5.16</td>
<td>0.85</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>19–24</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
<td>15.47</td>
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<td>0.57</td>
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<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>45–64</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>65+</td>
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<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
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</tbody>
</table>

Figure 4.2b. Brisson et al. Matrix 1

<table>
<thead>
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<th>2–4</th>
<th>5–11</th>
<th>12–18</th>
<th>19–24</th>
<th>25–44</th>
<th>45–64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0.69</td>
<td>0.69</td>
<td>0.69</td>
<td>0.69</td>
<td>1.01</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>2–4</td>
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<td>4.42</td>
<td>1.20</td>
<td>1.20</td>
<td>1.01</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>5–11</td>
<td>0.69</td>
<td>1.20</td>
<td>5.15</td>
<td>1.20</td>
<td>1.01</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>12–18</td>
<td>0.69</td>
<td>1.20</td>
<td>1.20</td>
<td>5.15</td>
<td>1.01</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>19–24</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>10.30</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>25–44</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>45–64</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
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<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>65+</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Table 4.3. Base parameter values and range used in sensitivity analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Value</th>
<th>Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varphi$</td>
<td>0.25</td>
<td>0.05 – 0.4</td>
<td>Sub-Optimal Response Rate</td>
</tr>
<tr>
<td>$b$</td>
<td>0.6</td>
<td>0.3 – 0.9</td>
<td>Residual susceptibility of vaccinated susceptibles</td>
</tr>
<tr>
<td>$m$</td>
<td>0.33</td>
<td>0.2 – 0.8</td>
<td>Reduced infectiousness of mild breakthrough cases</td>
</tr>
<tr>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
<td>0.5 or 0.75</td>
<td>Second dose coverage rate</td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.0333/year (30 Year Duration)</td>
<td>1 to 100 year duration</td>
<td>Waning of vaccine induced immunity</td>
</tr>
<tr>
<td>Mixing Matrix</td>
<td>Base and Matrix 1</td>
<td>N/A</td>
<td>Refer to figure 4.2</td>
</tr>
</tbody>
</table>
D. References


V. The Honeymoon is Over: A Model for the Epidemiology of Varicella under a Two-Dose Vaccination Strategy

Steven Valeika, Alun L. Lloyd, and Annelies Van Rie

(Submitted to the Journal of Infectious Diseases)

A. Abstract

In 1995 in the United States implemented a single-dose strategy of varicella vaccination in infants. Varicella incidence, morbidity, and mortality declined dramatically, though outbreaks continued, even in highly vaccinated populations, and the incidence of varicella began rising in 2003. These events prompted the recommendation of a two-dose vaccination strategy in 2005. A deterministic, age-structured transmission model of the two-dose strategy predicts a large epidemic of varicella in the near future, even with high second-dose coverage rates. In the long-term, incidence rates under a two-dose regime will be 10% or less compared with pre-vaccination rates, compared with up to 50% with a continued one-dose strategy. Varicella cases will consist mostly of mild, breakthrough disease in previously vaccinated individuals. As the average age of infection increases, a higher proportion of varicella infections will occur in the 15 to 25 year old age group, raising concern over congenital varicella syndrome.
B. Introduction

Between 1995 and 2003 the incidence, morbidity, and mortality from varicella in the United States dropped by roughly 80% as a result of the introduction of the Varicella Zoster Virus (VZV) vaccine in 1995.\(^1\) The epidemiology of varicella in the United States is now largely characterized by outbreaks in daycare facilities and elementary schools, where observed attack rates have been high in both vaccinated and unvaccinated children. In some cases, vaccine effectiveness has fallen below 50%, compared to the 80% to 90% vaccine efficacy estimates obtained in pre-licensure vaccine trials.\(^2-4\)

The rate of breakthrough disease, defined as varicella in a vaccinated individual, is roughly 2%-3% per year, with larger attack rates during outbreaks.\(^2,3,5-12\) Breakthrough disease is typically mild; about 75% of cases have fewer than 50 vesicles and are 30% to 50% as infectious as more severe breakthrough or natural cases. Breakthrough cases with more than 50 lesions are nearly as infectious as naturally infected cases, and are similarly ill.\(^13\) The fact that breakthrough infections are typically mild is evidence of some degree of protection among these vaccinees, enough to attenuate the disease but not enough to prevent infection. Several serological studies have shown that breakthrough cases were often seronegative after vaccination. This suggests an important role for cellular immunity to provide protection against full-blown disease.\(^14,15\)

Younger ages of vaccination (<15 months) and time since vaccination (5+ years) have been associated with breakthrough disease in several outbreaks. Primary vaccine failure, maternal antibodies, sub-optimal immune response, and waning of vaccine-induced immunity have thus been posited as potential mechanisms for breakthrough disease.\(^2,3,8,16-19\) Primary vaccine failure is treated as different phenomena by different
authors, with some referring to the situations of improper injection, expired vaccine, and instances where the vaccinee mounts no immune response at all, while others refer to situations of sub-optimal immune response.\textsuperscript{13,20} A recent population-based study utilized the highly sensitive and specific fluorescent antibody against membrane antigen test, and found that only 76\% of vaccinees seroconverted after one-dose, indicating that primary failure or suboptimal vaccine response due to a weak humoral response may be more frequent than previously believed based on studies using the gpELISA assay.\textsuperscript{20} We ignore primary failure as described above, and concentrate on the sub-optimal immune response.

Interference of maternal antibodies with vaccination has been demonstrated for other vaccine preventable childhood diseases such as measles\textsuperscript{21}, but is unlikely to occur for varicella vaccine as maternal antibodies against VZV are typically no longer present at 12-months of age.\textsuperscript{22}

Waning of vaccine-induced immunity has been difficult to study. More than 90\% of single-dose vaccinees had demonstrable antibodies in pre-licensure clinical trials, with a persistent titer for 6-10 years, but these trials took place when the background rate of varicella was still very high, resulting in exposure to wild-type virus.\textsuperscript{5,23-25}

The Advisory Committee on Immunization Practices (ACIP) recommended the institution of a 2-dose vaccine regimen in 2005, following a string of well-publicized varicella outbreaks in situations with high vaccine coverage.\textsuperscript{1} The first dose continues to be given at 12-15 months, and the second dose is recommended for 4 to 6 year olds, as pre-school begins.\textsuperscript{1} Some have argued for earlier administration of the second dose.\textsuperscript{26}
While a number of modeling studies investigated the effects of a single dose regimen, no predictions have been made regarding the effect of a second dose.\(^7,27,28\)

In this study, we explore the impact of the implementation of a two-dose campaign on varicella epidemiology over time, the effect on the peak age of infection, and the relative number of mild vs. severe breakthrough cases. In addition, we assess the optimal timing of the second dose in light of calls for scrutiny of the current recommendation.\(^26\)

C. Methods

A deterministic, age-structured model was used to examine the transmission dynamics of varicella zoster virus (VZV). The model is adapted from Brisson et al., with differences taking into account recent findings and refining the model structure and parameterization.\(^2,28\) The structure of the model is given in Figure 5.1; model parameters are presented in Table 5.1.

Birth and aging occur at the beginning of each year, with the entire age cohort aging at once. Individuals are born into the susceptible class. There are 66 yearly age classes, with those 65 years and older grouped together in the oldest age group, \(N_{65}\). Mortality rates (\(\mu\)) are age-dependent, where \(\mu_a\) equals zero if \(a\) is less than 65, and equals 0.1 otherwise, resulting in an average lifespan of 75 years. Before age 1, individuals are half as susceptible to infection as other age groups, accounting for maternal antibody protection (\(z\)); there is no maternal antibody interference with vaccination.\(^22\) Effective contacts, \textit{i.e.} ones that lead to infection, occur at rate \(\lambda_{a,1}\), which is the force of infection, and newly infected susceptibles move into an infected but not
infectious compartment (E). Individuals pass from this exposed class to the infectious class (I), at rate $\sigma$ ($1/\sigma$ is equal to the latent period of 14 days). Cases recover to a permanently immune class (R) at a constant rate $\gamma$ ($1/\gamma$ is equal to the infectious period of 7 days). This infection pathway is referred to as natural infection, i.e. infection in a previously unvaccinated individual. Immunity from natural infection is assumed to be life-long.

Vaccination of susceptibles occurs as they turn 1 year of age. Vaccination rates are taken from the current U.S. average of 88%, rounded to 90%. The parameter $c_1$ holds this value. Vaccinees move into either a temporarily but completely protected class (VP), or to a partially susceptible class (VS) with probability $\phi$. This represents the probability that an individual will have a sub-optimal response to vaccination, and is set equal to 25% in the base case, an estimate based on a recent seroprevalence study and household contact study.\textsuperscript{13,20}

From VP, individuals can flow into the VS compartment at waning rate $\omega$. Estimates of the duration of vaccine induced immunity, based on seropositivity, range from 2 years to lifelong.\textsuperscript{3,11,18,31} Alternatively, individuals in VP can enter the permanently immune class VV after receiving a second-dose of vaccine, at coverage rate $c_2$, or upon exposure to an infectious individual at rate $k \lambda_{\text{inf}}$. The second dose is given at 5 years of age to reflect the current recommendations, and at 2 years of age to inspect an alternate strategy. The parameter $k$ modifies the rate at which individuals in VP move to VV after an effective contact. Thus $(1-k)$ of VP who have an effective contact remain in VP after such contact.
We assume permanent immunity for the VV class based on two-dose efficacy trials. Rates for a second dose are assumed to be less than coverage rates for the first dose; similar to what is observed in other multi-dose regimens.

Members of VS who have effective contact with an infectious individual become infected (breakthrough infection) at rate $b \lambda_{a,t}$, or become permanently immune by moving into VV at rate $(1-b)\lambda_{a,t}$. The partial susceptibility, $b$, of vaccinees relative to unvaccinated susceptibles is set at 60% based on estimates from household contact attack rates and values used in other modeling studies.

Breakthrough infections are either mild (VEm and VIm) or severe (VEs and VI). The proportion of effective contacts that are with breakthrough cases ($\pi_{a,t}$) determines the proportion of VS who move to VEm vs. VEs. Mild cases are assumed to be 33% as infectious ($m$) as a severe breakthrough or natural case. Based on a household contact study, we assume that 90% ($\alpha$) of VS move to VEm if effectively exposed to a breakthrough case, whereas 75% ($\epsilon$) of VS move to VEm if effective exposure is to a naturally infectious individual (I), or to a severe, fully infectious breakthrough case (VEs). Immunity following breakthrough infection is, similar to natural disease, considered to be life-long; additionally breakthrough cases have the same latent and infectious periods as natural cases.

The who acquires infection from whom (WAIFW) matrix, defines the effective contact rate, $\beta_{a,a'}$, between age groups $a$ and $a'$, and consists of eight age classes: infants (0-1), pre-schoolers (2-4), younger school children (5-11), adolescents (12-18), young adults (19-24), parental ages (25-44), older adults (45-64), and seniors (65+). The effective contact rate accounts for the actual contact rate, and the transmission probability
given a contact between a (naive) susceptible and (natural) infective. The matrices used are identical to the base matrix and matrix 1 of Brisson et al.\textsuperscript{28} The base matrix has high contact rates among school children, between parents and infants, and within 15 to 18 year olds, in addition to very high contact rates within the 19-24 year age group. Matrix 1 is similar, but contact within the 19-24 year age class is decreased by 33\%. Rather than modeling the impact of herpes zoster directly, a constant is added to the force of infection to account for zoster related transmission.\textsuperscript{28}

The model runs by integrating a set of differential equations (table 5.2) with a one-day time-step. The model starts in 1994 at the pre-vaccine endemic equilibrium and runs for 100 years post vaccine implementation in 1995. The second dose campaign (when present) is implemented in 2005, corresponding to the US recommendations.

A sensitivity analysis was performed to assess the effect of changing parameter values on the output of the model. Univariate and multivariate, deterministic sensitivity analyses were performed. First we changed the value of a parameter of interest against a background of the base values for other parameters. Second we held the parameter of interest at a constant value, compared to a background of all possible model outcomes from variation in all other parameters. The outcomes measured for the sensitivity analysis were the peak post-honeymoon incidence, and the total number of cases during this epidemic.

The model simulations were run from handwritten C++ code (SV and AL), statistics and graphics were produced with STATA v9.0 (College Station, Texas).
D. Results

The predicted pre-vaccination era incidence rate of 13.4 cases per 1,000 population is similar to pre-vaccination data observed in the United States and estimates from other modeling studies, which gives us confidence in our model.\textsuperscript{28,38} The age-specific incidence rates per 1,000 person years are 86.5, 73.29, 21.43, and 8.72 for the 0-4, 5-9, 10-14, and 15-18 year age classes respectively, and are also similar to the observed rates in the U.S. before vaccination. For instance, data from the Behavioral Risk Factor Surveillance Study (BRFSS) observed incidence rates of 100.0, 78.9, and 13.8 for the 0-4, 5-9, and 10-14 year age classes respectively.\textsuperscript{39}

The model output for the first 10 years of routine single dose varicella vaccination program predicts a dramatic decrease in incidence, followed by a temporary increase a few years later and a resurgence beginning in 2003. The predicted pattern is similar to what has been observed in the United States, though the model has the temporary increase in incidence occurring in 1999 rather than 1997 as was observed (figure 5.2). The resurgence that begins in 2003 is predicted to continue, and reach high incidence rates of up to 50% to 80% of the pre-vaccine incidence (figure 5.3). This so-called “post-honeymoon” epidemic is a phenomenon that has been seen following other wide-scale vaccination campaigns, and has been predicted by other varicella models.\textsuperscript{28,40-42}

Following a brief lull, a second epidemic occurs around 2025, 10 years after the first, followed by an approach to the steady state incidence rate 50 years after the introduction of the vaccine program.

The two dose vaccination model predicts that the currently observed resurgence will continue (figure 5.3). However, with the two-dose strategy the second epidemic is
prevented, and much lower incidence rates are achieved at steady state. Within 50 years after the introduction of the two-dose strategy, the incidence drops to very low rates and remains at incidence levels 10% or less than those observed in the pre-vaccine era. Furthermore, when 75% coverage of the second dose is achieved, the disease is nearly eliminated. Changing the age of administration of a second dose to 2 years of age produces a much higher resurgent peak (figure 5.3). In the long-term, the age of administration makes no difference.

Before 2005, the predicted incidences are largely independent of the WAIFW matrix used. However, following the beginning of the two-dose strategy in 2005, the predicted outcomes diverge depending on whether the base mixing matrix or mixing matrix 1 is used. The conclusion that we are at the cusp of a varicella epidemic remains unchanged; however the magnitude of the epidemic we can expect to occur depends on which of the two matrices best represents the true contact patterns in the United States (data not shown).

The proportion of each age group in classes R, VRm, or VRs, makes up the model-predicted age-specific seroprevalence from prior infection. We do not include vaccinated individuals who were never infected individuals in these seroprevalence curves. The pre-vaccination seroprevalence in the model mirrors the seroprevalence curves for most temperate, industrialized countries (figure 5.4).\(^{43-45}\) Similar to observational data, the model predicts that the average age of infection will increase as time since vaccination increases (figure 5.4). Following 10 years of single dose vaccination, the peak incidence occurs between about 10 years of age and 15 years (evidenced by the steepest part of the slope in the prevalence curves).\(^{46}\) The model
predicts that by 2015, a large proportion of varicella infections will occur in the 16 to 24 year age group. Implementing a second dose of vaccine does not substantially influence the changes in the average age of infection.

The relative amounts of mild and severe breakthrough disease, and disease in the unvaccinated, is shown in figure 5.5. Over time, mild breakthrough disease becomes the prominent form of chickenpox. In the short term, higher vaccination coverage favors mild disease, but as the incidence approaches the post-vaccination steady state, the relative amounts of the disease types is identical regardless of the second dose coverage rate. The age of second dose vaccination did not impact the percentages of disease types (not shown).

The sensitivity analysis revealed that breakthrough incidence was more sensitive to model inputs than the incidence in unvaccinated individuals. The model was most sensitive to the estimated rate of waning of vaccine-induced immunity, and the influence of other parameters was dependent upon the value of this parameter. This emphasizes the need for more accurate estimates of the rate of waning of vaccine-induced immunity.

E. Discussion

This study predicts that the resurgence in varicella incidence that has been observed since 2003 will continue and peak in 2015, 20 years after the beginning of the single dose varicella vaccination strategy. The resurgence is a result of a buildup of susceptibles (S) protected by herd-immunity, as well as a buildup of partially susceptible vaccinated individuals (VS) due to waning immunity or sub-optimal response to vaccine, compounded by the decreasing circulation of VZV. The magnitude of the resurgent peak
is striking, with incidence rates approaching pre-vaccination rates. While this seems unrealistic at first glance, such peaks have been observed in post-vaccination measles epidemics as well as by other models of varicella transmission.\textsuperscript{28,40} The incidence rates at the eventual steady state under a one-dose strategy are 50% to 60% of the prevaccination incidence rates.

A two dose campaign will result in markedly lower incidence in the long term, even at modest (50%) second dose coverage rates, but will only minimally attenuate the size of the short-term resurgence. Concern over the timing of the second dose has been expressed due to the possibility of breakthrough infection occurring in pre-schoolers who had a suboptimal response to the first dose of vaccine.\textsuperscript{26} Our results predict a similar steady state incidence between administration of the second dose at 2 or 5 years of age, but a second dose at age 2 years results in a higher peak incidence in the next 15 years.

Over time, mild breakthrough varicella will predominate. Second dose coverage rates and age at vaccination does not appreciably alter the relative proportions of disease caused by natural, severe breakthrough, or mild breakthrough illness. The age distribution of varicella incidence will also change over time. Currently, the highest incidence rates are seen between 10 and 14 years of age. As the average age of infection increases, a higher proportion of varicella infections will occur in the 15 to 25 year old age group, raising concern over the incidence of congenital varicella. Such perverse effects of vaccination are well known for rubella.\textsuperscript{47} However, as the majority of these cases will have mild breakthrough disease they may not suffer the severe adverse effects of natural infection seen in older age groups. It is also unknown how the fetus is affected by breakthrough varicella relative to natural disease.
There are several limitations to this study. As with any modeling study, uncertainty remains about parameter values, model structure and assumptions. The output of this model is highly sensitive to the duration of immunity, which has the least certain estimates of any parameters in our model. Another problem is the precision of the estimates for contact rates, especially in the older age groups. Mixing matrices are determined by the pre-vaccination age specific changes in incidence. Since most older children and adults have experienced past infection, there is very little change in the seroprevalence with age, and determination of their contact rates become problematic. Mixing matrices that are based on observed contact rates, collected by using diaries, rather than rates inferred from the age specific forces of infection, will greatly improve the accuracy of future models.33,36,42,48

Despite these uncertainties, the general qualitative predictions of this model are likely to hold true. In contrast with previous modeling studies, this study has the benefit of 10 years of varicella incidence data collected since the start of vaccination to validate its results. The predictions of the model for the years 1995 to 2006 are highly consistent with what has been observed in terms of incidence rates, seroprevalence, and an increasing burden in older age groups. We therefore are confident that the resurgence of varicella will continue for the next 10 to 15 years, despite a successfully implemented two-dose campaign.

The varicella vaccine is already refused more than any other mandatory childhood vaccine in the United States.49,50 Outbreaks are well publicized, and occur in highly vaccinated populations. This fuels a belief that the vaccine is not beneficial. Unfortunately, it appears that this belief may persist over the next 10 years. Our model,
to our knowledge the first to examine the effect of two doses of vaccine, indicates that the two-dose campaign will be successful in greatly decreasing the incidence of varicella over time. Thus the short-term increase in incidence, which appears to be unavoidable, should not be taken as evidence that the vaccine is ineffective, or that the current recommendations from ACIP are incorrect. Whether a concerned public or policy makers will be patient enough to wait for the benefits of the current recommendations to appear is not known, however the results of our study suggest that patience will eventually pay off.
Figure 5.1. The Base Model, Illustration of the flows between different compartments. The processes are numbered and defined in Table 1. For clarity, arrows depicting deaths are omitted. S=Susceptible to infection; E = Infected but not yet infectious; I=Infectious; R=Recovered and permanently immune; VP = Vaccinated protected (full but temporary protection from infection after a single dose of vaccine); VS = Vaccinated susceptibles (sub-optimal response and thus somewhat susceptible to infection after a single dose); VE= vaccinated, infected but not yet infectious, VI = vaccinated infectious, e.g. a breakthrough case; VR=Recovered and permanently immune after breakthrough infection; the subscripts m and s refer to mild disease and severe disease respectively; VV=Permanently immune from either two doses of vaccine, or one dose of vaccine followed exogenous boosting of immunity without becoming infectious.
### Table 5.1. Description and values of parameters and flows between compartments.

<table>
<thead>
<tr>
<th>Flow</th>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Births</td>
<td>B</td>
<td>400,000/year</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>$\mu_a$</td>
<td>0 for $a&lt;65$, 0.1/year for $a\geq 65$</td>
</tr>
<tr>
<td>2</td>
<td>$S \rightarrow E$</td>
<td>$\lambda_{a,t}$</td>
<td>Varies with time and age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\lambda_z$</td>
<td>0.00000274</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$z_a$</td>
<td>0.5 for $a=0$, 0 for $a\geq 1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$m$</td>
<td>0.33</td>
</tr>
<tr>
<td>3</td>
<td>$E \rightarrow I$</td>
<td>$\sigma$</td>
<td>0.0714/day</td>
</tr>
<tr>
<td>4</td>
<td>$I \rightarrow R$</td>
<td>$\gamma$</td>
<td>0.1429/day</td>
</tr>
<tr>
<td>5</td>
<td>$S \rightarrow VP$</td>
<td>$c_1$</td>
<td>0 or 0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(1-\varphi)$</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>$S \rightarrow VS$</td>
<td>$\varphi$</td>
<td>0.25</td>
</tr>
<tr>
<td>7</td>
<td>$VP \rightarrow VS$</td>
<td>$\omega$</td>
<td>0.0333/year</td>
</tr>
<tr>
<td>8</td>
<td>$VP \rightarrow VV$</td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td>9</td>
<td>$VP \rightarrow VV$</td>
<td>$k$</td>
<td>0.91</td>
</tr>
<tr>
<td>10</td>
<td>$VS \rightarrow VV$</td>
<td>$c_2$</td>
<td>0.5 or 0.75</td>
</tr>
<tr>
<td>11</td>
<td>$VS \rightarrow VV$</td>
<td>$(1-b)$</td>
<td>0.25</td>
</tr>
<tr>
<td>12</td>
<td>$VS \rightarrow VEm$</td>
<td>$\alpha$</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\varepsilon$</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\pi_{a,t}$</td>
<td>Varies</td>
</tr>
<tr>
<td>13</td>
<td>$VS \rightarrow VEs$</td>
<td>$(1-\alpha)$</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(1-\varepsilon)$</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Table 2. Mathematical Representation of the Model (Numbers below terms link these equations with the pathways in figure 1.) Births, deaths, aging, and vaccination events are treated as discrete processes that occur at year-end. These terms, therefore, do not appear in the differential equations.

\[
\begin{align*}
\frac{dS_{a,t}}{dt} &= -\lambda_{a,t} S_{a,t} \\
\frac{dE_{a,t}}{dt} &= \lambda_{a,t} S_{a,t} - \alpha E_{a,t} + \beta_{a',t} \left( \frac{I_{a',t}}{N_{a',t}} + \frac{V_{a',t}}{N_{a',t}} + m \frac{Im_{a',t}}{N_{a',t}} \right) \\
\frac{dI_{a,t}}{dt} &= \alpha E_{a,t} - \gamma I_{a,t} + \gamma V_{a,t} + \gamma V_{a,m} - \gamma V_{a,s} \\
\frac{dR_{a,t}}{dt} &= \gamma I_{a,t} \\
\frac{dVP_{a,t}}{dt} &= -(\omega + k\lambda_{a,t})VP_{a,t} \\
\frac{dVS_{a,t}}{dt} &= \omega VP_{a,t} - \lambda_{a,t} VS_{a,t} \\
\frac{dVV_{a,t}}{dt} &= k\lambda_{a,t} VP_{a,t} + (1-b)\lambda_{a,t} VS_{a,t} \\
\frac{dVEm_{a,t}}{dt} &= (\alpha \pi_{a,t} + \beta_{a',t} \lambda_{a,t}) b\lambda_{a,t} VS_{a,t} - \alpha VEm_{a,t} \\
\frac{dVIm_{a,t}}{dt} &= \alpha VEm_{a,t} - \gamma VIm_{a,t} \\
\frac{dVIm_{a',t}}{dt} &= \gamma VIm_{a,t} \\
\frac{dVIm_{a,m}}{dt} &= \gamma VIm_{a,t} \\
\frac{dVIm_{a,s}}{dt} &= \gamma VIm_{a,t} \\
\frac{dVIs_{a,t}}{dt} &= \alpha VEm_{a,t} - \gamma VIs_{a,t} \\
\frac{dVIs_{a,m}}{dt} &= \gamma VIm_{a,t} \\
\frac{dVIs_{a,s}}{dt} &= \gamma VIs_{a,t}
\end{align*}
\]
Figure 5.2. Base model validation: Model Predicted Incidence (Dashed) and Observed Incidence (Solid) from 1994 to 2006. Both curves are scaled relative to their 1994 rates to facilitate comparisons.
Figure 5.3. Predicted varicella incidence rates from 2005 to 2055 under a one-dose and two-dose vaccination strategy, by second dose coverage and age of administration of the second dose.
Figure 5.4. Age specific seroprevalence curves at various times since the implementation of routine one-dose varicella vaccination. These curves indicate past infection, either as a natural case or a breakthrough case. The base values for all parameters and the base mixing matrix was used in these simulations, and there is no second dose.
Figure 5.5. Percentage of each disease type by second dose coverage rate and year. In vaccinated individuals, disease can be mild, or severe. Severe breakthrough disease is similar to disease in unvaccinated individuals.
F. References


VI. A Systematic Method for Sensitivity Analysis of a Deterministic Model of Infectious Disease Transmission

Steven Valeika, Alun L. Lloyd, and Annelies Van Rie

A. Abstract

A sensitivity analysis is used to determine the sensitivity of the model output to the values of input parameters, and model structure, and should be performed for all models of disease transmission. Simple techniques like univariate sensitivity analysis and best vs. worst-case scenario analyses overlook parameter interactions and non-linear relationships between parameters and outcome. Probabilistic methods, such as Latin Hypercube Sampling are powerful and efficient, however they are associated with statistical assumptions that may not always be valid, and are not always tested. In this study we present a simple, systematic method to perform sensitivity analysis of a deterministic mathematical model of infection transmission. The methods can be used as a complete sensitivity analysis, or to investigate any possible violations of the assumptions of more complex probabilistic techniques.

B. Introduction

Sensitivity (or uncertainty) analysis is a critical component in the analysis of models of infectious disease transmission as it allows modelers to assess how uncertainty
in the model’s structure, assumptions and parameter values affect the outcome. The choice of parameter values for the base case model is informed by estimates found in the literature, original data collection, or expert opinion. Additionally, the range of parameter values from prior models may provide a starting point for parameter selection.

Uncertainty regarding a parameter’s value may relate to the mean value, its variance, or both. Some parameters have a known mean and limited variance around the mean, making sensitivity or uncertainty analysis redundant except in specific situations such as outbreaks in small populations. Other parameters may have a known mean and a known, but important variance. Incorporating this range in a model is important for generalizability of the results. Other parameters may have a known mean but unknown variance (either in size or distribution). When estimates from different studies vary widely, there is important uncertainty regarding both the mean and variance. Finally, for some parameters for which we do not have good estimates of the mean or variance.2

There is no standard method to conduct sensitivity analyses in transmission modeling studies. The simplest type of sensitivity analysis is univariate analysis, where one examines how changes in the values of a parameter change the value of the outcome, typically in relation to the output of a pre-defined, base model. For a model with \( k \) parameters, \( k - 1 \) parameters are held at their baseline values, while a parameter of interest is varied. This technique assumes that parameters are independent of each other, and that the values of other parameters are known with a relatively high degree of precision and certainty.3,4

In many modeling papers, modelers choose an \textit{a priori} determined best and worst-case scenario for the values of model parameters, often based on expert opinion.
Using this approach, these models make an implicit assumption of a monotonic relationship between the parameter and outcome values. This assumption is problematic when modeling large, non-linear systems where single parameters may affect the outcome in a non-linear fashion, for example if there is a U-shaped relationship between the values of a parameter and the output.

Probabilistic methods, in which both a range and distribution of parameter values are assigned, and which use sampling techniques such as Latin hypercube sampling (LHS) or Monte Carlo methods, have become a popular method to assign input vectors. Random samples are drawn without replacement from parameter distributions, and these samples are used as input vectors into the model. This method is powerful and efficient, especially for complex models with large numbers of parameters. A disadvantage of this method is that the distributional form for all of the parameters, which may not be known, must be specified. Additionally, this method assumes that each parameter is monotonically associated with the outcome, and that the parameters are independent.\(^3\)

Even though it is well known that biological and ecological systems have parameters that interact with each other, violating the assumption that parameter estimates are independent of each other, these assumptions often go unaddressed.\(^1\)

In this paper we apply a systematically performed sensitivity analysis of an age-structured, deterministic, compartmental transmission model. This study concentrates on uncertainty in parameter values rather than in model structure. A full-factorial analysis, where all possible parameter combinations are used, explores the entire \(k\)-dimensional parameter space. The input into a transmission model can be thought of as a vector of size \(k\), where \(k\) is the number of parameters. The number of possible vectors scales with
where $N$ is the number of distinct parameter values. This method can result in very large numbers of vectors that need to be inspected. An advantage of this method is that no assumptions about the distributions of parameter values, or of interactions between parameters, is needed.\textsuperscript{3,5}

We test the assumptions of LHS by determining if there are interactions between parameters, or if parameters have non-linear or non-monotonic relationships with the outcome. We define the parameters that correspond to the best and worst case scenarios based on the output of the full factorial sensitivity analysis, and compare these to the \textit{a priori} determined best and worst-case scenarios. Finally we assess how sensitivity analysis is outcome specific, parameters that appear important for one outcome may not affect the sensitivity of a related outcome.\textsuperscript{1} We demonstrate the value of this new approach to sensitivity analysis using a published deterministic method of varicella transmission.

\textbf{C. Methods}

1. Model structure and parameters

The model has been described previously. Briefly, it is a compartmental model where susceptible individuals can either become infected and permanently immune, successfully vaccinated and permanently immune, or vaccinated with an incomplete response, leading to infection (breakthrough case), and then permanently immune following recovery. Four parameters of interest for the sensitivity analysis are (1) the probability of a sub-optimal immune response to vaccination $\varphi$, which defines the proportion of vaccinees that move into a class of vaccinated but susceptible individuals;
(2) the susceptibility of vaccinated susceptibles relative to unvaccinated susceptibles, \( b \);
(3) the relative infectiousness of mild breakthrough cases, \( m \); and (4) the rate that
immunity to a first dose of vaccine wanes, \( \omega \). We study three different outcomes, the
cumulative number of cases in unvaccinated, cumulative number of breakthrough cases
in vaccinated individuals, and the peak incidence rate during a post-vaccination epidemic.

2. Selection of base model parameters

The base values for these parameters were determined from an extensive review
of the literature (table 6.1). The sub-optimal response rate \( \varphi \), sometimes referred to as the
failure rate, is an example of a parameter where different estimates for the mean are
found in the literature, introducing important uncertainty. In a large population based
serosurvey which used the fluorescent antibody membrane antigen (FAMA) test, the gold
standard for serologic testing for varicella antibodies, 76\% (\( \varphi = 0.24 \)) of vaccinated
children were seropositive 6-weeks after vaccination, with values ranging from 67\%
(\( \varphi = 0.33 \)) to 87\% (\( \varphi = 0.13 \)) depending on study site.\(^6\) Pre-licensure trials using the more
widely available but less specific glycoprotein ELISA indicated that >95\% (\( \varphi = 0.05 \)) of
vaccinees had positive varicella titers.\(^7\)–\(^{11}\) We therefore choose 0.25 as the base value for
\( \varphi \), with a range from 0.05 to 0.40

Values for the residual susceptibility of sub-optimal responders, \( b \), and the
relative infectiousness, \( m \), are primarily taken from household contact studies.\(^6\),\(^9\),\(^{12}\) In a
contact studies 77\% of FAMA negative, unvaccinated individuals and 46\% of FAMA
negative vaccinated individuals (the vaccinated susceptibles or sub-optimal responders)
became infected after contact with an unvaccinated case, corresponding to a residual
susceptibility $b$, of 0.59.\textsuperscript{6, 9, 13} We used a value of 0.6 for this parameter, and assigned a range of 0.30 to 0.90.

In a household contact study, breakthrough cases with mild disease (<50 lesions), were one-third as infectious as unvaccinated cases, and breakthrough cases with more severe disease were just as contagious as unvaccinated cases.\textsuperscript{12} Therefore we assign 0.33 to the baseline value for $m$, the relative infectiousness of mild breakthrough cases. Given that our estimate comes from a single study, a wide range of values (0.2 to 0.8) is used in the sensitivity analysis.

The value for parameter $\omega$, the waning rate of vaccine-induced immunity, is the most uncertain. Studies performed prior to the routine implementation of VZV vaccination, i.e. at times of high levels of wild VZV circulation in the community, found humoral persistence for at least 10 years\textsuperscript{9, 20-22}, in contrast several outbreak investigations, as well as data from an active surveillance site, documented increasing risk of breakthrough infection with increasing time since vaccination.\textsuperscript{23-28} We vary $\omega$ to give an average duration of full protection ($1/\omega$) from 1 year to lifelong, and choose 30 years for the base case.

3. Validation of base model parameters

To validate the choice of our base parameter values, the output from our base model is compared against data of the annual varicella incidence rates observed since 1995, when the United States implemented routine single-dose vaccination of infants.
4. Sensitivity analysis

Using a full factorial analysis, the model was run using every parameter combination possible. Each combination can be thought of as an input vector, with a single value for each parameter. To create vectors, the continuous distribution of parameters was reduced to a series of discrete values close enough together as to not miss any possible departures from linearity in the relationship between the parameter and output. For parameters distributed between 0 and 1, we added or subtracted 0.05 from the base value to the upper and lower values of the range.

First we perform univariate analysis, in which one parameter is varied from its base case while all other parameters are set to their base values, and display the results with spider plots. The relative change in the parameter from its base value is graphed against the relative change in the outcomes.

Parameter interactions are analyzed using box plots. The box plot displays all possible outcomes across different values of a single parameter. In the absence of interaction, the effect of any parameter on the outcome should be the same across the values of another parameter. With one parameter held at a single value, variability that is observed in the outcomes is thus due to variability and interaction with other parameters.

Next we assess the linearity of the relationship between each parameter and the outcome, independently of the other parameters, using the partial correlation coefficient. This statistic gives a value of -1 to 1, which represents complete inverse and positive linearity respectively, with 0 indicating a lack of a linear relationship. This is a useful technique, but it assumes independent relationships amongst the parameters, unless
interaction terms are explicitly specified. However, if there is no evidence of a linear relationship, this does not mean there is not some other type of relationship.\textsuperscript{29}

Then an analysis of extremes is undertaken. Typically, “best” and “worst” case scenarios are determined \textit{a priori}. In our case, the worst-case vector would include the following parameter values: $\varphi=0.4$, $b=0.9$, $m=0.8$, and $1/\omega=1$ year, while the best case would use the opposite extremes: $\varphi=0.05$, $b=0.3$, $m=0.2$, and $\omega=0$. Examining only these extremes implicitly assumes a monotonic relationship between parameter values and the outcome. If this assumption does not hold, due to non-linearity introduced by interaction between parameters, the true worst case could occur with vectors that would not \textit{a priori} be thought of as a worst case. The full factorial analysis is used to identify the vectors that rise to the actual best and worst case outcomes.

Finally we examined the possibility that different but related outcomes may differ in their sensitivity to parameters in the model using scatter plot that graph the relationship between different outcomes.

\textbf{D. Results}

The annual incidence rates, observed and model based, for the first 10 years of vaccination, before a second dose recommendation became standard, are shown in figure 6.1. The similarity between the observed annual incidence rates in the United States compared with the annual incidence rates generated with the base case model gives confidence for the future predictions of the model. As we did not use the observed incidence rate data to specify our parameter values, the match between observed data and
model output was not pre-determined, and thus qualitatively validates the base model parameters.

Figure 6.2 shows the range of total number of cases (outcomes) generated by runs of the model using different parameter values. A scatter plot (figure 6.3) compares the total number infected in the unvaccinated with the total number of breakthrough cases in vaccinated individuals. While there is a general positive association (correlation coefficient 0.73) between unvaccinated and breakthrough cumulative incidence, there are situations where high numbers of unvaccinated cases are associated with low numbers of breakthrough cases and vice versa.

The spider plots in figures 6.4a and 6.4b explore the sensitivity of the model outcomes to changes in the relative infectiousness, $m$, of mild breakthrough cases. In contrast to the positive linear relationship between $m$ and the total number of cases (figure 6.4a), we did not find a linear relationship between $m$ and the peak incidence rate (figure 6.4b), highlighting how the choice of the outcome of interest affects the results of the sensitivity analysis.

Table 6.3 gives the partial correlation coefficients for the associations of the parameters with the number of unvaccinated and breakthrough cases, under a condition of 75% second dose coverage, quantifying the strength of a linear relationship with these outcomes. Each of the four parameters displays moderate to strong linear relationships with number of breakthrough cases, but weak to moderate relationships with unvaccinated cases. These relationships quantify the linear effects that were seen in the spider plots.
Using box plots we found evidence of interaction between parameters. The model was highly sensitive to the values of $\omega$, and its sensitivity to all other parameters in the model was dependent upon the value of $\omega$ (figure 6.5). This is evidenced by the decreasing amount of variability in the outcome values as $1/\omega$ increases. For example, the model is insensitive to changes in $b$ when $\omega$ is low, but very sensitive to $b$ when $\omega$ is high (figure 6.6).

Based on the *a priori* determined best and worst-case scenarios, the predicted minimum and maximum number of cases during the course of the epidemic is 787,423 and 1,445,730 respectively for unvaccinated cases, and 47,810 and 5,975,570 respectively for breakthrough cases. The actual best and worst-case outcome, as predicted by the full-factorial sensitivity analysis was 787,423 and 1,590,960 respectively for unvaccinated cases, and 47,810 and 5,975,570 respectively for breakthrough cases (table 6.2). The actual parameter vector associated with the highest number of unvaccinated cases is: $\phi=0.05$, $b=0.4$, $m=0.8$, and $1/\omega=1$, rather than our *a priori* determined worst vector of: $\phi=0.40$, $b=0.90$, $m=0.80$, $1/\omega=1$ year. The *a priori* best-case vector: $\phi=0.05$, $b=0.30$, $m=0.20$, $1/\omega = 100$ years, matched the actual lowest number of unvaccinated and breakthrough cases. The *a priori* worst-case vector predicted the actual number of maximum breakthrough cases.

**E. Discussion**

This study developed a step-by-step method for examining the sensitivity of various model outputs to the input parameters using a full-factorial analysis. This method uses all possible parameter values and does not require knowledge of parameter
distributions or assumptions regarding monotonicity between parameters and outcomes or assumptions about interactions between parameters. Graphical methods convey an instant understanding of relationships between variables. Quantitative techniques confirm conclusions drawn from graphical data. It synthesizes methods from the economic and risk analysis literature and methods currently used by some infection modelers and thus presents the most cohesive strategy for uncertainty analysis in infectious disease modeling studies.

Using this approach, we were able to define the range of outcomes and their frequency, determine which parameters the model was most sensitive to, identify parameter interactions, assess the assumptions needed for LHS, and examine how to check that the \textit{a priori} best and worst-case scenario matches the actual lowest and highest number of cases.

Quantitative results for the linear relationship between the parameters and outcomes can be modeled using partial correlation coefficients (table 6.4). In our case, the partial correlation coefficients did not give much additional information over our graphical analysis.

We used box plots to convey information about the multivariate effects of parameters. In figure 6.6, there is a large increase in the variability of the total number of cases at high values of \( \omega \), and very little variability at lower values. This is evidence of interaction between \( \omega \) and one or more parameters in the model. Other parameters have different effects on the outcome at different values \( \omega \), indicating that the linear changes displayed in the spider plots may not hold when multiple parameters are varied from the
base value. Such an interaction is shown between $\omega$ and $b$ in figure 6.7. At low values of $\omega$, $b$ has very little effect, however as $\omega$ increases, the effect of $b$ becomes greater.

We also demonstrated that the choice of outcome that is analyzed could lead to different conclusions about the sensitivity of the model to certain parameters (figures 6.4a vs. 6.4b). For example, we found a positive linear relationship between $m$ and the number of infections in both vaccinated and unvaccinated individuals, but no linear relationship with the peak, post-vaccination incidence rates under a one-dose vaccine strategy. These disparate results seem to indicate some problem in the model. However, with increased infectiousness, breakthrough cases will give rise to a slow increase in breakthrough and unvaccinated incidence rates over time, resulting in fewer vaccinated and unvaccinated susceptibles available to trigger a large epidemic, providing a rational explanation for the seemingly counter-intuitive result.

Analysis of best and worst case scenarios are often helpful for communicating the results of models to policy makers and health economists. In this model, the $a$ priori choices for best and worst case parameter combinations produced numbers of infections that were very close to the best and worst-case outcomes as determined using the full-factorial analysis. This technique is valuable in that it demonstrates the presence or absence of a monotonic relationship between the parameters and the output, and displays whether it is appropriate to consider the $a$ priori identified best and worst case input vectors. The actual maximum number of unvaccinated cases arose from a different vector than our pre-determined worst-case vector. The source of the discrepancy is unclear. The parameters had stronger relationships with breakthrough infection. The exact match for
the observed and *a priori* expected number of cases for the other values is good evidence that the relationship between the parameters and the outcome is monotonic.

In conclusion, we were able to assess the relationships between the parameters and the outcomes of interest, and the relationships between parameters. The techniques we describe are easy to perform for relatively simple models with a limited number of parameters, and are amenable to intuitive interpretations based on graphical analysis. A full-factorial analysis does not rely on assumptions about the independence of parameters or the linearity of relationships between the parameters and the outcomes. In this sense this method is valuable and should be used before more complex probabilistic techniques such as LHS, which require more assumptions, are used. If it is shown that those assumptions are not violated, then probabilistic methods like LHS can be used with confidence. Using this technique we were also able to confirm the appropriateness of pre-determined best and worst-case scenarios, as well as demonstrate that important interactions existed between some parameters. This type of information is invaluable when assessing the validity and plausibility of transmission models, and makes the techniques of the sensitivity analysis clear.
Table 6.1. Base parameter values and range used in sensitivity analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Value</th>
<th>Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varphi$</td>
<td>0.25</td>
<td>0.05 – 0.4</td>
<td>Sub-Optimal Response Rate</td>
</tr>
<tr>
<td>$b$</td>
<td>0.6</td>
<td>0.3 – 0.9</td>
<td>Residual susceptibility of vaccinated susceptibles</td>
</tr>
<tr>
<td>$m$</td>
<td>0.33</td>
<td>0.2 – 0.8</td>
<td>Reduced infectiousness of mild breakthrough cases</td>
</tr>
<tr>
<td>$\omega$</td>
<td>0.0333/y (30 Year Duration)</td>
<td>1 to 100 year duration</td>
<td>Waning of vaccine induced immunity</td>
</tr>
</tbody>
</table>
Figure 6.1. Model Predicted Incidence (Dashed) and Observed Incidence (Solid) from 1994 to 2006. Both curves are scaled relative to their 1994 rates to facilitate comparisons.
Figure 6.2. Distribution of the Post-Vaccination Total Number of Cases
Figure 6.3. Relationship between number of unvaccinated cases and number of breakthrough cases.
Figure 6.4a

Relative Change in Total Number of Cases by Variation of Relative Infectiousness

Base Matrix No Second Dose

Relative Change in Total Number of Cases

Relative Change in Relative Infectiousness of Breakthrough Case

Breakthrough Cases
Unvaccinated Cases
Figure 6.4b.

Figure 6.4. Changes in the relative infectiousness of mild breakthrough cases are relative to its base value of 0.33, changes in the number of infections predicted are relative to the number of infections predicted with the base case model (6.4a), and changes in the peak post-vaccine incidence rates are relative to the base case peak incidence rate (6.4b).
Figure 6.5. Box plots summarizing the values for the total number of cases the duration of immunity in years, $1/\omega$. The box is the interquartile range, the line within the box is the median, the whiskers represent the range for most values, and the dots are outliers.
Figure 6.6. Relationship between number of cases and $b$, the residual susceptibility of sub-optimal responders over different levels of the waning rate, $\omega$. 

Breakthrough Infections as Residual Susceptibility Increases for Different Waning Rates

Base Matrix No Second Dose

![Graph showing the relationship between number of breakthrough cases and residual susceptibility of vaccinated susceptibles for different waning rates.](image-url)
Table 6.2. The model observed, and \textit{a priori} predicted maximum and minimum number of cases over the course of the outbreak. These simulations used a single dose vaccination strategy, and the base mixing matrix.

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Breakthrough</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Observed</td>
<td>1,590,960$^a$</td>
<td>787,423</td>
<td>5,975,570</td>
</tr>
<tr>
<td>\textit{a priori} predicted</td>
<td>1,445,730</td>
<td>787,423</td>
<td>5,975,570</td>
</tr>
</tbody>
</table>

$^a$ The parameter vector that produced the actual maximum number of cases in the unvaccinated was $\varphi=0.05$, $b=0.4$, $m=0.8$, and $1/\omega=1$.

Table 6.3. Partial correlation coefficients of the relationship of the parameters with the number infected with 75\% second dose coverage. Do one dose strategy! (check on IR vs. Cumulative)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unvaccinated</th>
<th>Breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varphi$</td>
<td>-0.0461</td>
<td>0.1382</td>
</tr>
<tr>
<td>$b$</td>
<td>0.0618</td>
<td>0.7032</td>
</tr>
<tr>
<td>$m$</td>
<td>0.1714</td>
<td>0.3017</td>
</tr>
<tr>
<td>$\omega$</td>
<td>-0.0845</td>
<td>0.6004</td>
</tr>
</tbody>
</table>
F. References


VII. Discussion and Conclusions

This dissertation is the first study to model the effect of a two-dose varicella vaccination regime. It expands on other models, not only by analyzing the effect of a second dose, but also in its more detailed structure and parameterization recognizing the most recent data. It provides information about the near term epidemiology of varicella, the long-term epidemiology, and the changes in the average ages of infection compared with the pre-vaccination, and one-dose vaccination eras.

Our model contributes to the understanding and expectations of the effect of both one and two dose vaccination for varicella in the following ways. 1) It uses the most specific estimate of the relative infectiousness of breakthrough cases, 2) it accounts for mild and severe breakthrough disease, and identifying their contribution to the epidemiology of varicella, 3) provides data-driven estimate for the residual susceptibility of vaccinees with a poor response to vaccination, 4) and recognizes the importance of a sub-optimal immune response as a driving force behind breakthrough infection, demonstrating how the vaccine effectiveness in the field is less than that predicted by pre-licensure efficacy studies, 5) it predicts that the United States is on the cusp of a large, post-vaccination resurgent epidemic, 6) it examines the impact of a two-dose vaccination regimen, 7) compares different age recommendations for giving the second dose of vaccine, and 8) provides the most thorough sensitivity analysis of a varicella model to date.
The sensitivity analysis determines the parameters with the most associated uncertainty. It also is the first study to present a systematic, step-by-step, qualitative technique for sensitivity analysis in infection modeling studies. It synthesizes methods from the economic and risk analysis literature, and methods currently used by some infection modelers, to present the most cohesive strategy for uncertainty analysis in modeling studies. Additionally, it incorporates simple methods that have not been used previously that can be used to address interactions between parameters, and to perform multivariate techniques. This strategy can stand alone, but it is also a valuable complementary method to other techniques.

A. Predicted epidemiology of varicella with different vaccination strategies

This study predicts that the resurgence in varicella incidence that began in 2003 will continue through 2015. The resurgence is a result of a buildup of susceptibles (S) protected by herd-immunity, as well as a buildup of partially susceptible vaccinated individuals (VS) as immunity either wanes or sub-optimal responses fail to be boosted as VZV circulation decreases. The magnitude of the resurgent peak is striking, with incidence rates approaching pre-vaccination rates. While this seems unrealistic at first glance, such peaks have been observed in post-vaccination measles epidemics as well as by other models of varicella transmission.\textsuperscript{1,2}

A two dose campaign will result in markedly lower incidence in the long term, even at modest (50%) second dose coverage rates, but will only minimally attenuate the size of the short-term resurgence. Concern over the timing of the second dose has been expressed due to the possibility of breakthrough infection occurring in pre-schoolers who
had a suboptimal response to the first dose of vaccine. However, our results indicate that giving the second dose at age 2 rather than at age 5 will result in a higher peak incidence in the next 15 years. Giving the second dose at 5 years may reduce the number of susceptibles at school entry, a time when mixing rates increase dramatically. In the long-term, receiving a second dose at 2 vs. 5 years makes little difference.

B. Severity of disease and age of infection

Over time, mild breakthrough varicella will predominate. Second dose coverage rates and age at vaccination does not appreciably alter the relative proportions of disease caused by natural, severe breakthrough, or mild breakthrough illness. The age distribution of varicella incidence will also change over time. This is a well-studied effect of any vaccination campaign. Currently, the highest incidence rates are seen between 10 and 14 years of age. As the average age of infection increases, a higher proportion of varicella infections will occur in the 15 to 25 year old age group, raising concern over the incidence of congenital varicella. Such perverse effects of vaccination are well known for rubella. However, as the majority of these cases will have mild breakthrough disease they may not suffer the severe adverse effects of natural infection seen in older age groups. It is also unknown how the fetus is affected by breakthrough varicella relative to natural disease.

C. New estimates for important parameters

The base values for the model parameters were determined from an extensive review of the literature. The sub-optimal response rate $\varphi$ is an example of a parameter
where different estimates for the mean are found in the literature, introducing important uncertainty.

We were able to utilize a recent review of studies where sub-optimal response to vaccination was confirmed with a lack of humoral response documented by the FAMA test. The attack rate in sub-optimal responders vs. the attack rate in completely susceptible, unvaccinated individuals provides the first use of a data-driven value for this parameter in a varicella modeling study.\textsuperscript{8, 12, 13}

Breakthrough cases were previously considered half as infectious as unvaccinated cases.\textsuperscript{2, 14, 15} However, this value is the average infectiousness of both mild and severe breakthrough cases. We used data from a household contagiousness study that determined the infectious of mild vs. severe breakthrough cases. This allowed us to specifically model mild and severe cases, and use a more specific estimate of $m$ for mild breakthrough cases alone. This is an advantage when considering the long-term epidemiology of varicella. Since mild cases are expected to increase relative to severe and natural cases, the use of a single measure of infectiousness for all breakthrough cases will be overestimate the true infectiousness of these cases.\textsuperscript{11}

The base case was validated qualitatively by comparing the observed varicella incidence from 1995 to 2005 with the model predicted incidence over the same time period. The model was not fit to those previously observed data, thus the similar patterns between our model and the data reflect the suitability of our parameter choices.
D. Insights from the sensitivity analysis

1. Parameter uncertainty

With univariate analysis, we were able to show that the cumulative incidence of breakthrough infection had a modest linear relationship with the sub-optimal response probability, $\varphi$, and incidence in the unvaccinated was almost completely insensitive to different values of $\varphi$. The residual susceptibility of vaccinated susceptibles, $b$, had a strong linear relationship with breakthrough infection, and a weaker linear relationship with infection in unvaccinated individuals. Increases in the infectiousness of breakthrough cases, $m$, was positively associated with both the number of breakthrough infections and infections in unvaccinated.

We show that the parameter with the greatest uncertainty, the waning rate of first dose immunity $\omega$, was also the parameter that the output of the model was most sensitive to. This combination of high uncertainty with high sensitivity indicates a great need for better estimates for $\omega$ in order to have precise results from transmission models.

We demonstrated how the choice of outcome that is analyzed could lead to different conclusions about the effect of some parameters. We showed a positive relationship between $m$ and the number of infections in both vaccinated and unvaccinated individuals. If the peak incidence rate during the post-vaccination resurgent epidemic were used as our outcome instead, our conclusion regarding $m$ would have been that increasing the infectiousness of breakthrough cases decreases the impact of the epidemic, and has an inverse relationship with total, unvaccinated, and breakthrough incidence rates. This could lead to opposite conclusions about the effect of this parameter. This highlighted
the importance of understanding what outcomes are measured when assessing the effect of a parameter, especially when values from one study are applied to another.

Multivariate analysis, visualized with box plots, revealed interactions between $\omega$ and all of the other parameters. The evidence for this is the change in the variation in outcome values across different values of $\omega$. When $\omega$ is held at a single value, the variation in outcome measures is related to the sensitivity of the model to other parameters in the model. There was relatively little variation in the value of the cumulative incidence at low values of $\omega$. At such values, the model is less sensitive to the values of other parameters in the model.

We showed direct evidence of the interaction of $\omega$ and $b$, the relative susceptibility of vaccinated susceptibles. At high values of $\omega$, there was no linear relationship between $b$ and the outcome. However, at higher values for $\omega$, the model outcome was quite sensitive to $b$. Similar interactions were found between $\omega$ and $\varphi$. Thus, the modest linear effect seen between $\varphi$ and the outcome in the univariate analysis was partially due to the strong effect of $\omega$; at high values for $\omega$, there was a stronger linear relationship between $\varphi$ and the total number of infections.

2. Sensitivity analysis methodology

We demonstrated the synergy associated with the comparison of multiple methods of sensitivity analysis vs. just choosing a single method. A highlight of our sensitivity analysis is its simplicity. Calculating precise statistics in the sensitivity analysis is not helpful if precise predictions were not a goal of the original transmission model. Thus,
graphical techniques, which can be qualitative in nature while conveying an instant understanding of parameter-outcome relationships is ideal.

We used a full-factorial analysis to identify every possible output of the transmission model with every possible combination of input parameter values.\textsuperscript{16-19} No assumptions are required about the distributional form that the values for each parameter follow, nor are there assumptions of independence among parameters. In fact, our method makes it easy to highlight when such interactions occur. The ability of the analysis to uncover interactions between parameters so simply, and without any statistical assumptions, is a highlight of our sensitivity and uncertainty analysis methods. Our method should be a first step before performing other types of sensitivity analysis. It can validate the appropriateness of the commonly used best and worst-case scenario analysis, and highlight violations in the assumptions that could make probabilistic techniques problematic.

\textbf{E. Strengths and Limitations}

1. Varicella transmission study

There are several limitations to this study. Uncertainty remains about parameter values, model structure and assumptions. The output of this model was highly sensitive to the duration of immunity, which is also the parameter estimated with the least amount of certainty. Another problem is our reliance on possibly non-precise estimates for contact and transmission rates within and between age groups, especially in the older age groups. Mixing matrices are determined by the pre-vaccination age specific changes in incidence. Since most older children and adults have experienced past infection, there is
very little change in the seroprevalence with age, and determination of their contact rates become problematic. To compound this problem, vaccination increases the average age of infection, increasing the epidemiologic importance of these older age groups. Thus there is uncertainty about the accuracy of the long-term predictions of this model, causing our confidence in the results to decrease as time increases.\textsuperscript{4, 5, 20, 21}

The timing of events that we predict may also lack some precision. We show a remarkable fit between our model predicted incidence and the actual observed incidence between 1995 and 2005, but the results from our model trails the observed outcomes in the early part of the simulation. This lag is likely due to the catch-up vaccination program that was aimed at older susceptible children and adults who had not had varicella, and who were not vaccinated as children. Our model did not include such catch-up vaccination, as the estimates for its coverage rates were not precisely estimated, and under different assumptions of catch-up rates, our simulations showed little difference in the long-term epidemiology of varicella.

Another limitation in our model is that we do not account for immigration into the system. Currently the United States is the only country with routine varicella vaccination. Thus imported cases will contribute to the maintenance of infection in the population, and possibly lead to outbreaks in certain situations.

In spite of these uncertainties, the general qualitative predictions of this model are likely to hold true, especially in the short-term. We have the benefit of more than 10 years of incidence data collected since universal vaccination started. This enabled us to validate our model in ways that earlier models were unable to do. The predictions of the model for the years 1995 to 2006 are highly consistent with what has been observed in
terms of incidence rates, seroprevalence, and an increasing burden in older age groups. Additionally, the consistency was only seen with the base matrix and matrix 1, which allowed us to eliminate several other estimates of contact patterns.

The purpose of this model was to highlight expected trends in varicella incidence over time. Thus we can confidently state that a continued resurgence of varicella incidence is expected for the next 10 to 15 years. This resurgence is attenuated by, but not prevented by the new two-dose strategy.

The public health impact of this resurgence is important. The varicella vaccine is already refused more than any other mandatory childhood vaccine in the United States.\textsuperscript{22} Outbreaks are expected to continue in highly vaccinated populations, especially in school and day-care settings. This will fuel the belief that the vaccine is not beneficial. However we show that the recommended two-dose strategy will be successful in eventually decreasing the incidence of varicella. Even low coverage levels for the second dose will greatly reduce the incidence of varicella.

2. Sensitivity Analysis

We were constrained in our sensitivity analysis by the number of parameter vectors we could analyze. Highly complex models with many parameters are not amenable to the full-factorial design. While multivariate analysis techniques such as the box plot will still reveal the presence of interactions between parameters, it gets difficult to figure out which specific parameters are interacting. Such complex models are better served by probabilistic methods of sensitivity analysis, as long as the assumptions of those methods hold.
The methods we describe allowed us to confidently assess the relationships between the parameters and the outcomes of interest, and the relationships between the parameters themselves. The full-factorial analysis design does not require assumptions about the relationships between parameters and the outcome, and between parameters like probabilistic methods do. The full-factorial design is thus ideal when there is uncertainty about the distributions for the values of the parameters, and when non-monotonic relationships may be present between the parameters and the outcome. This method tests the assumptions that underlie best and worst-case scenario analysis and probabilistic analysis methods. Our techniques will help transmission modelers perform more valid sensitivity analyses, however it will also give consumers of transmission models, for instance policy makers or economists, a simply tool to evaluate the results of the model.

F. Conclusions

This study predicts an important public health event looming as a post-honeymoon outbreak of varicella is expected. Other models also show an imminent resurgence, but our model, which has the most current parameter and model structure estimates, predicts that the outbreak will be large, under some scenarios approaching pre-vaccination incidence rates. We also show that the current two-dose recommendation will make little difference in the magnitude of the upcoming epidemic. However, we are the first to give estimates for the expected epidemiologic effects of the two-dose recommendation, and find that it is highly beneficial in the long term, even with generally low coverage as compared with first dose coverage.
Our sensitivity analysis confirms the robustness of our model to the changes in some parameter values, and predicts an epidemic under most scenarios. We were also able to identify the parameter the model was most sensitive to is the waning rate of first dose vaccination, \( \omega \). This happens to be the parameter that has the most uncertain estimates of its value. Thus the need for precise estimates of this parameter is highlighted. We are also the first to present a step-by-step method for qualitative, deterministic sensitivity analysis of transmission models. Since many transmission models are designed to give qualitative predictions, such a simple and qualitative analysis could be an important tool for future transmission modeling studies. Additionally, our methods are a helpful complement to methods that aim to be more quantitative, such as Latin Hypercube Sampling.
G. References


