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SYSTEM DYNAMICS MODELING STUDY OF THE POSSIBILITY OF ENDEMIC MEASLES IN THE STATE OF VIRGINIA

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Dedication

To my friends who are making an effort to balance personal freedoms with public health in their children's lives.

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Abstract

After an effective vaccine was widely available, measles incidence fell by 98%. Immunization programs and surveillance systems in the United States (US) are so successful there has been no endemic spread since 2000. The threat from measles lies in its high infectivity, an asymptomatic infectious state that lasts an average of four days and the decreasing popularity of vaccination. The lack of first-hand experience with the infection (due to immunization) has caused some to wonder if the vaccine is necessary. Herd immunity threshold is a measure of the fraction of immune individuals present in a population to keep disease reproduction rate below one. This threshold varies with population and disease characteristics. While below herd immunity threshold an index case could cause a small outbreak. In contrast, a gradual decrease in vaccination rates (or an increase in exemption rates) above herd immunity threshold coupled with an index case can lead to an epidemic. Endemic state is attained if the chain of infection persists for greater than one calendar year. Such a return to endemic state as has been seen in the United Kingdom. This study uses System Dynamics methodology to create a Measles Aging Chain Susceptible-Exposed-Infected-Recovered model (named MACSEIR) to analyze the vaccination conditions under which outbreaks and possibly endemic spread of measles could occur in the state of Virginia. The model utilizes a fictional population with demographic characteristics taken from US census data in addition to epidemiologic data from the Virginia Department of Health and Centers for Disease Prevention and Control (CDC). Outbreaks have been simulated under varying vaccination conditions. The study shows that outbreaks will occur in any vaccination rate conditions while greater than 4% of the population is susceptible to measles. While measles incidence is infrequent in the US, healthcare providers should still maintain a high level of suspicion in differential diagnosis because it is endemic in many countries that American families frequent. Though national vaccination rates are still high, some community rates are not; they should be the focus of prevention efforts.

CHAPTER 1: BACKGROUND

Prior to 1963 there were an estimated 4 million annual cases of measles in the United States. Since then a safe, effective vaccine has been available across the globe so measles infects and kills less people. Incidence fell by 98% after the vaccine was introduced (Centers for Disease Control and Prevention, 2012b; Strebel, Papania, & Halsey, 2004). The evidence of the success of this program is that the United States (US) has not had an endemic case of measles since 2000 (Centers for Disease Control and Prevention, 2012a)[1]. The resounding success of the measles vaccine program is evidenced by a seeming absence of a measles threat. In response people have become complacent concerning the risk of measles infection; seeing more vaccine adverse events than actual measles infections, there is a likely growing population of unvaccinated people who have exercised their right to refuse vaccination and by so doing put other members of the public at risk (Bedford, 2011; Centers for Disease Control and Prevention, 2011b, 2012a; Henderson, Dunston, Fedson, & et al., 1991).

There were 222 reported measles cases in the US in 2011 compared to a median of 60 reported cases per annum between 2001 and 2010. Dr. Schuchat, the Director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention (CDC) cited several probable reasons for this increase, and warned against the assumption that there is no threat from this disease (Centers for Disease Control and Prevention, 2012a). There were seven measles cases in Virginia during 2011. As is common with the vast majority of cases occurring since elimination of endemic measles in the US, the index cases (four) were imported (Centers for Disease Control and Prevention, 2012c). In light of this a question arises; is it possible for a sustained chain of measles infections in Virginia? Whatever

[1] The date of measles elimination in the US is either 1993 (Gershon, 2010; Strebel et al., 2004), 1994 (Rota, Rota, Redd, Papania, & Bellini, 2004), 2000 (Centers for Disease Control and Prevention, 2012a) or 2002 (Centers for Disease Control and Prevention, 2012b).

the answer is, it would be prudent to have an idea of the conditions under which this might be possible, to assess the effect of vaccine exemptions on measles clusters in the state. The goal of this thesis is to use available epidemiologic and immunization data to populate an aging chain-disease system dynamics simulation model to explore these questions under different vaccination rate trend assumptions. This chapter gives an overview of measles.

Epidemiological Study of Measles

Public health significance

Measles is a highly contagious disease recorded in human history dating back to the 7th century. It was distinguished from smallpox in the 10th century, and was considered the worse of the two. After variolation proved effective against smallpox, and most physicians considered the two diseases related, it was unsuccessfully attempted with measles. Enders and Peebles isolated the virus in human and monkey kidney cultures in 1961, and after successful transfer to egg embryos work began on a vaccine that was licensed in 1963 (Strebel et al., 2004). This vaccine has enabled some control over a widespread, once devastating disease. Global vaccination programs, improved healthcare, nutrition and education have drastically reduced measles incidence and deaths. In 2008, 164,000 children died of measles worldwide compared to 2.6 million in 1980 (Seward & Orenstein, 2012). The success of vaccine programs in the US has led to the elimination of endemic measles (Harpaz, Papania, McCauley, & Redd, 2004; Rota et al., 2004; Seward & Orenstein, 2012). In spite of such resounding successes, measles is still a significant infection, and has the highest mortality among vaccine preventable illnesses (M. B. Oldstone, 2000; Strebel et al., 2004). Measles is a public health concern because:

It is highly communicable – by airborne transmission infectious particles, once aerosolized can be suspended in air for up to two hours and patients are contagious for an average of four days without symptoms (Centers for Disease Control and Prevention, 2012b; Heffernan &

Keeling, 2008). These characteristics increase the chance that the measles virus (MV) will infect susceptible individuals, even though they may be few and far between (Centers for Disease Control and Prevention, 2012a; Strebel et al., 2004).

- It is easily spread in our highly mobile society - frequent and rapid global travel coupled with pockets of unvaccinated people are increasing measles incidence in the US as the disease is imported from endemic regions and spread to non-vaccinated contacts (Centers for Disease Control and Prevention, 2012a; Harpaz et al., 2004; Rota et al., 2004).

- Immunization rates are decreasing – religious and philosophical vaccine exemptions are legal in the US and parents are taking them for fear of vaccine related conditions (Centers for Disease Control and Prevention, 2012a; Remley, 2011; Schwartz, 2012), state and medical community interference with parental autonomy (Schwartz, 2012), and at times because it is more convenient (Britten, 2009). If exempt children never get vaccinated or infected over time the population at risk will include more and more adults who tend to experience more severe infections than children. This could result in widespread atypical measles.

- MV infection suppresses the immune system – MV patients are at risk of opportunistic infections and resurgence of dormant infections such as latent tuberculosis (TB) or varicella zoster virus infections (shingles). An endemic measles state would likely increase incidence of secondary infections like pneumonia, encephalitis and the aforementioned TB to name a few (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004).

- HIV and other immune compromising conditions complicate vaccination of children – patients with immune compromised conditions whose onset was before measles

vaccination lose immunity and are at higher risk for atypical infection, misdiagnosis and complications (Centers for Disease Control and Prevention, 2012a; Helfand, Moss, Harpaz, Scott, & Cutts, 2005; Scott, Moss, Gilani, & Low, 2011).

- Outbreak control is expensive – estimates of outbreak costs range from $18, 000 (one case) to $400 million (multiple year outbreak) (Coleman et al., 2012; Takahashi, Ohkusa, & Kim, 2011).

Population at risk

Measles is a childhood disease affecting all children across the globe. It gains the designation 'childhood disease' because by 12-15 years of age, 90% of children in a pre-vaccine population would have had measles, with the highest incidence rate in the 5-9 year old population (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004). In 2011, the median measles patient was 14 years old and 61% of patients were younger than 19 years (McLean, 2012). Recovered patients gain lifelong resistance to subsequent infection, but uninfected and unvaccinated persons are at lifelong risk. In addition, adult onset measles is more severe and has higher mortality rate (Strebel et al., 2004).

Immune compromised persons are at higher risk of measles infection. Studies show persistence of humoral immunity in patients who were immunized first and became immune compromised later. Cell mediated immune compromise however, places patients at risk despite vaccination. This includes post-transplant, congenital immune compromised patients and those compromised secondary to cancer or high dose steroids (Gershon, 2010; Strebel et al., 2004).

Etiology

MV is a spherical, paramyxovirus, of the genus *Morbillivirus.* It is an enveloped, single stranded, negative sense RNA virus. Its genome codes for at least eight structural proteins. There are two types of MV, wild MV and vaccine (Edmonston strain) type MV distinguishable by

genetic sequencing (Centers for Disease Control and Prevention, 2012b; Gershon, 2010; Strebel et al., 2004). There are altogether 22 measles genotypes in seven classes which have similar antigens causing the same infection (Gershon, 2010; Harpaz et al., 2004; Rota et al., 2004). MV has two primary antigens in its envelope proteins, an H-glycoprotein which attaches to host cells by hemagglutination; and an F-glycoprotein which lyses cells and thus propagates the virus after infection (Centers for Disease Control and Prevention, 2012b; Gershon, 2010).

Transmission

MV is sensitive to strong light, drying, acid and proteolytic enzymes. It is however, capable of being suspended in air droplets for up to two hours, especially in relatively dry air. This accounts for its airborne or droplet transmission and the majority of outbreaks occurring in winter months in endemic regions (Centers for Disease Control and Prevention, 2012b; Gershon, 2010; Strebel et al., 2004). Before the MV vaccine and in measles endemic regions, there are 3-4 month long epidemics every 2-5 years in addition to annual, seasonal epidemics (Gershon, 2010; Moss & Griffin, 2012; World Health Organization, 2009), with attack rates as high as 99% (M. Oldstone, 2000). Once infected, a patient is infectious for about seven days. Of those, three to five days are asymptomatic (Heffernan & Keeling, 2008). This is a problem because during that time people go about their daily activities and spread the disease. This partly accounts for measles' rampant spread, the difficulty of outbreak control and surveillance in under vaccinated populations.

Vaccine and lab MV strains are pathogenic in primates because they carry the CD46 complement regulatory protein which is a primary MV receptor (Gershon, 2010), but it has no animal reservoir because wild MV cannot use CD46 (Noyce & Richardson, 2012). Pathogenesis studies are carried out in monkeys because they have been shown to suffer a mild infection from the vaccine and lab stains (Centers for Disease Control and Prevention, 2012b; Gershon, 2010;

Strebel et al., 2004). The absence of an animal reservoir makes it a good candidate for global eradication.

Natural History and Pathophysiology

After MV is inhaled, it infects the respiratory epithelial cells. The epithelial cell receptor is Nectin 4/Poliovirus receptor-like protein 4 (PVRL4), a protein that is part of the adherens junction structure (Gershon, 2010; Heffernan & Keeling, 2008; Noyce & Richardson, 2012). Its H-glycoprotein attaches the virus to CD46 complement regulating protein (only in vaccine and lab strains), and/or CD150 signaling lymph activation molecules (SLAMs) on regional lymphoid cells in the upper respiratory tract. SLAMs are thought to activate lymphocytes and control cytokine release (Gershon, 2010; Strebel et al., 2004) thus the virus begins by suppressing the host immune system response. MV replicates for 2-3 days then F-glycoprotein lyses respiratory epithelial and lymphoid cells; this is the primary viremia (Centers for Disease Control and Prevention, 2012b; Heffernan & Keeling, 2008; Strebel et al., 2004). There are particularly high viral loads in monocytes, B and T lymphocytes (Heffernan & Keeling, 2008). When these cells are lysed, they can be anywhere in the body, so it becomes a systemic infection. The virus attaches and replicates in distal reticuloendothelial sites, again favoring mononuclear white blood cells (Centers for Disease Control and Prevention, 2012b; Heffernan & Keeling, 2008) which usually make up about 50% of white blood cells.

There is a second viremia 5-7 days post-infection which infects the thymus, spleen, lymph nodes, liver, skin, conjunctiva, intestines, bladder and lungs. The virus continues to replicate in the epithelial cells of these organs (Centers for Disease Control and Prevention, 2012b; Gershon, 2010; Heffernan & Keeling, 2008). The spread of the virus both activates and cripples the immune system making the patient susceptible to opportunistic infections and the resurgence of dormant infections like tuberculosis thus increasing the risk of complications (M. B. Oldstone, 2000; Strebel et al., 2004).

About three days after the second viremia, infectiousness begins as viral particles are shed from the respiratory epithelium. This marks the earliest point symptoms could occur, and the end of the 10-14 day incubation period (Figure 1). The prodrome is marked by malaise, anorexia, fever that increases in a stepwise fashion going as high as 103° F, respiratory symptoms (cough, coryza), and Koplik's spots (Centers for Disease Control and Prevention, 2012b). The patient is most infectious during this period when the viral count peaks (Figure 1). The measles rash appears between days 14 and 17. Some authors (Gershon, 2010) say the rash coincides with the end of infectiousness, others (Centers for Disease Control and Prevention, 2012b; Heffernan & Keeling, 2008) say the patient may be infectious for another 2-4 days after rash onset. The rash itself is composed of red, flat, confluent specks that look like grains of sand on the patient's skin. The rash covers the skin, starting at the hairline progressing downwards to the toes (Gershon, 2010). Koplik's spots are blue-grey specks on a red base occurring on the patient's oral mucosa and are pathognomic for measles (Centers for Disease Control and Prevention, 2012b; Gershon, 2010). Cellular hypersensitivity response immune complexes and giant MV infected skin cells form the characteristic spots and the rash (Gershon, 2010; Heffernan & Keeling, 2008). Patients with deficient cellular immunity do not develop the rash. About five days after rash onset, it disappears as it came, starting at the face going down to the toes; the symptoms subside about two days after rash onset (Gershon, 2010).

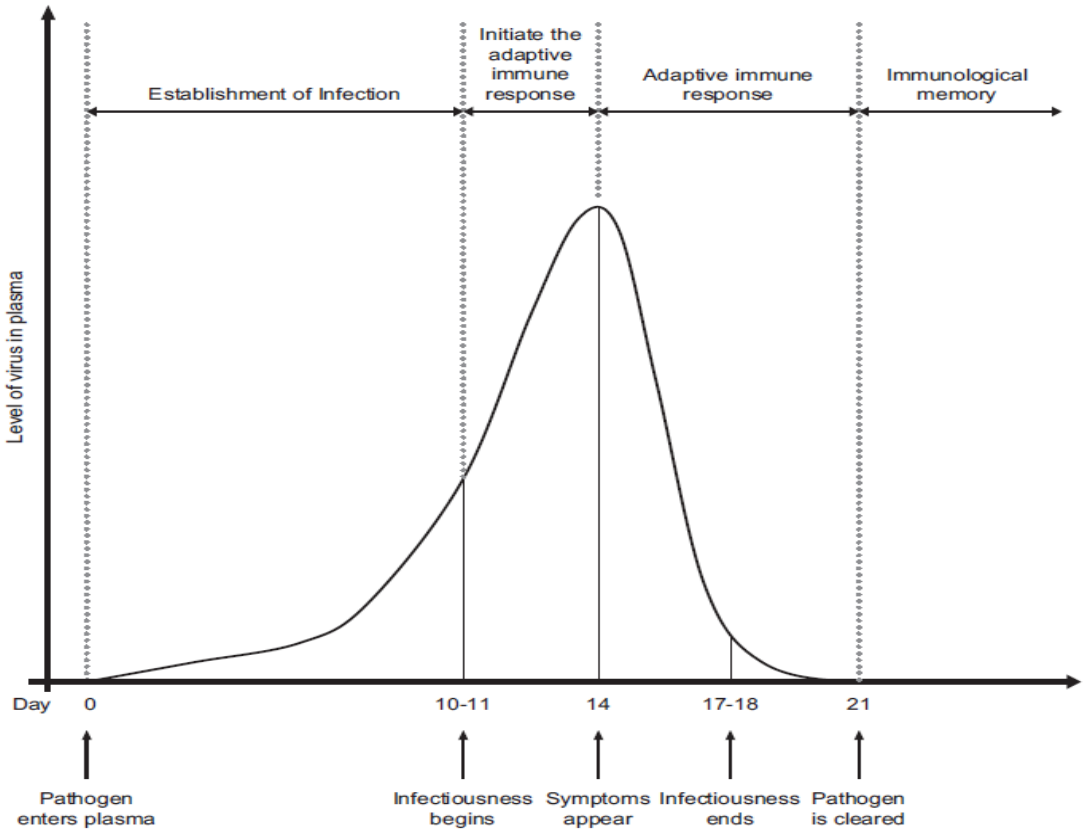


Figure 1: Immune response and measles pathogenesis. This figure shows the progression of viral load and corresponding immune response to a measles infection (Centers for Disease Control and Prevention, 2012b; Heffernan & Keeling, 2008).

Treatment

There is no treatment for measles; combinations of interferon, ribavirin and immunoglobulin (IG) with high doses of Vitamin A have been shown to reduce morbidity and mortality by aiding the body's immune response (Strebel et al., 2004). Vitamin A deficiency was associated (by observation alone) with increased mortality; in response the World Health Organization (WHO) recommended vitamin supplement with treatment (and vaccine) especially in malnourished patients (Benn, 2012). Other treatments in addition to this are in response to complications. Unless there is a secondary bacterial infection antibiotics are neither useful nor necessary (Strebel et al., 2004).

Complications

Immune response to measles concurrently hampers response to other pathogens for weeks and even months after recovery. This makes patients highly susceptible to new and latent opportunistic infections (Moss & Griffin, 2012). Thirty to forty percent of all measles cases have complications (Centers for Disease Control and Prevention, 2012b; Moss & Griffin, 2012) due to the systemic nature of the infection and depression of the immune system. Complications are more common among children under five years of age and adults over 20 years of age (Centers for Disease Control and Prevention, 2012b). The most frequently reported complications are diarrhea, otitis media, pneumonia, encephalitis, seizures and death. Pneumonia can be due to viral or bacterial super-infection, a state in which a patient has two or more infectious processes concurrently. The death rate is about 0.2%, most of those from secondary pneumonia (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004).

In addition to encephalitis as a secondary infection, sub-acute sclerosing panencephalitis (SSPE) is a post-infection complication that can occur. It is a chronic degenerative, probably autoimmune, fatal neurologic illness that occurs in some patients 6-15 years after recovery from a MV infection occurring after two years of age. Incidence of SSPE has decreased since the vaccine; it is clearly not a response to the vaccine (Gershon, 2010; Gutierrez, Issacson, & Koppel, 2010). SSPE is thought to be caused by a persistent infection by a mutant MV to which the body responds as it would to wild-type measles causing an increase in MV antibody titers which do little against the actual causative agent. Pathogenesis is thought to be a combination of host-factors and viral replication processes (Gershon, 2010). SSPE is uncommon in the US, but it is however higher in the rest of the world especially Asia, and is being seen more frequently in the US after adoption of Asian children (Gutierrez et al., 2010).

Surveillance

Case Definition

A case of measles is defined by the appearance of symptoms in conjunction with a laboratory diagnosis. Due to the highly contagious nature of the disease, any suspected cases are going to be treated as positive until proven otherwise. A measles case is defined either clinically or by laboratory methods; so a laboratory confirmed case does not have to meet the clinical case definition (Guris et al., 2004).

1. Clinical case definition
    a. Any person in whom a clinician suspects measles OR
    b. Any person with
        i. Fever (earliest symptom), and
        ii. generalized maculopapular (i.e. non-vesicular) rash and pathognomic Koplik's spots (beginning after two to six of preceding symptoms) for ≥ 3 days, and
        iii. any one of cough, coryza (i.e. runny nose) or conjunctivitis (i.e. red eyes) (concurrent with fever)
2. Laboratory defined case
    a. A positive anti-measles virus IgM by enzyme-linked immunoassay (preferred) OR,
    b. A fourfold increase in IgG titer shown by two serum collection, the first as soon as possible after rash onset, and the second 10-30 days later, both tested at the same time with the same testing methodology AND/OR

c. A positive MV culture collected within three days of rash onset (six to ten days after infection) when MV is most likely to be isolated by culture from urine, nasopharyngeal or throat swabs and/or whole heparinized blood(Centers for Disease Control and Prevention, 2012b; Gershon, 2010; Guris et al., 2004; World Health Organization, 2009)

US Surveillance System

Measles surveillance in the US is carried out through a passive reporting, active investigation system. The focus is to quickly identify measles cases, promptly control and identify risk factors (Guris et al., 2004). The surveillance case definition is similar to the clinical, but has three classes;

1. Suspected: febrile illness and rash,
2. Probable: meets clinical case definition, questionable or no laboratory confirmation and not epidemiologically linked to a confirmed case,
3. Confirmed: either laboratory confirmed or meets clinical case definition and is epidemiologically linked to a confirmed case.

In keeping with a passive system, follow-up is initiated by a case reported to a local health department when a patient seeks medical aid. Reports can come from concerned parents, patients, school or daycare employees and (rarely) airline attendants and immigration officers (Guris et al., 2004). Figure 2 shows the reporting processes in response to a suspected measles case and give an idea of the labor intensity (and expense) of the investigation. The Virginia Department of Health (VDH) has deemed measles an emergent reportable disease by laboratories and healthcare providers which has to be reported within 24 hours by the most rapid means possible (Guris et al., 2004).

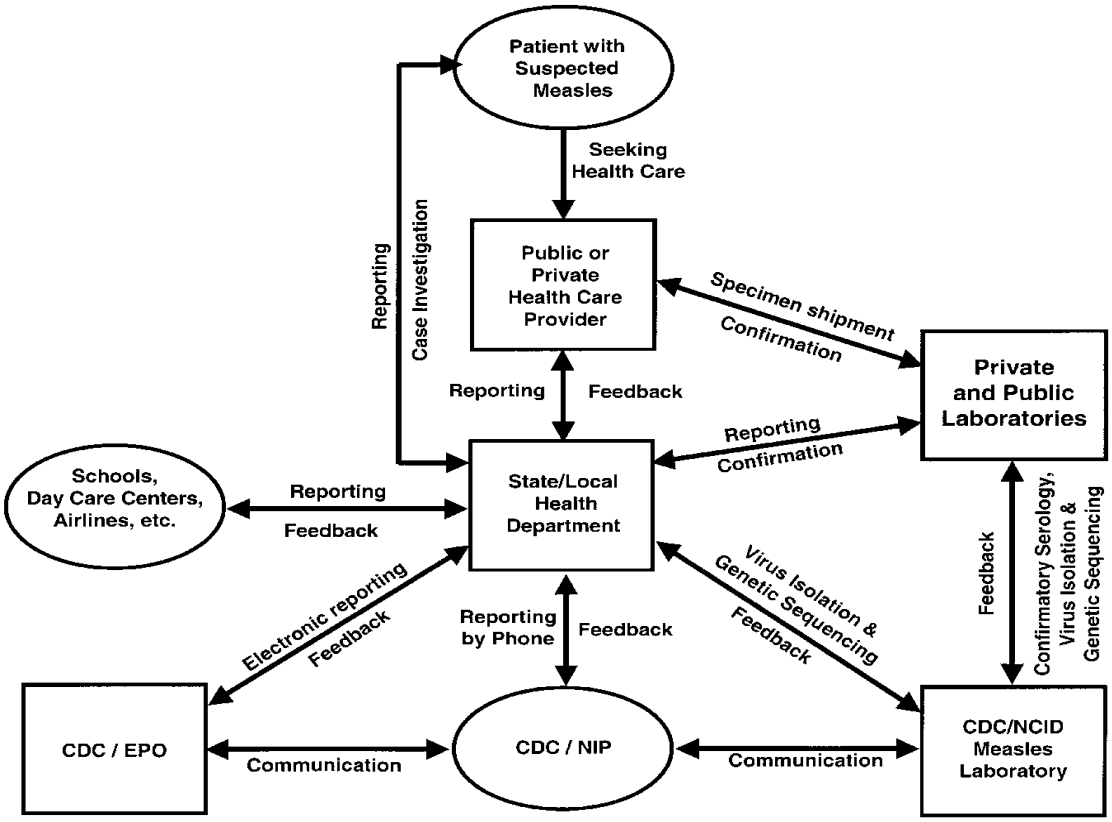


Figure 2: Measles surveillance in the US. This illustrates the pathways and agencies involved in measles surveillance. CDC, Centers for Disease Control and Prevention; EPO, Expanded Program on Immunization; NCID, National Center for Infectious Diseases (Guris, Harpaz, Redd, Smith, & Papania, 2004).

The Central Shenandoah health district requires that such reports be given to an actual person by telephone (not voicemail) and the paperwork faxed during regular operational hours. The follow-up is standardized by use of a case investigation flowchart (Appendix A) and case investigation worksheets.

MV cultures are routinely sent to the Measles Virus Laboratory at the CDC for gene typing. Genetic testing verifies the elimination of endemic measles in the US. The working definition for endemic measles is a single chain of infection lasting at least one calendar year. (Centers for Disease Control and Prevention, 2012d; Gershon, 2010; Harpaz et al., 2004). A few genotypes in an outbreak indicate an endemic source, whereas imported infections show many

different genotypes as has been seen in US outbreaks since elimination of endemic measles (Rota et al., 2004)

Outbreak response

Outbreak response is coordinated by the local health department; they conduct follow up investigations with all contacts of the index case(s) and verify vaccination documentation using the case investigation flowchart (Appendix A) and case investigation worksheets. If there is a large enough exposure, they will educate the communities involved on measles infection, signs and symptoms. Messages are sent by electronic-mail and fax to local healthcare providers. All unvaccinated persons and those with unverified vaccination state should receive vaccine (most effective within 72 hours of exposure) or IG (most effective within 6 days of exposure) from their health care provider or the health department. Contacts with whom vaccine is contraindicated (e.g. pregnant women, infants younger than 12 months, AIDS patients and other immune compromised people) will receive IG. IG should not be used to control outbreaks because it provides temporary protection and does not prevent subsequent outbreaks. (Centers for Disease Control and Prevention, 2012b; Guris et al., 2004; Strebel et al., 2004; World Health Organization, 2009).

Measles Vaccine

The current vaccine strain used in the US is the Edmonston B derived Moraten strain. The vaccine is distributed as a freeze dried powder to be reconstituted with sterile water. Inactive ingredients include human albumin, neomycin, sorbitol and gelatin. It is available as a Measles-Mumps-Rubella (MMR) or a Measles-Rubella (MR VAX) combination vaccine (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004).

Immune response to the measles vaccine is similar to that of natural infection. There is an initial spike in IgA, IgM and IgG. Only the IgG antibody persists. Titers decrease over time, but

increase on challenge by either wild-type or vaccine MV (Strebel et al., 2004). Serologic testing in studies and current epidemiological data shows that though antibody titers fall and are lower post-vaccination compared to natural infection, they are still high enough to provide the necessary, lifelong protection (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004).

Maternal antibodies inactivate vaccine virus before it has a chance to cause an immune response so the vaccination age is a balance between the earliest age for seroconversion and the age of greatest risk of infection. These values change with geographic location, mother's immune status and transplacental transfer efficiency. The age of immunization in the US has changed over the years from as early as nine months to as late as 15 months of age. The current recommendation is between 12 and 15 months of age for children born to immunocompetent mothers. Children born to HIV infected mothers should be vaccinated before 12 months of age. Adult onset HIV patients do not lose their measles immunity, but this is not the case with children. If measles vaccine or infection occurs after HIV infection their immunity wanes and they do not always respond well to repeat vaccination (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004). The WHO recommendation is 9 months of age in developing countries due to higher risk of infection (Strebel et al., 2004) which should be considered when traveling with infants.

Primary vaccine failure with one dose occurs in 2-5% of recipients. This is usually due to passive antibody persistence (if infants) or vaccine handled inappropriately (Centers for Disease Control and Prevention, 2012b). Newer vaccines are more stable at a wider range of temperatures (Strebel et al., 2004).

Primary vaccine failure rate for two doses is about 1%; this is part of the reasoning behind the two dose recommendation – this way 99% of vaccinated people are immune. (Centers

for Disease Control and Prevention, 2012b). The other is because anamnestic response increases the baseline antibody titer. Retrospective review of a spike in measles cases between 1989 and 1991 showed highest incidence in children younger than five years old and many of them younger than the recommended age (12 to 15 months) to receive MMR. These infants were also born to mothers who were immunized as children, it was postulated they did not have enough maternal antibody and so the two dose MMR vaccine program was initiated (Centers for Disease Control and Prevention, 2012b).

US Vaccination rates

Figure 3 shows the US measles vaccination rates beginning in 1967. There are no data available between 1985 and 1991 because no surveys were carried out by the CDC (Black, 2012). According to the chart, the 2010 rate is 91.5%. Though these are high rates, they are coupled with increasing incidence of measles at a population level and at community levels (Seward & Orenstein, 2012). Herd immunity is protection non-vaccinated people gain from being part of a highly vaccinated society. Herd immunity reduces incidence risk hence the risk of an otherwise susceptible person acquiring an infection. The herd immunity threshold (HIT) for measles is 83-

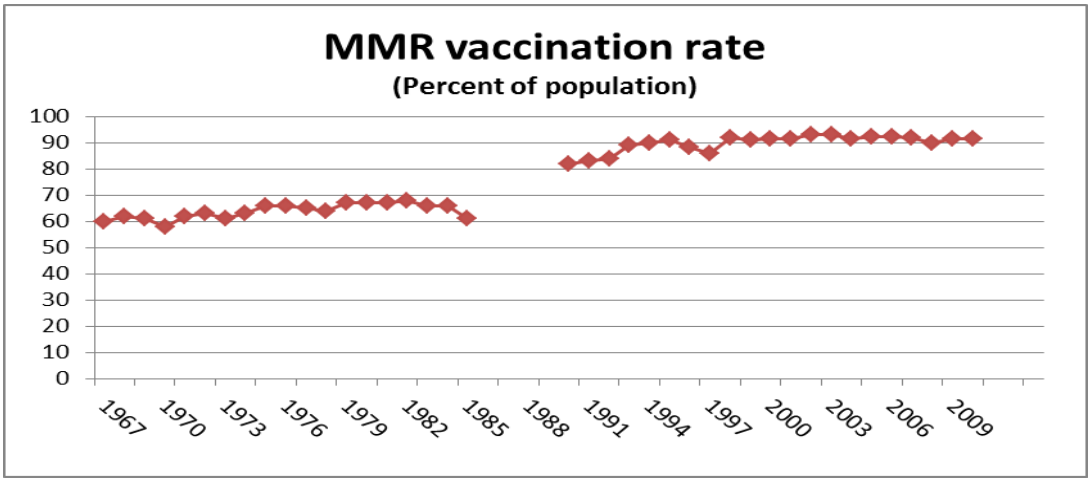


Figure 3: US vaccination trends. Chart shows two-dose MMR coverage from 1967 to 2010. Data from National Health Interview Survey (NHIS) and US Immunization Survey (USIS) (Black, 2012).

94% (Vynnycky & White, 2010). Herd immunity threshold is used to provide a goal for immunization programs. It is an estimate at best, for example the United Kingdom (UK) has a vaccination rate of 89% but is in an endemic measles state (Bedford, 2011; Vynnycky & White, 2010).

Vaccine Safety

The safety of vaccines has been question by skeptics since they were first used. A cartoon published in 1802 by James Gillray showed cows erupting from Edward Jenner's patients. Historically medical science has been sufficiently wrong about drugs and their side-effects to warrant skepticism; thalidomide and Vioxx are two of many examples. In addition, new research continually tests and at times changes 'current' knowledge; scientists consider this improvement while patients would lose confidence. Vaccine safety is especially sensitive because the majority of vaccine adverse events occur in healthy infants. In comparison, the side effects of other drugs (such as antibiotic associated diarrhea) occur in already sick people (Chen, 1999). Demonstrated, biologically plausible vaccine adverse events include malaise, fever, rash, thrombocytopenia, anaphylaxis, encephalopathy, residual seizures and Guillain-Barre syndrome (Bedford, 2011; Institute of Medicine, 1993; Strebel et al., 2004).

Figure 4 shows a plot of the variables in play over the lifetime of an immunization program. Of key importance to this discussion are stages 3 and 4 where confidence in vaccine decreases due to an increase in adverse events relative to disease incidence.

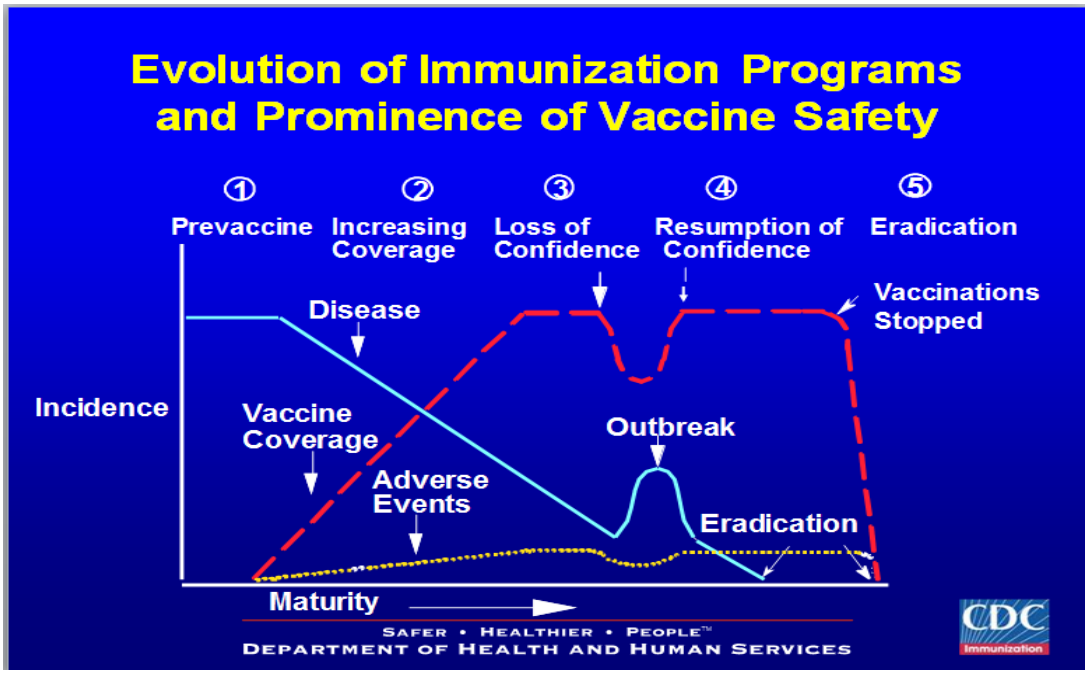


Figure 4: Evolution of Immunization Programs and Prominence of Vaccine Safety. Representation of the changes in vaccine coverage relative to adverse event rate and vaccine preventable disease rate (Centers for Disease Control and Prevention, 2003a; Chen, 1999).

Thompson and Duintjer Tebbensc proposed a negative feedback loop describing wavering commitment to vaccine programs due to cost (2008). The same mechanism can be applied to the outbreak between stages 3 and 4 in Figure 4 and is depicted in Figure 5. Blue arrows (causal links) connect a variable that causes a change in another. A plus sign at the arrowhead shows a change in the same direction, either an increase causes another increase or a decrease causes a decrease. A minus sign indicates an inverse relationship, an increase causing a decrease and vice versa. In Figure 5 an increase in measles incidence increases risk of infection to all susceptible individuals. As people around them are infected, the non-vaccinated for fear of the adverse effects of vaccine will likely tend to be more willing to vaccinate if they weight the likelihood of infection against the likelihood of a vaccine reaction. The ensuing increase in willingness to vaccinate increased the vaccinated fraction of the population which reduces the disease incidence. This is an example of a balancing feedback loop. Figure 5 describes what is currently occurring in the US and UK. Stratton et al said in an Institute of Medicine (IOM)

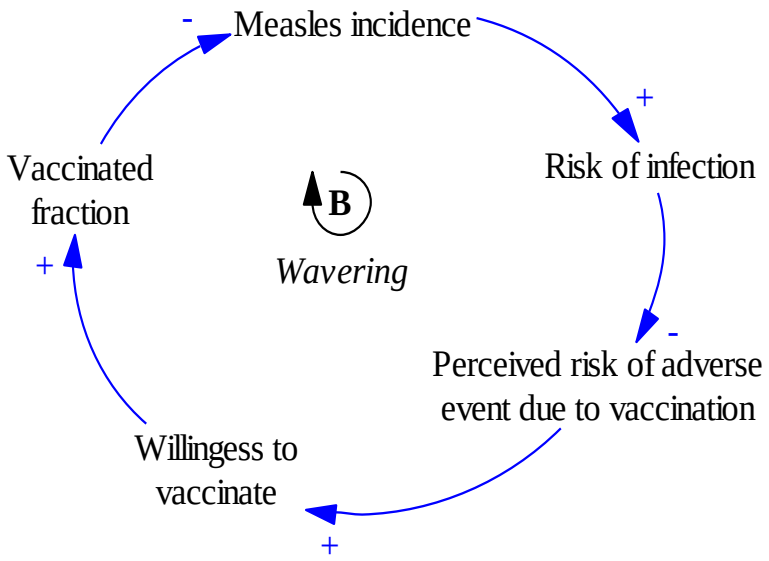


Figure 5: A balancing feedback loop describing changing perception of vaccination risk with disease incidence and the subsequent effect on vaccination rate. Adapted from Thompson and Duintjer Tebbens (2008)

report, "Ironically, the successes of vaccine coverage in the US have made it more diffcult for the public to weigh the benefits and complications of vaccines because the now-controlled dieases and their often-serious risks are no longer familiar" (2001). The lack of proximity to measles infection has led some parents to focus instead on adverse events (Schwartz, 2012; Shim, Grefenstette, Albert, Cakouros, & Burke, 2012) and refuse vaccination for their children.

The Lancet published a paper in 1998 in which Andrew Wakefield reported 8 children (out of a group of 12) showed autism symptoms (developmental regression) and gastrointestinal problems beginning after receipt of MMR (Brown et al., 2012; Institute of Medicine, 2001; A. J. Wakefield et al., 1998; A.J. Wakefield, 1998). Though the paper states the need for more evidence, it caused wide reaching MMR mis-trust. It received a lot of media and celebrity attention highlighting the danger of MMR vaccine. After further investigation and an absence of reproducible evidence the paper was retracted in 2011, an incident that was not as publicized. The paper is still the starting point of many anti-vaccine debates. Many different studies have been conducted showing no link between MMR and autism (Brown et al., 2012; Fitzpatrick, 2004; Hornig et al., 2008; Institute of Medicine, 2001). Of note is a paper by Gerber and Offit (2009) which reviews thirteen published studies with different designs, publication dates and locations.

All the studies do not support an association between MMR and austism. They go on to tackle two other vaccine-linked autism hypotheses: thimerosal and too many vaccines(Yapko, 2003). Gerber and Offit (2009) also show no association based on seven studies. The UK Department of Health, WHO, the American Academy of Pediatrics and IOM seperately released statements in 2001 all saying there were no data to support Wakefield's claims (Institute of Medicine, 2001). Observed increase in autism incidence could be due to increasing awareness and a diagnostic definition that casts a wider net than before (Gerber & Offit, 2009; Yapko, 2003).

The 1993 and 2001 Institute of Medicine vaccine safety reports have concluded the following:

- There still is a limited understanding of the pathophysiology of vaccine adverse events
- Adverse events data are usually sourced from incomplete case reports and cannot always be verified
- There is limited follow up (by epidemiologic studies)
- Surveillance systems(Appendix B) are not able to show evidence of causation because there are few experimental studies relative to all studies published on the topic; many adverse events have demonstrated biologic plausibility but there is indeterminate or no data from controlled studies to test hypotheses
- There are no incidence rates calculable from adverse events reports, the best metric is a reporting rate to which there is no comparison against events due to chance

A summary of the findings of the Institute of Medicine's 1993 report on measles containing vaccines, *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Casuality* is provided in Appendix C. The decision to vaccinate is a balance between risk of infection, risk of adverse event and benefits of vaccine. Once vaccinated it is prudent for parents

and physicians to monitor patients specifically for adverse events, with the understanding that not all events following vaccination are caused by the vaccine. This practice would make better data available in adverse event surveillance systems so better decisions can be made and safer vaccines created.

Opposition to vaccination is no longer a local, grassroots movement. Ready and widespread internet access gives critics a medium through which to speak to whole nations with no regard of their credentials. Online forums, blogs and websites are the source of information for many parents averse to vaccination (Insel, 2012; Schwartz, 2012). Though internet also gives ready access to reputable peer-reviewed sources, the peer-review process is not perfect and most people search for corroboration, not necessarily correction or balanced views.

Virginia Cases

Seven measles cases were reported in Virginia during 2011 (Centers for Disease Control and Prevention, 2012c). Only three were indigenous (patients acquired the infection within the US). Three of the seven cases occurred in Charlottesville, this study will focus on this cluster because it is the only one for which documentation was available. A woman infected while travelling abroad exposed two children without direct contact; the children came into a room after she departed while she was infectious. The children then attended school and visited several local businesses while they were infectious. Once informed, the Thomas Jefferson Health District (TJHD) branch of the VDH began an investigation. They determined the need for public awareness and two IG/vaccination clinics which were set up with assistance from VDH staff from other health districts; all this was done in less than 18 hours. Over the following two days, 200 people were evaluated (Virginia Department of Health, 2011). This case exemplifies local health departments' non-pharmaceutical (education) and pharmaceutical interventions to infectious disease emergencies.

Social Impact

The documented public health event reported above exemplifies the potential for widespread social disruption. The primary factor is that patients are infectious for four days before symptom onset. When symptoms start they will seem like cold symptoms and many patients may go about their daily activities convinced of a common cold. The following observations assess the impact of a sustained chain of infection.

Education

While infectious and lacking symptoms, children with measles have access to many potentially susceptible children at school or day-care. The contact rate varies with class size and activities, but contact encompasses events like riding the bus, assembly, dining hall, gym and extra-curricular activities indoors. The infectiousness of MV and its longevity in the air (two hours) makes it conceivable to have infectious contact with 30 to 100 (or more) students and staff.

Vaccine rates vary between public and private schools. In Virginia, during the 2010-2011 school year 93% and 86% of kindergarteners had two-dose MMR vaccine in public and private school respectively. In both public and private middle schools, rates were above 95% (Sommer & Farrell, 2011). If vaccine rates were to trend downwards, the most aggressive spread of infection would most likely occur in the school-going population. Outbreaks are most often seen where there are pockets of susceptible individuals (Centers for Disease Control and Prevention, 2005; Moss & Griffin, 2012). This puts private school students, staff and families at higher risk because they show lower vaccination rates in Virginia.

Industry

If school-aged children comprise the largest base of susceptible persons, a sustained infection chain will disrupt working adults as they will tend to their infected children. This will

lead to many missed work days and widespread disruption of industry and local economy. Sustained low or decreasing vaccination rates without an outbreak will reduce herd immunity so that a late occurring outbreak would infect both children and adults. According to the CDC's National Immunization Survey and the immunization Services Division, adult vaccine rates are best estimated from available (historical) school immunizations (Black, 2012).

Healthcare providers

Thirty to forty percent of measles patients have complications. Otitis media, diarrhea and pneumonia are the most common (Centers for Disease Control and Prevention, 2012b; Moss & Griffin, 2012). In 2011 thirty percent of all infections reported in the US were hospitalized (Centers for Disease Control and Prevention, 2011a). A sustained infection chain would impact healthcare providers by increasing census with patients who are resource intensive and by reducing available staff.

Measles patients require negative air isolation rooms which ensure infectious particles are exhausted outside the facility. Once the patient leaves, the room should not be used for at least two hours (Remley, 2011). All healthcare workers caring for patients require an N95 respirator which can only be used after individual fitting and education by a trained occupational health professional. Treating measles patients is thus material resource and physical plant intensive. In addition, healthcare providing facilities could easily be understaffed if some staff has to be home caring for their own infected children, family members or if they are sick.

Financial cost

The costs due to measles (before vaccine licensing) in 1963 are estimated to range from $1.4 billion (M. B. Oldstone, 2000) to $3.4 billion (Strebel et al., 2004) in direct healthcare costs[2]. A 2011 study estimated cost of measles cases seen in Japan between 1999 and 2003 at US$ 404 million. In contrast, vaccination of all the infected patients would have cost US$165 million. These values include direct healthcare cost and indirect costs such as working days lost (Takahashi et al., 2011). Another study estimated the cost of one measles case in the US between $18,000 and $28,000 in healthcare and public health resources. In comparison the cost of one dose of vaccine, excluding administrative cost ranged from only $0.92 to $18.63 (Coleman et al., 2012).

System Dynamics Methodology

Introduction to System Dynamics

System dynamics (SD) is a method of analyzing and modeling interactions in complex systems. An event oriented world view would depict a simple system with variable A causing B which causes C (Figure 6). These variables are assumed to change in isolation and are analyzed as such. In contrast, SD analyses system behavior as a product of system structure which includes any feedback between dynamically changing system characteristics as shown in Figure 6.

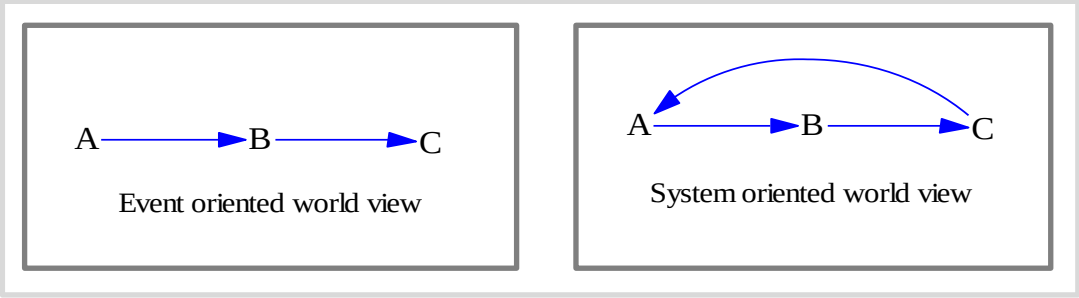


Figure 6: Event oriented and system oriented world views.

[2] Values are adjusted for inflation to 2010 dollar value using The Inflation Calculator at http://www.westegg.com/inflation/

Characteristics of Complex Systems (John. D. Sterman, 2000)

Dynamic

Complex systems are in a constant state of change. Many 'static' systems when viewed on a long enough time scale will show change (John. D. Sterman, 2000). Gaining and losing of herd immunity is one such process, it is a slow and long change. This model's dynamics arise from the inclusion of births, deaths and aging. For example, in the UK endemic measles transmission was halted in 1994. MMR rates started to decline in 1998; it was 2006 until the first measles outbreaks began. By 2008 measles was declared endemic and a public health response initiated (Bedford, 2011; Editorial team, 2008). Looking at problems on a long time scale allows the analyst to see unintended consequences, effects of time delays and system inertia – in short it gives a clearer picture of the scope and full behavior of the system. This use of long time scales gives SD methodology a high-level view of systems or problems; high enough to detect action in the system without necessarily seeing the individuals behind the action (Milstein, 2008).

Tightly coupled

Tightly coupled systems are characterized by a widespread ripple effect, changing one variable while the others are static is near impossible. SD modeling assists analysis of tightly coupled systems by providing a visual result of all (selected) downstream changes so the analyst can see the extent of the ripple. Controlling an infectious disease has biological, social and economic elements. This thesis will focus on the biological and slightly on the social, but the full effects of an outbreak are far reaching. SD methodology allows multi-disciplinary analysis. The model presented here could be extended to include study topics such as vaccination decision making processes, analysis of the social and/or financial impact among others.

Feedback

In a tightly coupled system a reaction will influence the next action (John. D. Sterman, 2000). As discussed in the section on Vaccine Safety, there is balancing feedback between

incidence of disease and vaccination rates (Chen, 1999) which leads to a wavering of commitment to vaccinate children. An example of reinforcing feedback in this system occurs in an outbreak. The presence of more infected people increases the rate of infection which results in larger infected populations. These and other feedback cycles are characteristic of this system.

Nonlinear and Counterintuitive

Another characteristic of complex systems is nonlinearity of change. The size of a change in a system depends on feedback dominance in that moment. Though an outbreak is driven by competing reinforcing and balancing feedback dynamics, the instantaneous changes in system state depend on which of those dynamics are currently dominating. Such interactions cause the nonlinear and counterintuitive behavior of complex systems such that the most obvious policy changes do not always provide the greatest leverage (John. D. Sterman, 2000). Though vaccination rates are high in the US, there has been a definite increase in measles incidence and it is not immediately clear why this is so (Centers for Disease Control and Prevention, 2011a, 2012a).

Policy Resistance

SD methodology also accounts for the potential of unintended consequences and policy resistance. Both these terms refer to how complex systems often adapt to changes or interventions, thereby yielding outcomes that can sometimes befuddle policymakers. These outcomes can dilute, delay or entirely defeat the policy. An example is the increased use of antibiotics (policy) which has fueled (in part) the increased prevalence of multidrug resistant bacteria. Low nicotine and/or low tar cigarettes increase consumption by smokers as they try to get the level of nicotine they are accustomed to (John D. Sterman, 2006). The high efficacy of anti-retroviral treatments for HIV/AIDS have increased quality of life for patients, but increases risky behavior thereby increasing infection rate and resistant strains (Rice, Batterham, & Rotheram-Borus, 2006). As discussed in the Vaccine Safety section is the decreased confidence

in vaccines stemming from the public's ignorance of the reality of measles morbidity and mortality borne from the success of the vaccine.

Organized immunization resistance groups began with the passing of vaccination acts in Europe and America in the 19th century. Anti-vaccination groups saw these laws as a breach of civil liberty. Groups thrived even in countries where vaccination was not required by government (Wolfe & Sharp, 2002).

System Dynamics Application

SD was born as a business analysis tool but has been applied to many fields including medicine, epidemiology and public health (J. B. Homer & Hirsch, 2006a, 2006b; J. Homer, Hirsch, & Milstein, 2007; Milstein, 2008; Milstein, Homer, & Hirsch, 2010; Milstein et al., 2007; John. D. Sterman, 2000; Trochim, Cabrera, Milstein, Gallagher, & Leischow, 2006). It is a beneficial tool because in spite of the exact and rigorous nature of most medical research science, disease occurs in an uncontrolled environment and is dependent on people's behavior and other host factors. SD analysis is precise enough to match the science yet can also account for behaviors and decisions that may lack strict measurements by using curve fitting and regression methods (J. B. Homer & Hirsch, 2006b).

SD and mathematical modeling is useful to analyze and better understand system interactions by creating a simplified mock-up of a real system. Models thus contain simplifying assumptions chosen so that they do not interfere greatly with system structure and behavior (Choisy, J.-F., & Rohani, 2007; Sattenspiel, 2002; John. D. Sterman, 2002). A model therefore allows the testing of ideas and theories that may be dangerous, unethical, expensive or otherwise prohibitive in experimental execution. And as mentioned earlier, complex systems have time delays and action dilutions that make real-time experimentation infeasible for present cause-future effect analysis. For these reasons there is no study in which subjects are denied vaccine to

see the size and duration of resulting outbreaks. Modeling allows extensive analysis of such scenarios affordably, with no harm to people and in a few minutes.

CHAPTER 2: SEIR-AGING CHAIN MEASLES MODEL

Model Purpose

This chapter outlines the model used for this thesis. It is a population-based, deterministic model in continuous time (Anderson & May, 2004; Vynnycky & White, 2010) built using STELLA©, version 9.1.4. The purpose of the model is to explore conditions under which an imaginary population might experience endemic measles, given that a small fraction of newborns are either not inoculated (due to parental preferences or inaccessibility to appropriate care), or are inoculated but still susceptible (due to the limitations in the effectiveness of the vaccine). Under such conditions, the susceptible fraction of the population will increase over time to a point that, given the introduction of an index case, epidemic conditions could be realized. The goal is to determine the conditions under which this could happen. The types of conditions considered are vaccination fraction (proportion of the population that is vaccinated) and susceptible fraction (proportion of the population that is not immune to measles).

Since measles is a childhood disease, there are many studies focused on children. Disease and population dynamics differ with age so this model goes beyond childhood to analyze the long term effects of childhood vaccine exemption. In order to accomplish these goals, the model is designed to mimic an imaginary population that starts with 100,000 people, in four different age cohorts as shown in Figure 7. The initial population is distributed in proportions consistent with US census values for 2010. The model only allows for changes to population size through births and deaths (i.e. no migration into or out of the population). The cohorts are populated with equilibrium starting values and people age down the structure.

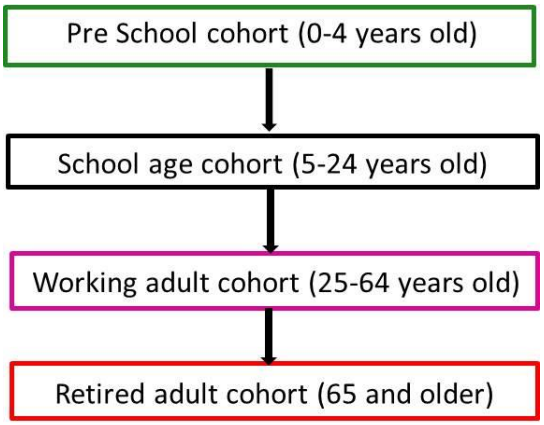


Figure 7: Age cohorts

Modeling terminology

Figure 8 shows the icons used in the model developed for this thesis. The terminology is also defined.

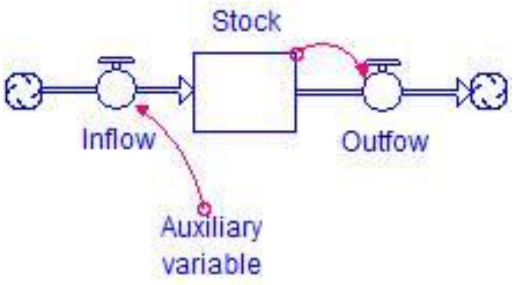


Figure 8: Modeling icons and terms

- ***Stocks*** are rectangles in which materials, in this case people, accumulate. They represent 'states' through which people pass, or might reside for extended periods of time. At any point in the simulation, the numeric value of a stock indicates the number of people in that particular state.
- ***Sources*** or ***sinks*** (represented by the cloud icons) initiate or terminate a flow into or out of a stock. Since the dynamics creating these sources or sinks are not specified, they represent what is beyond the model boundary. In the current context, stocks are used to represent categories or states that individuals in the

population can occupy (such as “infected individuals” or “recovered individuals”)

- ***Flows*** are double-lined arrows with that fill or drain stocks at a rate dependent on the level of the stock and the time spent in the stock (wait time). In the model described in this thesis, the flows will represent rates at which people transition from one state to the next (from “susceptible” to “infected,” for example)
- ***Auxiliary variables*** can depend on other parts of the system and hence vary over time (i.e. endogenous variables), or they can be fixed values set by the user (i.e. exogenous variables). They often represent properties or characteristics of the phenomenon under study. They help to regulate the behavior of the system. Examples of auxiliary variables in our model are characteristics of the disease, such as its *infectivity* and the *duration of infection*, etc.
- ***Causal links*** are red arrows which show that one element affects another according to a mathematical formula.

The SEIR Backbone

The natural history of measles determines the model structure; within each cohort a Susceptible-Exposed-Infected-Recovered model structure (Britten, 2009; Vynnycky & White, 2010) is used to mimic and track the progression of the disease, assuming contact between infected and susceptible individuals occurs across age cohorts, as well as within each cohort (total mixing).

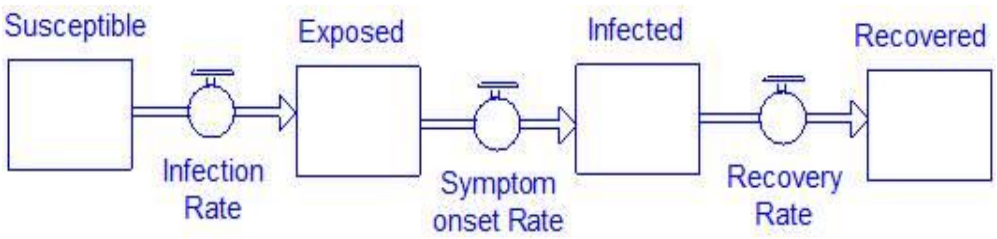


Figure 9: Basic SEIR structure

The basic SEIR structure is extended in this model to account for birth, death, immunization and immunization omission (by exemption, oversight or lack of access to care). This extended SEIR structure is shown in Figure 10.

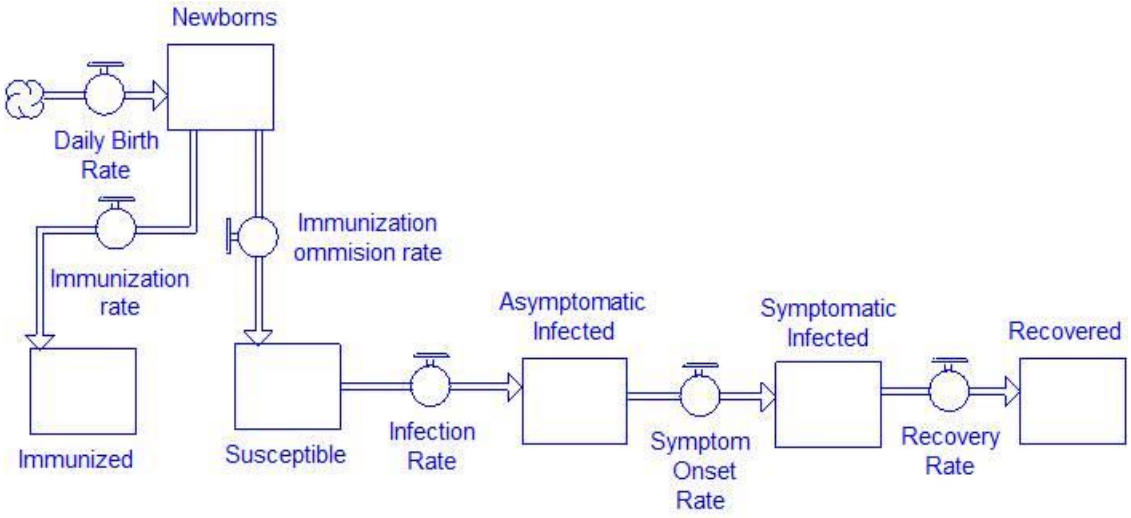


Figure 10: Extended SEIR structure

The model seeks to explore measles disease dynamics using the aging chain (age cohorts). The SEIR structure is embedded within each cohort. For example the SEIR structure for the pre-school age cohort is shown in Figure 10. The acronym MACSEIR ("Mac-seer") is the model name, where MACSEIR stands for "**M**easles **A**ge **C**ohort **SEIR**". An overview of the aging chain with the embedded SEIR structures is shown in Figure 11.

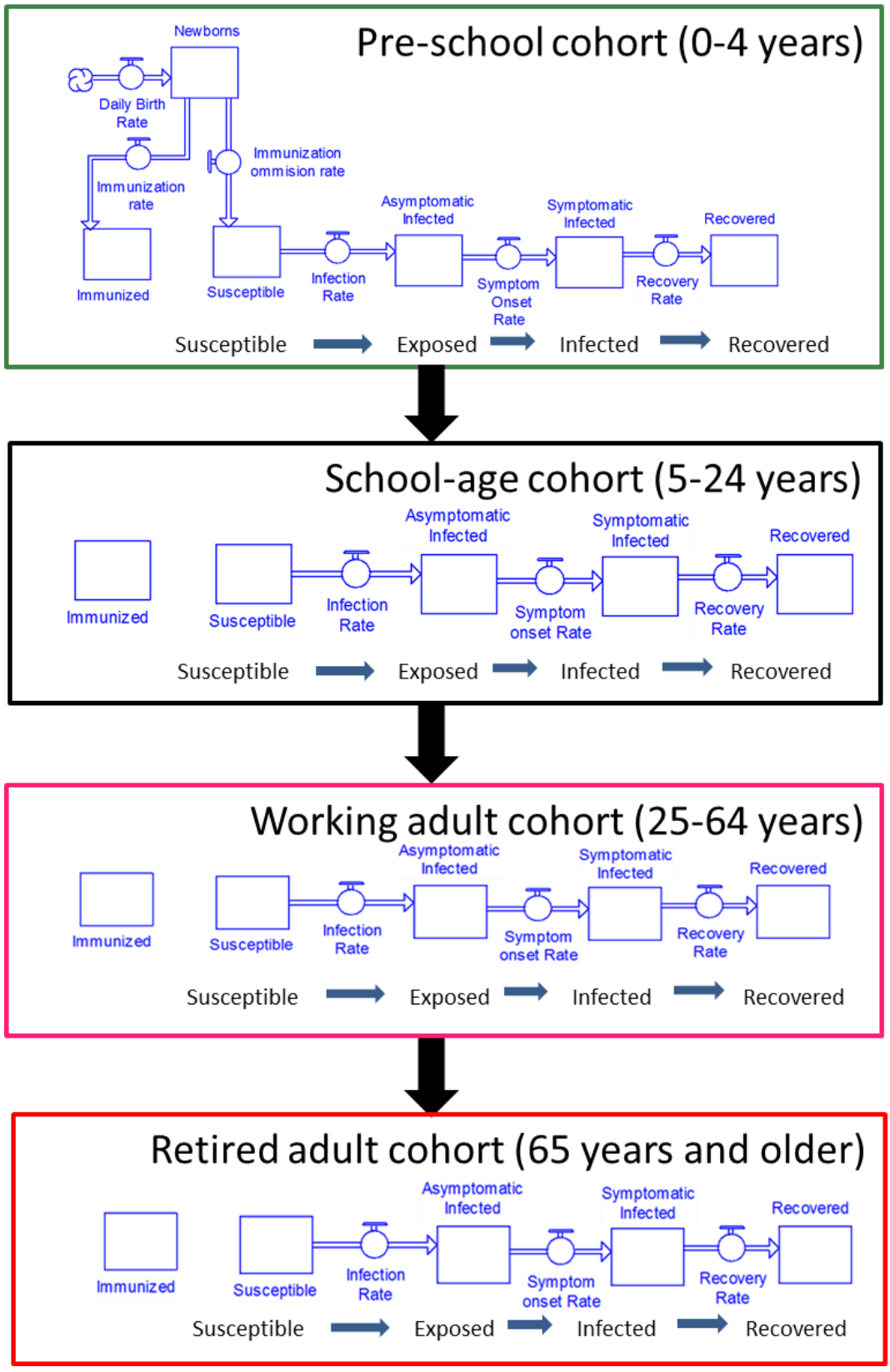


Figure 11: Full MACSEIR structure

Assumptions

This model assumes all newborns carry maternal antibodies for an average of seven months (Strebel et al., 2004). In reality this only applies to babies born to immune mothers (Centers for Disease Control and Prevention, 2012b; Strebel et al., 2004). After the seven month wait time newborns flow into a susceptible state (*Immunization omission rate* in Figure 11) or they can be immunized by vaccination (*Immunization rate* in Figure 11).

The model assumes all immunization occurs in the pre-school cohort (green panel in Figure 11) and immunity gained from vaccine is permanent. Ongoing studies show sustained vaccination immunity up to 33 years in immunocompetent people (Dine et al., 2004). Some immune compromised people can lose immunity which makes measles prevention problematic in areas with high HIV prevalence for example (Griffin, Moss, & Cutts, 1999; Helfand et al., 2005; Nair et al., 2009). The model also assumes full (two dose) immunization hence the use of 99% for vaccine efficacy (Centers for Disease Control and Prevention, 2012b).

The infected population in each age cohort in Figure 11 is disaggregated into asymptomatic and symptomatic stocks to account for three to five day period during which people are infectious without symptoms (Heffernan & Keeling, 2008). It is during this period that most exposures occur as people go about their activities of daily living, once symptomatic they succumb to the infection and self-quarantine until they are fully recovered. There is no outbreak intervention in the model apart from this self-quarantine. This leads to an overestimation of outbreak size.

The model also assumes total mixing which allows infection to spread beyond cohort borders (Figure 11). Some cohorts have higher contact rates, thus higher chances of infection-causing contact. Infection rate equations are cohort specific; inter-cohort spread arises from

incorporation of total symptomatic infected and total asymptomatic infected population proportions used in place of the term (I/N) in the equation used by Sterman:

$$Infection\ Rate\ (IR) = (ciS)\left(\frac{I}{N}\right)$$

c = contact rate,

i = infectivity,

S = Susceptible,

I = Infectious

N = Total population (John. D. Sterman, 2000).

This equation is modified in the model so that $IR = (caI * i * S)\left(\frac{aI}{N}\right) + (csI * i * S)\left(\frac{sI}{N}\right)$ the first term refers solely to asymptomatic infected people and the second refers to symptomatic infected. These terms inherently account for the reduction of the reproductive number (R_0) seen in immunized populations (Plans Rubió, 2012).

Model Age Cohorts

Age cohort in the MACSEIR structure allows the simulation of a scenario in which a susceptible working adult is infected abroad, returns home and infects susceptible children who then infect class mates and/or play mates. This capability is not often considered in measles models.

Pre School Cohort

The pre-school sector contains newborns up to four year olds. The stock and flow structure is shown in Figure 12. *Daily Birth Rate* is calculated from an annual birth rate per woman of childbearing age. After seven months they leave the *Newborns* stock. The majority of them will receive their vaccine after an average of 28 days (Brown et al., 2012; Orenstein, Rodewald, & Hinman, 2004) and flow through *Immunization rate* into the *Immunized* stock. The second fraction flows through *Immunization omission rate*. These children are not vaccinated

intentionally (because their parents claim vaccination exemption) or unintentionally (because they fall through the cracks of vaccination programs). These two groups will age without immunity, become infected and recover or die in this sector. National exemption rates ranged from <0.1% to 7.0% (median = 1.5%) and Virginia reported 1.0% among kindergarteners in the 2011-2012 school year (Centers for Disease Control and Prevention, 2012e). Though all children entering schools should show proof of vaccination or exemption some children are inadvertently missed (Centers for Disease Control and Prevention, 2003b). Kindergarten surveys for Virginia report 93% MMR vaccination rate and 1% exemption rate leaving 6% of kindergarteners in this flow (Centers for Disease Control and Prevention, 2012e). Greby at the CDC defines this value as children "whose records were not updated by the time the school vaccination reports were due" (2013). Britten suggests these children have fallen through the cracks of the immunization program (2009). Another cause of this discrepancy could be lack of access to primary care. Whatever the cause is, they are assumed to be susceptible and their proportion is calculated in the model by adding the vaccination fraction and exemption fraction and subtracting that from one. These children will age without immunity, become infected and recover or die in this sector. This model assumes all vaccination occurs in the pre-school age group. In reality people can be immunized at any time. The majority of people are immunized for school entry which is why immunization data is extracted from school admission data (Black, 2012).

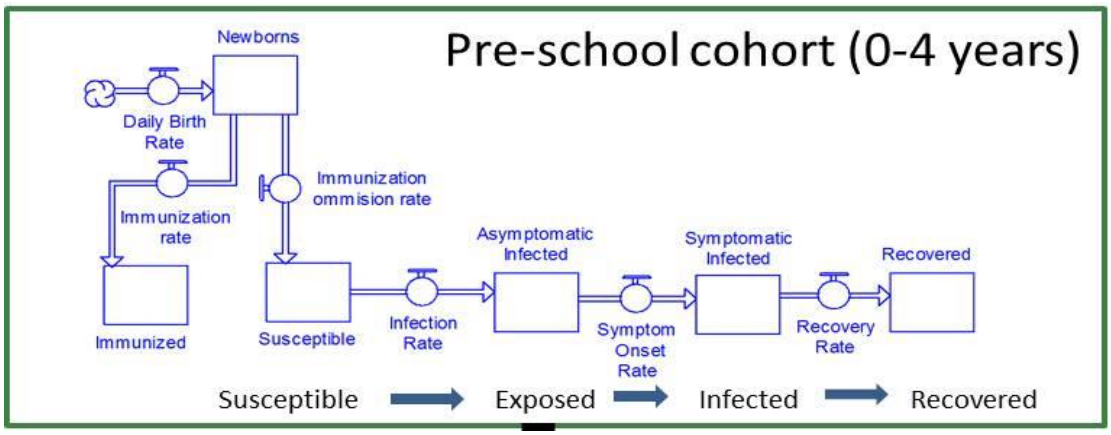


Figure 12: Stock and flow structure of the Pre School sector

The length of stay in the pre-school sector is four years. Earlier versions of the model over-estimated immunized fraction because this long delay. Earlier model versions had two pre-school susceptible flows (designated *PSc Sw Awaiting MMR* and *PSc Sn Never Immunized*) that aged out every four years. From the stock of children awaiting immunization a fraction (*PSc Vaccinated fraction*) was immunized every 28 days. The remnant of this stock was to account for the missed vaccinations, but it proved inaccurate. The longer the model ran the immunized fraction approached 92% regardless of the user-input value (vaccination fraction). This problem was solved by using first order delays with similar wait times instead of a second order delay with vastly different wait times. All the children who would not be vaccinated went into one stock of never immunized children and those awaiting immunization in their own stock.

Based on surveillance from 2001 to 2010, 30% of imported associated cases of measles were among travelers aged 6-23 months (Kaye, 2011). This cohort is highly likely to produce an index case because of travel with parents. Historically, transmission in this group most often occurs in day-care and health-care settings (Yip, Papania, & Redd, 2004).

School age cohort

The school age sector (Figure 13) contains the 5 to 24 year olds. The age bounds of this sector were decided upon in part by the availability of census data. This group has the highest contact rate and so the majority of infections. Between 1993 and 2001, 46% of all cases where in the 5 to

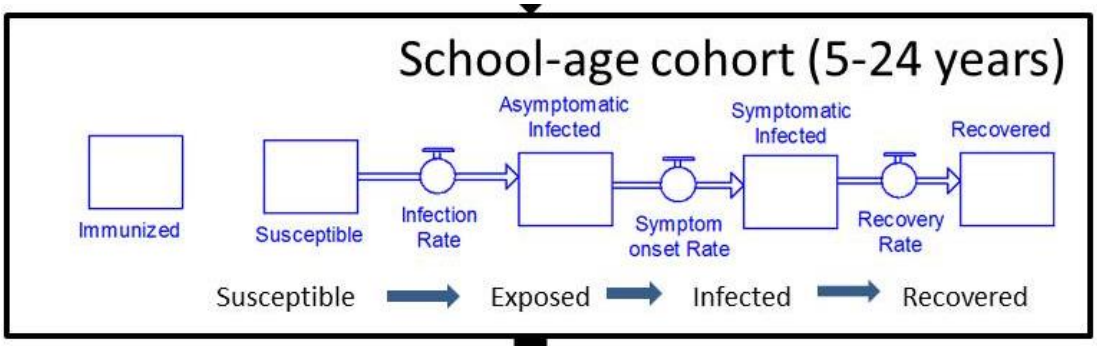


Figure 13: Stock and flow structure of the School age cohort

18 year age group and occurred in school (Yip et al., 2004). The wait time in this sector is 13 years. The immunized and recovered remain in their stocks and age or die. The susceptible could age into susceptible adulthood, be infected or die in this sector.

Working adult cohort

The working adult sector contains 35 to 64 years olds. This group has the second largest contact rate because of work and family activities. A portion of this group could be especially vulnerable due to occupational exposure – hospital, clinic, emergency services, teaching and child-care staff. If susceptible parents have an infected child, they will likely be infected while caring for the child before they have access to appropriate personal protective equipment.

This cohort's structure is identical to the school age cohort, and like the school age cohort, the majority of the working adult population will be either immunized or recovered because the incidence of childhood diseases decreases as people age (Anderson & May, 2004; Vynnycky & White, 2010). They will remain in their stocks and age into the next sector or die. Working adult susceptible people can be infected, age into the next cohort or die. According to available documents (Virginia Department of Health, 2011; Yip et al., 2004) this cohort is highly likely to travel abroad hence to produce an index case.

Retired adult cohort

This sector contains people older than 65. Since this is the last sector, the population tends to this sector in long runs. The risk of infection in this group will be smallest and the chances of an outbreak originating here are small, but still possible. Its structure is identical to the school age and working adult sectors.

Model output

The model provides plots of numerous values that can be used to evaluate the evolution of the population over time and the time-varying response to index measles cases (i.e. whether an

outbreak occurs, and also to determine at what point the population loses its herd immunity). Some of these values will be described here.

Susceptible Fraction

This value calculates the proportion of the total population that is susceptible to measles infection. It is the quotient of all susceptible stocks and the total population. Susceptible fraction increases were population increases without a concurrent increase in vaccinated fraction. In the presence of an index case an outbreak occurs when susceptible fraction surpasses a threshold value (Britten, 2009; Wallinga, Heijne, & Kretzschmar, 2005).

Fraction Immune

This value calculates the proportion of the population that is resistant to measles secondary to infection or vaccination. This population provides herd immunity, so the higher it is, the smaller the force of infection in the presence of an index case.

Fraction Immunized

This value is the proportion of the population that is resistant to measles secondary to vaccination alone.

Interface

STELLA allows a customizable control interface for ease of adjusting model parameters. Part of the MACSIER interface is shown in Figure 14. The first column contains immunization and cohort specific disease switches to control those model features. This allows easy transition from the baseline (no immunization) to the vaccination rate testing scenarios. These switches also allow the model to be run for disease in one cohort while the rest of the model runs as a population analysis tool. The next two columns contain slider inputs for vaccination fraction, exemption fraction and cohort specific number of index cases and index frequency. At the bottom of these two columns are the pulse start and birth rate sliders and below those the start and stop

buttons. Initial population values are externally calculated and entered into a table input tool. The rest of the interface contains graphic output tools. In the event that this tool is used in a seminar setting, these interface features can be customized to the intended use.

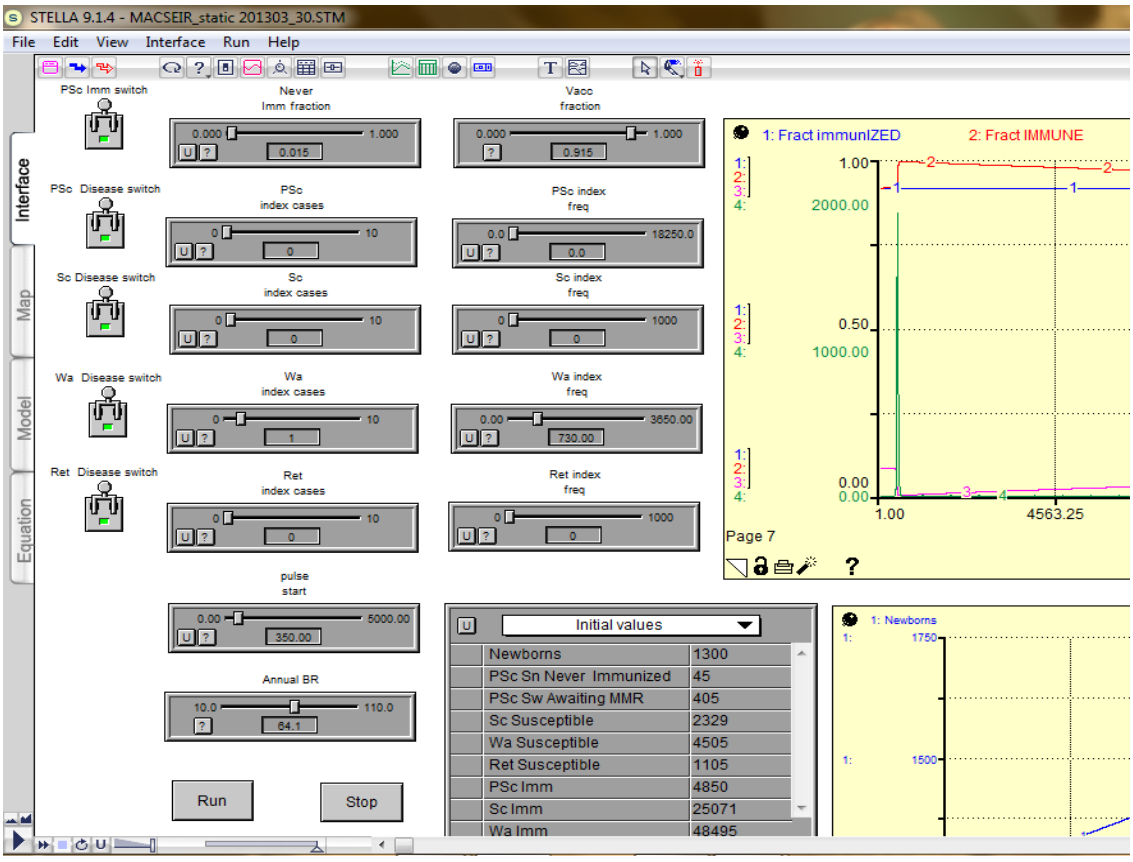


Figure 14: MACSEIR Interface

CHAPTER 3: MODEL TESTING

A model is a simplified, representation of reality useful to assist our understanding of the system it represents. According to John. D. Sterman (2002) all models are wrong, but if they are to be useful they have to mimic reality to a sufficient degree to guide decision making. Following Sterman (2000) this chapter describes the testing performed on the MACSEIR model.

Evaluation of Structural Validity

This tests how well the model's stock and flow structure, causal connections, and overall logic are consistent with what is known about the underlying system. The model was presented to members of the thesis committee whose expertise covers system dynamics modeling, virology and epidemiology. It was also presented to two state health department epidemiologists and adjusted in accordance to their recommendations.

Dimensional consistency

This ensures units in the model's equations are dimensionally consistent. During the model building process and after completion dimensional consistency was tested using a tool built into the STELLA® software.

Evaluation of Extreme Conditions and Behavior Anomalies

This test ensures the model produces plausible results when given extreme variables. Behavior anomaly tests the model's ability to attain and sustain equilibrium. Birth, aging, immunization and disease are controlled by switches inserted for testing the model which behaved as expected when these were switched off before and in the middle of runs. The birth rate switch ensured no births and the population decreased to extinction on long enough runs. Aging switches responded by the population accumulating in the oldest age sector available. Both these tests attest to the structural and logical integrity of the aging chain structure.

User-input values were subjected to extreme value testing. The salient problem that arose was the persistence and recurrence of infection due to fractional infectious population as shown in Figure 15. In between the peaks, infected populations were less than one but greater than zero and without a new index case these fractions added up to cause a new outbreak. This was countered by emptying any stock carrying infectious people whenever it fell below one.

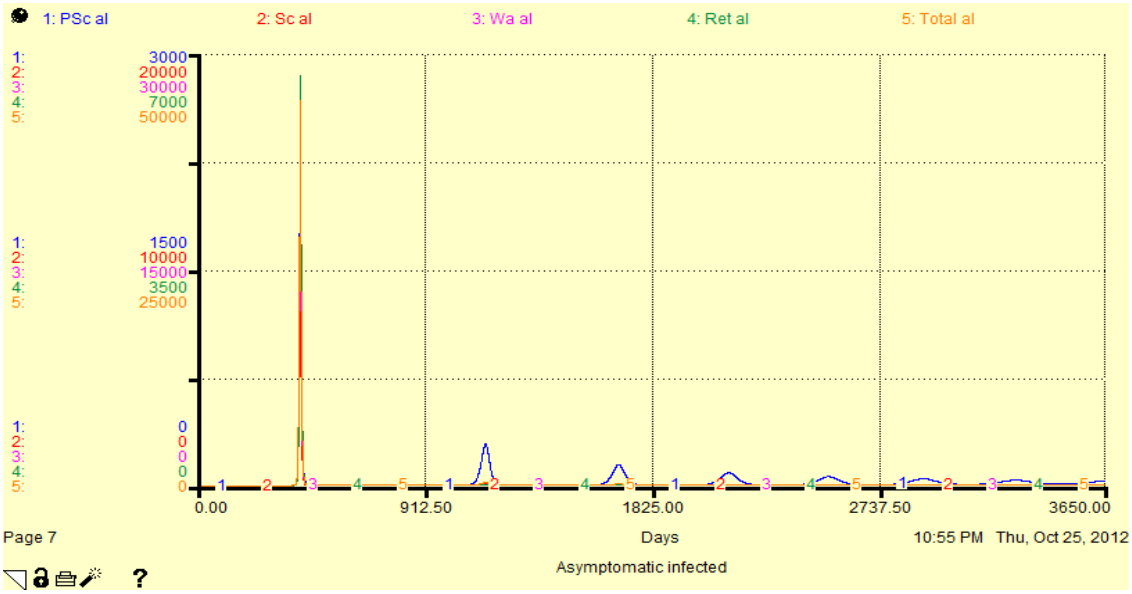


Figure 15: Accumulation of fractional infectious population.

Though initial population distribution is consistent with fractions calculated from 2010 census data, these proportions are not maintained at the end of a run; age cohort sizes change based on the length of time of analysis. Total population equilibrium is difficult to attain because of varied wait times in each cohort. Using the birth rate range available on the interface allows runs in which population increases or decreases.

Initial immunized population is calculated by an external spreadsheet and entered by the user. With enough time the model reaches these target vaccine fractions if a run is initiated in disequilibrium.

Test for Integration errors

This assessment tests for any change in results if integration method or if integration time step is changed. The model shows consistent results with either and both changes. It is set to run in Euler's integration with a time step that varies with the length of run time desired by the user.

Behavior reproduction

This test compares the model's results to results in the real system, other models and also tests if different runs produce the same results. Figure 16 shows the change in the population distributions when one infected individual is introduced in a totally susceptible population of 100,000. Each curve in Figure 16 has its own scale, indicated by the colored numbers on the left axis that correspond to the color of the line. The graph shows expected results.

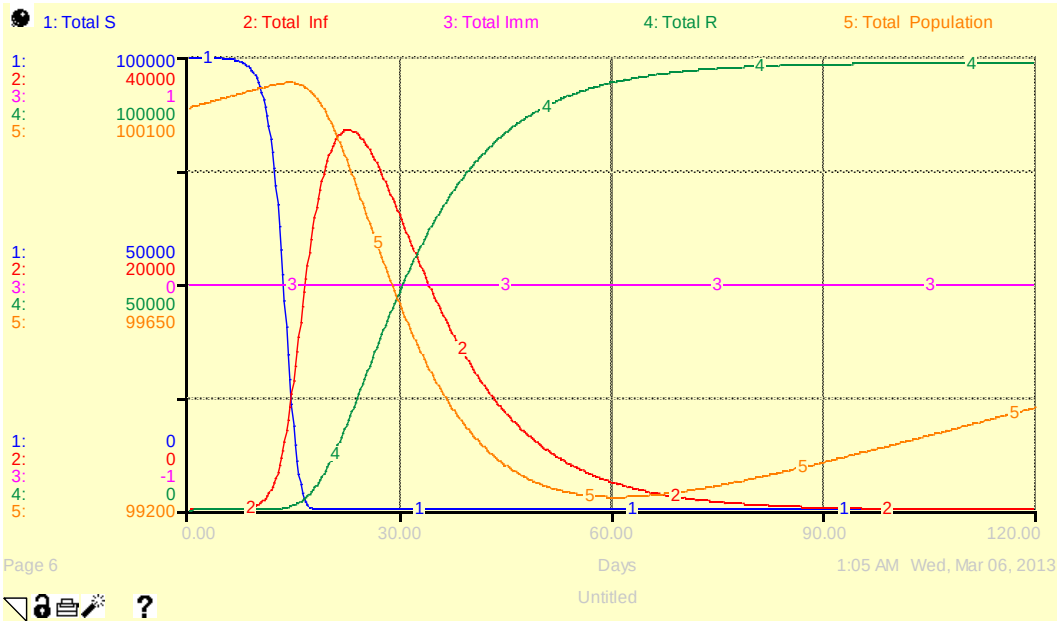


Figure 16: Index case in an unimmunized population. Run time = 120 days.

Because measles is episodic in the United States the results of this test will be based on the model's ability to predict a herd immunity vaccination threshold. This will be discussed in chapter 4.

CHAPTER 4: ANALYSIS

Run Parameters and Values

These auxiliary variables listed in Table 1 are standard for all model runs. The model's run time is set to 18250 days (50 years). Initial population is 100,000 people.

Table 1
Model parameters

Name	Full Name	Source	Value
Veff	Vaccine efficacy	(Centers for Disease Control and Prevention, 2012b)	0.99
infectivity	Infectivity	(Anderson & May, 2004; John. D. Sterman, 2000; Vynnycky & White, 2010)	0.9
Ts	Serial interval	(Anderson & May, 2004; Vynnycky & White, 2010)	12 days
Ta	Asymptomatic Interval	(Heffernan & Keeling, 2008)	4 days
Td	Symptomatic interval	(Heffernan & Keeling, 2008)	4 days
I f DR	Infected fractional death rate	(Centers for Disease Control and Prevention, 2012b)	1 per 365 days
pulse start	Pulse start	User	350 days
Vacc fraction	Vaccinated fraction	User	Varies
Never Imm fraction	Never immunized fraction	User	Varies, 0.015
Annual BR	Annual Birth rate	Calculated from 64.1 births per 1,000 woman of childbearing age per year (Hamilton, Martin, & Ventura, 2012)	Varies,
	Death rate	Calculated, (Hoyert & Xu, 2012; US Census Bureau, 2012)	Varies by cohort
	Asymptomatic contact rate	10 (pre-school), 15 (school age), 12 (working adult), 8 (Retired adult)	Varies by cohort
	Index cases	User (cohort specific)	1 person
	Index frequency	User (cohort specific)	730 days

Experimental Scenarios

Baseline

The baseline runs consisted of a single index case introduced to an unvaccinated population. The primary outbreak ran for 176 days and peaked with 34,805 cases. Subsequent (or secondary) outbreaks occurred every 4 years or with every other index case. They ran for a range of 218-238 days and showed a peak infected population range of 1,670-2,138 cases. Secondary outbreaks occurred when the susceptible fraction rose beyond 0.08. Without immunization, the

MACSEIR shows no outbreak running beyond a year. Outbreaks are larger and tend to run longer in the later years of the runs.

Threshold testing runs

Vaccination rate and vaccination fraction are used interchangeably to refer to the user-input level of immunization for the population. Immunization rate and immunized fraction refer to the model calculated values.

Increasing Vaccination rate

This run was set up with a constant exemption rate. The model was set to pause every five years at which the vaccination rate was increased by 0.02 so that over 50 years the vaccination rate increased from 0.80 to 0.99. There were three outbreaks altogether (green peaks in Figure 17) whose characteristics are shown in Table 2. Susceptible fraction threshold before each outbreak was 0.04. As expected, increasing vaccination rates were associated with decreases in frequency and size of outbreaks. Though increasing, the immunized fraction lags below the

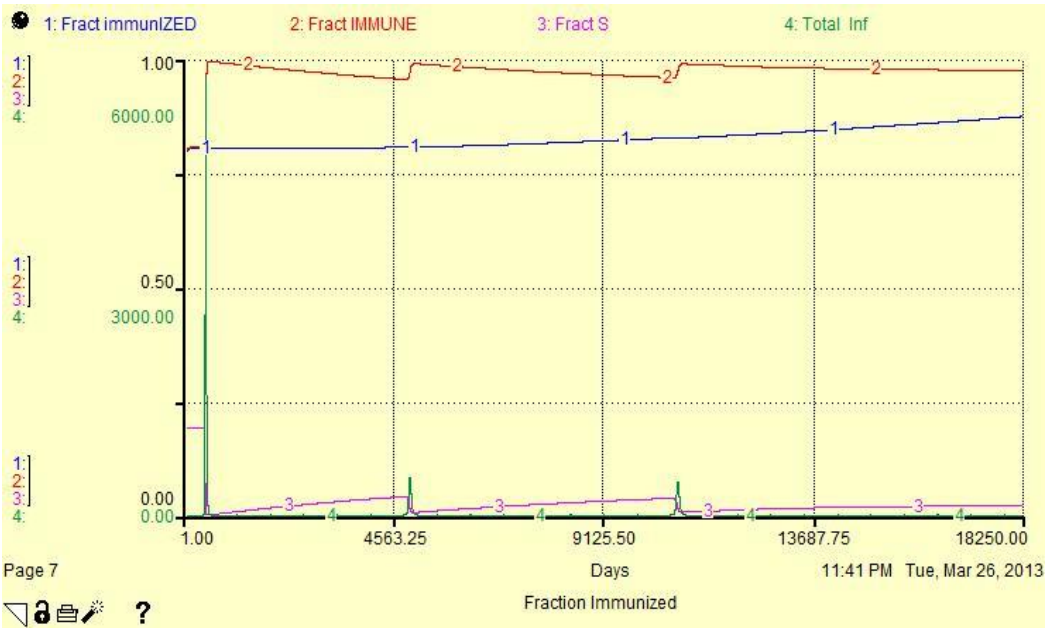


Figure 17: Population fractions with increasing vaccination rate

user-input value (vaccination rate) so that the final immunized fraction is 0.87 (vaccination rate = 0.99). Immunized fraction gains 0.07 points in the run; this is an example of delay and dilution of effort inherent in the system. Even though the vaccinated fraction is raised, the system continues to receive newborns and the exemptions force the immunized fraction down.

Table 2
Characteristics of outbreaks with increasing vaccination fraction

Year of outbreak	Length of outbreak (days)	Time between outbreaks (years)	Peak Infected	Fraction immunized
1	167	n/a	5786	0.80
13	298	12	499	0.81
29	334	14	444	0.82
Baseline	176-238	4	34,085	0.00

Static Vaccination rate

Static vaccination rate runs were set up with the same model parameters except that the vaccination rate remained the same for the 50 year run time. Characteristics of primary and secondary peaks were recorded. Experimental vaccination fractions used are shown in Table 3. Results analyzed are length of outbreak, time between outbreaks and peak number of people infected in the outbreak.

Table 3
Vaccination fractions used in static runs

Vaccination rate	Reason for selection
0.99	High value
0.96	Corresponds to model's susceptible fraction threshold
0.94	Herd immunity threshold (HIT) upper limit (Vynnycky & White, 2010)
0.915	2010 US value (Black, 2012)
0.89	2011 UK value (2003-2004) (Bedford, 2011)
0.83	HIT lower limit (Vynnycky & White, 2010)
0.80	Lowest UK value (2003-2004) (Bedford, 2011)
0	Low (baseline) value

Length of outbreak. There is no endemic transmission in any of the scenarios. Figure 18 shows the graphical results. Primary outbreaks are more dependent on vaccination rate than secondary outbreaks since they occur early in the run. The larger the vaccine-exempt population, the faster the outbreak grows and dies out. At 0.96 vaccination fraction the primary outbreak was the longest. Based on the peak infected data, it was a small outbreak which allowed slower spread of the infection contrasted to the explosive growth seen in other runs.

There are secondary outbreaks at all vaccination fractions except 0.96 and 0.99. The longest outbreaks were 346 days (secondary outbreaks with vaccination fraction = 0.94 and 0.89). Secondary outbreaks ran longer than most primary outbreaks. The length of secondary outbreaks seems more dependent on the susceptible fraction than it is on vaccination rate alone. As in the prior run, the susceptible fraction threshold is 0.04.

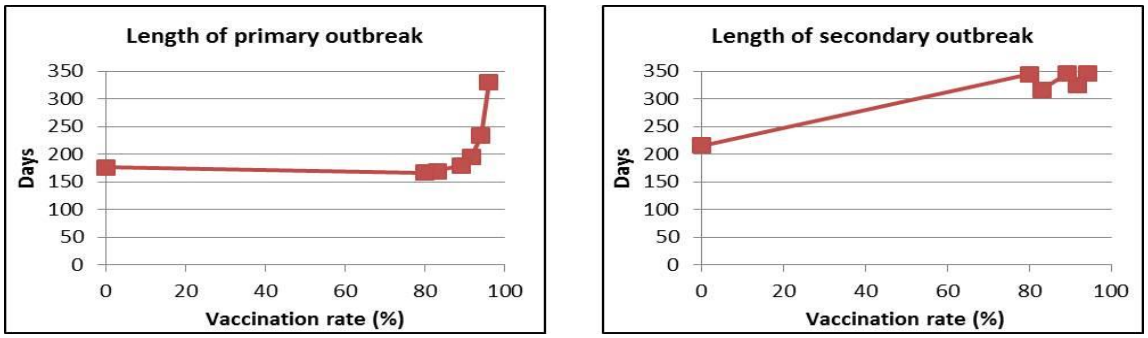


Figure 18: Length of outbreak for static vaccination rate

Time between subsequent outbreaks. There is no secondary transmission at 0.96 and 0.99 vaccination rate as shown in Figure 20. As expected the lower the vaccination rate, the shorter the time between outbreaks - the susceptible fraction threshold is attained quicker because exemption rate is higher.

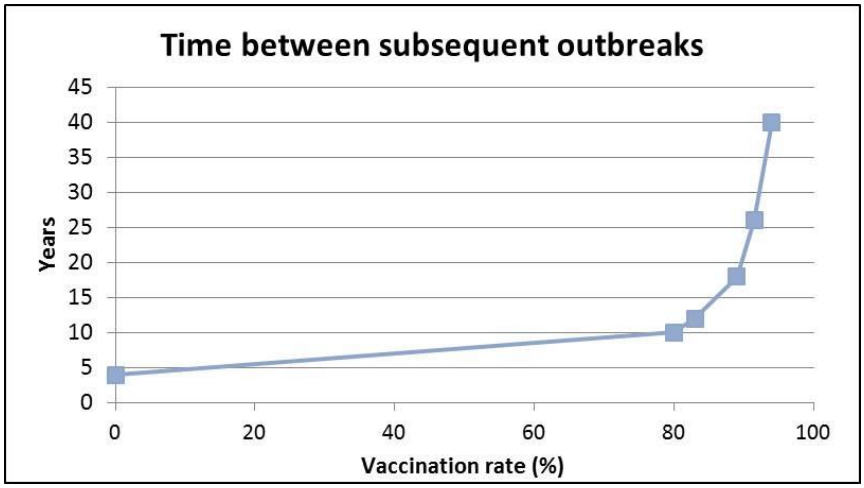


Figure 20: Time between secondary outbreaks for static vaccination rate

Peak infected. As expected, the lower vaccination rates show higher primary infection spikes, but all secondary outbreaks peak between 300 and 500 cases, the effect of vaccination rate is not apparent (Figure 19).

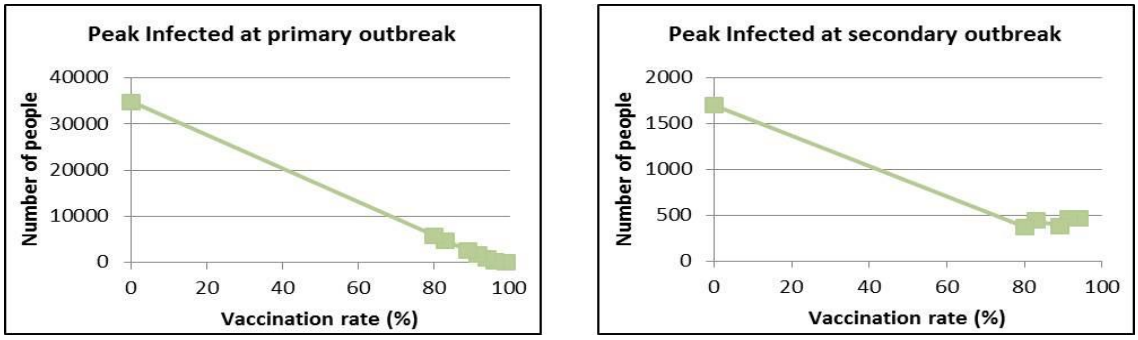


Figure 19: Peak infected for static vaccination rate

Decreasing Vaccination rate

This run's setup is similar to the run with increasing vaccination fraction. In this instance the vaccination rate is decreased in a stepwise manner from 0.99 to 0.80. There were two outbreaks (green peaks in Figure 21) whose characteristics are shown in **Error! Reference source not found.**. Susceptible fraction threshold was 0.04 in both outbreaks. As expected, increasing vaccination rate decreases frequency and size of outbreaks. Immunized fraction does not fall as quickly as the input value (vaccination fraction) but falls faster than it rose in first run

(Increasing vaccination rate). The final immunized fraction is 0.90 (vaccinated fraction = 0.80) - it loses 0.09 points from the initial value. On its own, the immunized fraction tends downwards in response to the persistent addition vaccine exempt fraction from newborns. It is thus easier for

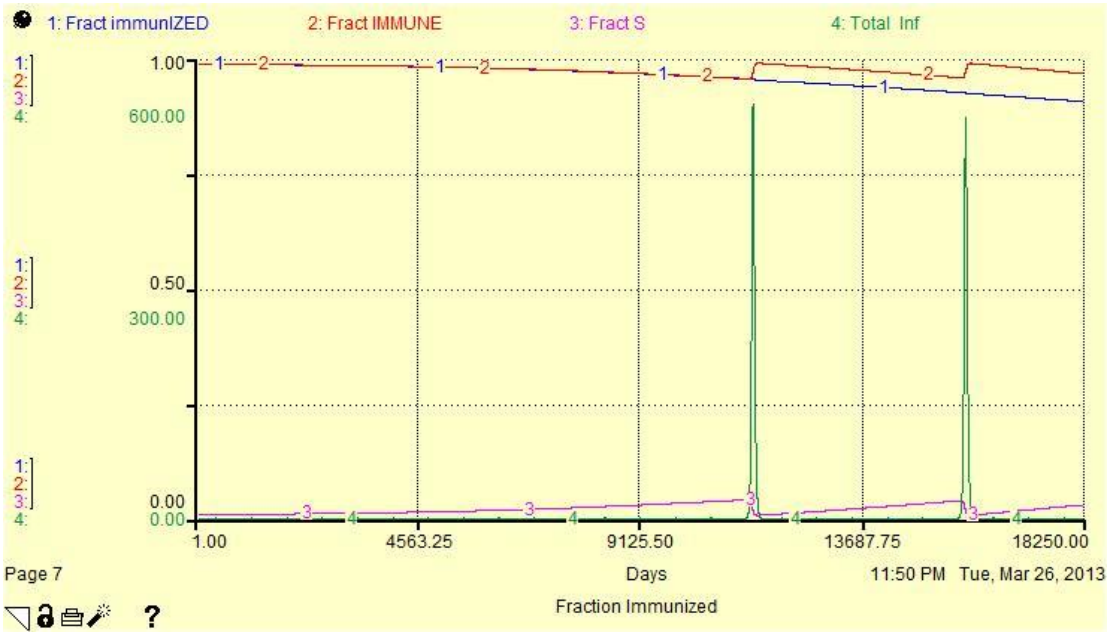


Figure 21: Population fractions with decreasing vaccination rate

this value to decrease.

Table 4
Characteristics of outbreaks with decreasing vaccination fraction

Year of outbreak	Length of outbreak (days)	Time between outbreaks (years)	Peak Infected	Fraction Immunized
31	314	n/a	542	0.96
43	338	12	525	0.93
Baseline	176-238	4	34,085	0.00

Interpretation

The purpose of this study was to develop a model and simulate the vaccination conditions under which endemic measles transmission or significant outbreaks could occur in a fictional population with characteristics similar to US population based on census data. The model shows that sporadic outbreaks will occur at any immunized fraction less than 0.96. This is the solid herd

immunity value for measles in this model. The higher the immunized fraction however, the smaller and less frequent the associated outbreaks are.

Length of outbreak

Based on the population characteristics used, the MACSEIR did not show endemic measles transmission in any of the tests that were ran. The longest outbreaks were 346 day long secondary outbreaks at two different vaccination fractions. This is due to the virus' high infectivity. It leads to an explosive outbreak that quickly moves almost all available susceptible people into an infected state.

Time between outbreaks

All three scenarios consistently showed that time between outbreaks increased (or outbreaks became less frequent) at higher immunized fractions. If solid herd immunity is not attained the closer a population is to it the fewer outbreaks there will be. While there should be concern at a measles outbreak, there is need for public health practitioners, epidemiologists and healthcare providers to realize that it will happen as a population approaches susceptible fraction threshold.

Peak infected

This metric has been used to measure the size of an outbreak. When model results were presented to public health department epidemiologists these values ran higher than expected, but were useful for scaled comparison of outbreaks. In other words, the MACSEIR is not a good tool for predicting the numerical size of outbreaks.

The MACSEIR shows that in a single event outbreak size depends on vaccination rate, the higher the immunized fraction the smaller the outbreak. When there are subsequent outbreaks,

size is bound by the susceptible fraction threshold. In the model, outbreaks persisted until susceptible fraction was less than 0.01. It can thus be concluded that outbreak size depends on the size of the pool of susceptible people in a population which is a function of immune fraction.

Susceptible fraction

This metric became significant as the MACSEIR was run. Though the literature emphasizes vaccination rates, it seems outbreaks are more sensitive to this value. Vaccination rates are the proportion of the population that has received the MMR, a more accurate measure of population resistance is the immune fraction which includes people with natural immunity. The sum of the immune fraction and the susceptible fraction make up the entire population. Whichever of these two is more easily acquired is a better metric than vaccination fraction. The susceptible fraction threshold according to the MACSEIR is 0.04. The threshold value calculated using historical data from the Netherlands by Wallinga et al (2005) is 0.043.

Implications

As long as immune fraction is less than 0.96, there will be sporadic measles outbreaks (Wallinga et al., 2005). The higher the vaccination fraction however, the smaller the outbreaks will be. More attention should be paid to the susceptible fraction. This will require immunologic population surveys. Though the US vaccination rate is high, the measles outbreaks of 2011 show a community level high susceptible fraction (Centers for Disease Control and Prevention, 2012a) hence a need for more community focused assessment of immune status. Some communities are built around shared ideologies such as non-vaccination (Britten, 2009; Salmon et al., 1999) creating pockets of susceptibility. If infected these individuals could carry the infection to similar communities causing a wide-spread infection chain.

Studies have shown that parents make vaccine decisions based on physician input (Brown et al., 2012; Insel, 2012; Kennedy, Basket, & Sheedy, 2011). In light of this primary care providers should make it a point to discuss their patients' vaccine status. Healthcare providers need ready access to educational materials for parents that cater to the parents as individuals. Educational material should meet the needs of the majority, but also the very educated and scientifically aware parent (Chen, 1999) as studies show that highly educated parents are more likely to refuse vaccination based on vaccine safety arguments (Insel, 2012). There is a niche for parental educational material that addresses the parents who would find the idea of multiple shots for their infant a more emotional than scientific decision (Britten, 2009). It would also be worthwhile for healthcare providers to make themselves knowledgeable on both sides of the vaccine safety argument so that they can have constructive debate with parents.

Rare, but high impact diseases like measles should always be included in the training of healthcare providers so that it is identified early. In its early stages measles symptom are very generic, providers need to be vigilant and carry a high level of suspicion based on the patient's medical history, travel history and vaccine status.

Vaccine exemptions are classified as medical (legal in all states), religious (legal in 48 states) and philosophical exemptions (legal in 15 states) (Feikin et al., 2000). The prevalent reason for vaccine exemption is unfortunately fear (Brown et al., 2012; Centers for Disease Control and Prevention, 2012a; Feikin et al., 2000; Insel, 2012). In some states the exemption process is as simple as signing an affidavit (Centers for Disease Control and Prevention, 2012a; Salmon et al., 1999). If this process is made more involving it might sway parents who are 'too busy' to vaccinate and see little risk of disease (Centers for Disease Control and Prevention, 2012a) and those who are not entirely convinced with regards to vaccination (Britten, 2009). If a more extensive submission that had to be renewed were developed it might serve as a deterrent while providing surveillance information. This data could later be used to contact exempt children

about vaccination once they become adults and are making their own decisions. Another gap in vaccination rate is due to lack of access to healthcare, but this is a very complex problem deserving individual study.

Chen (1999) suggests a need for greater transparency on vaccine safety risks by pharmaceutical companies. In light of the presence of a sector of the population that questions vaccine safety and the consequence of exemption, it is a reasonable response by vaccine manufacturers is to increase the standards and transparency of vaccine safety. Chen suggested a National Transport Safety Board equivalent (1999). Since the publication of his research the CDC has an Immunization Safety Office whose mission is to provide vaccine safety surveillance and research (http://www.cdc.gov/vaccinesafety/Activities/About_ISO.html). Johns Hopkins has an Institute for Vaccine Safety that provides the same service (http://www.vaccinesafety.edu).

Further research recommendations

The MACSEIR model would be more useful for public health professionals with the inclusion of outbreak interventions and their approximate cost. This would be useful for education and planning.

The immunization module can be extended to every cohort since people can get immunized at any age. This feature would be useful to depict pharmaceutical interventions by public health departments in response to outbreaks or periodic mass vaccinations.

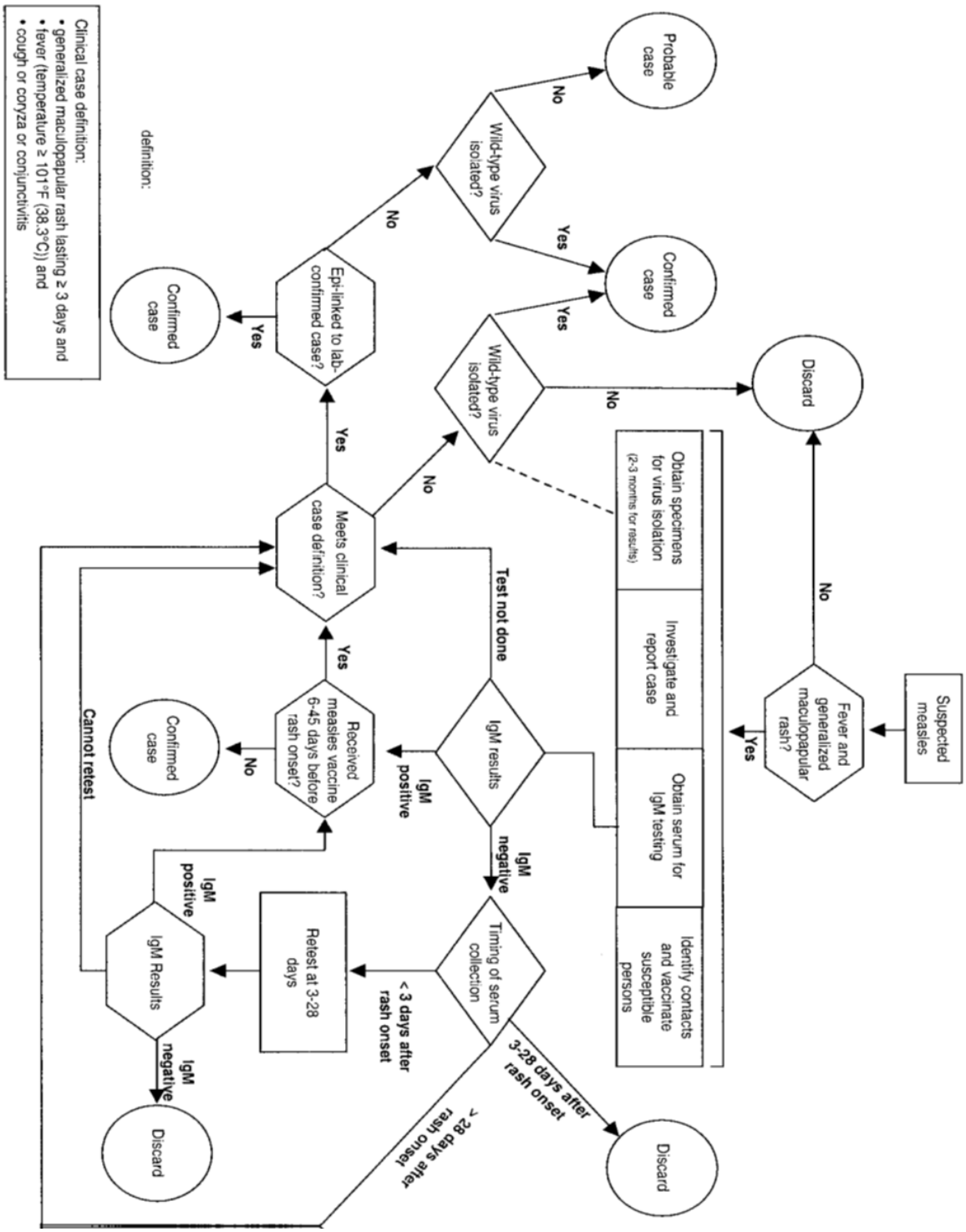
Analysis of disease spread by contact patterns may need a different modeling methodology, but would provide a better picture of transmission dynamics than total mixing. Based on their situation, some people have more potential than others to be super spreaders. A model that explores this would be useful for community level analysis, education and prevention efforts.

In its current state, the MACSEIR is beneficial for educating healthcare workers and policymakers. A game based model showing effects of an individual's vaccine decisions on a community would be an excellent tool to introduce public health concepts to an individual. Though people seek community well-being, they start with their families and their children. Vaccination decisions are a good example of the tragedy of the commons, but once people know the big picture effect of their decisions, they are well equipped to make better decisions.

Conclusion

Though there is low incidence compared to other parts of the world, the US is still at risk for measles outbreaks or varying size if exemption rates increase. This study sought to find vaccination conditions for endemic measles or significant outbreaks. Sporadic outbreaks will occur whenever the susceptible fraction is greater than, or equal to 4% of the population, and the outbreak length, size and frequency will depend on the vaccination fraction - the higher the vaccination rate, the better off. The decision to vaccinate will always be based on a balance of the risk of disease, the risk of adverse events, public health and personal freedom.

Appendix A: Measles case investigation and case classification flowchart (Guris et al., 2004)



Appendix B: Vaccine Safety Surveillance systems

1. The Vaccine Adverse Events Reporting System (VAERS)

   http://vaers.hhs.gov

2. The Vaccine Safety Datalink Project (VSD)

   http://www.cdc.gov/vaccinesafety/activities/vsd.html

3. Clinical Immunization Safety Assessment Centers (CISA)

   http://www.cdc.gov/vaccinesafety/activities/cisa.html

4. Institute of Medicine Vaccine Safety Reviews

   http://www.iom.edu/Reports.aspx (keyword search: vaccine)

Appendix C: Summary of Institute of Medicine findings on Measles vaccine and MMR

(Institute of Medicine, 1993)

Adverse Event	Incidence Rate[3] Reporting Rate	Biologic Plausibility	Case Reports, Series and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Category 2: evidence inadequate to accept or reject causal relation				
Encephalopathy – acquired brain injury	50 to 300 per million (5 to 30 per 100,000) 1 to 3.7 per million doses	Demonstrated	Indeterminate	Indeterminate
Sub-acute sclerosing panencephalitis – encephalopathy secondary to inflammation with demyelination	0.01 per million, (1963: 0.61 per million) (Gutierrez et al., 2010) 2 reports between 1989 and 1993, 0.7 per million doses (Centers for Disease Control and Prevention, 1982)	Demonstrated	Indeterminate	Indeterminate
Residual seizure – seizure within 72 hours post vaccination and at least two more in the next 12 months	0.5-2% (epilepsy) 0.15-1.53% of doses	Demonstrated	Indeterminate	No data
Sensorineural deafness – deafness due to cochlea damage	None available, occurs in 4% of mumps cases 2 cases reported before 1993	Theoretical only	Indeterminate (MMR)	No data
Optic neuritis – transient or permanent damage to one or both eyes due to optic nerve demyelination	5 per 100,000 (Holdeman, Nguyen, & Tang, 2012) 12 cases reported between 1978 and 1993	Demonstrated	Indeterminate	No data
Transverse myelitis – acute onset spinal cord demyelination	5 per million (Agmon-Levin, Kivity, Szyper-Kravitz, & Shoenfeld, 2009) 2 cases before 1993	Demonstrated	Indeterminate	No data
Guillain-Barre syndrome – acute onset motor weakness and peripheral nerve demyelination	1 per 100,000 1 per 1.8 million doses	Demonstrated	Indeterminate	No data

[3] Incidence rate = New cases/Persons at risk * multiplier
Report rate = Cases reported/Vaccine doses administered * multiplier (Varricchio et al., 2004)

Thrombocytopenia – low platelet count	31.9 per million (usually transient secondary to viral infection) 1 per 30,000-40,000 doses (in Finland and Sweden)	Demonstrated	Indeterminate (monovalent measles)	Indeterminate (monovalent measles)
Insulin dependent diabetes mellitus (IDDM)[4] – insufficient or absent insulin secretion by pancreatic beta cells	12-14 per 100,000 children 1 per 250,000 doses of mumps vaccine (in the former West Germany)	Theoretical only	Indeterminate	No data
Category 4: The evidence is adequate to accept causal relation				
Anaphylaxis – allergic reaction to components	4% (egg) (Savage, Matsui, Skripak, & Wood, 2007) 5 cases in 174 million doses	Theoretical only	For	No data
Category 5: Evidence establishes causal relation				
Thrombocytopenia (MMR) – low platelet count	31.9 per million (usually transient secondary to viral infection) 1 per 30,000-40,000 doses (in Finland and Sweden)	Demonstrated	For (MMR)	No data (MMR)
Anaphylaxis (MMR) – allergic reaction to components	4% (egg) (Savage et al., 2007) 5 cases in 174 million doses	Theoretical only	For (MMR)	No data (MMR)
Death from vaccine strain measles infection	N/A Low risk, possible in immunocompromised persons	Demonstrated	For	No data

[4] Pancreatitis and IDDM are well recorded following epidemic mumps (Institute of Medicine, 1993)

Appendix D: MACSEIR Model equations

```
Newborns(t) = Newborns(t - dt) + (dBR - Aging_to__Imm - Refuse_Imm__Aging_to_S -
        Missed_Imm_aging_to_S - Neonatal__DR) * dt
INIT Newborns = 1300
INFLOWS:
dBR = Daily_Live_f_BR*(Total_Sc_of__child_bearing__age+Total_Wa_population)*BR_switch
OUTFLOWS:
Aging_to__Imm = IF PSc_Imm_switch = 1
THEN to_PSc_aging_switch*(Newborns*Vacc_fraction)/days__until_S
ELSE PSc_Imm_switch
Refuse_Imm__Aging_to_S = to_PSc_aging_switch*((Newborns*Never_Imm_fraction)/days__until_S)
Missed_Imm_aging_to_S = to_PSc_aging_switch*(Newborns*(1-
        (Vacc_fraction+Never_Imm_fraction)))/days__until_S
Neonatal__DR = Newborns*Neonatal__mortality
PSc_aI(t) = PSc_aI(t - dt) + (PSc_becoming_infectious + PSc_Index - PSc_SoR) * dt
INIT PSc_aI = 0
INFLOWS:
PSc_becoming_infectious = If (Total__Inf<1) then (PSc_Exposed_incubating)
else
(PSc_Exposed_incubating/Ts)
PSc_Index = PULSE((PSc__index_cases*PSc__Disease_switch),pulse__start,PSc_index_freq)
OUTFLOWS:
PSc_SoR = If (Total__Inf<1)
Then (PSc_aI)
Else (PSc_aI/Ta)
PSc_Exposed_incubating(t) = PSc_Exposed_incubating(t - dt) + (PSc_'Not_yet__vaccinated'_IR +
        PSc_'Never_be_vaccinated'_IR - PSc_becoming_infectious) * dt
INIT PSc_Exposed_incubating = 0
INFLOWS:
PSc_'Not_yet__vaccinated'_IR = if (Total__Inf<1) then (0)
else
((infectivity*PSc_aI_CR*PSc_Sw_Awaiting_MMR)*aI_population_proportion)+((infectivity*PSc_sI_CR
        *PSc_Sw_Awaiting_MMR)*sI_population_proportion)
PSc_'Never_be_vaccinated'_IR = if(Total__Inf<1) then (0)
else
((infectivity*PSc_aI_CR*PSc_Sn_Never__Immunized)*aI_population_proportion)+((infectivity*PSc_sI_
        CR*PSc_Sn_Never__Immunized)*sI_population_proportion)
OUTFLOWS:
PSc_becoming_infectious = If (Total__Inf<1) then (PSc_Exposed_incubating)
else
(PSc_Exposed_incubating/Ts)
PSc_Imm(t) = PSc_Imm(t - dt) + (PSc__Imm_R - PSc_Imm_Aging - PSc_Imm_DR) * dt
INIT PSc_Imm = 4770
INFLOWS:
PSc__Imm_R = PSc__Immunized/PSc_days__to_Imm
OUTFLOWS:
PSc_Imm_Aging = to_Sc_aging_switch*(PSc_Imm/PSc_aging_time)
PSc_Imm_DR = PSc_Imm*PSc_f_DR
PSc_R(t) = PSc_R(t - dt) + (PSc_RR - PSc_R_DR - PSc_R_Aging) * dt
INIT PSc_R = 0
INFLOWS:
PSc_RR = If (Total__Inf<1)
Then (PSc_sI)
Else (PSc_sI/Td)
OUTFLOWS:
```

```
PSc_R_DR = PSc_R*PSc_f_DR
PSc_R_Aging = to_Sc_aging_switch*(PSc_R/PSc_aging_time)
PSc_sI(t) = PSc_sI(t - dt) + (PSc_SoR - PSc_RR - PSc_sI__DR) * dt
INIT PSc_sI = 0
INFLOWS:
PSc_SoR = If (Total__Inf<1)
Then (PSc_aI)
Else (PSc_aI/Ta)
OUTFLOWS:
PSc_RR = If (Total__Inf<1)
Then (PSc_sI)
Else (PSc_sI/Td)
PSc_sI__DR = (PSc_sI*PSc_f_DR)+(PSc_sI*I__f_DR)
PSc_Sn_Never__Immunized(t) = PSc_Sn_Never__Immunized(t - dt) + (Refuse_Imm__Aging_to_S +
        Missed_Imm_aging_to_S - PSc_Sn__DR - PSc_'Never_be_vaccinated'_IR - PSc_Sn__Aging) *
        dt
INIT PSc_Sn_Never__Immunized = 27
INFLOWS:
Refuse_Imm__Aging_to_S = to_PSc_aging_switch*((Newborns*Never_Imm_fraction)/days__until_S)
Missed_Imm_aging_to_S = to_PSc_aging_switch*(Newborns*(1-
        (Vacc_fraction+Never_Imm_fraction)))/days__until_S
OUTFLOWS:
PSc_Sn__DR = PSc_Sn_Never__Immunized*PSc_f_DR
PSc_'Never_be_vaccinated'_IR = if(Total__Inf<1) then (0)
else
((infectivity*PSc_aI_CR*PSc_Sn_Never__Immunized)*aI_population_proportion)+((infectivity*PSc_sI_
        CR*PSc_Sn_Never__Immunized)*sI_population_proportion)
PSc_Sn__Aging = to_Sc_aging_switch*(PSc_Sn_Never__Immunized/PSc_aging_time)
PSc_Sw_Awaiting_MMR(t) = PSc_Sw_Awaiting_MMR(t - dt) + (Aging_to__Imm - PSc__Imm_R -
        PSc_'Not_yet__vaccinated'_IR - PSc_Sw_DR) * dt
INIT PSc_Sw_Awaiting_MMR = 503
INFLOWS:
Aging_to__Imm = IF PSc_Imm_switch = 1
THEN to_PSc_aging_switch*(Newborns*Vacc_fraction)/days__until_S
ELSE PSc_Imm_switch
OUTFLOWS:
PSc__Imm_R = PSc__Immunized/PSc_days__to_Imm
PSc_'Not_yet__vaccinated'_IR = if (Total__Inf<1) then (0)
else
((infectivity*PSc_aI_CR*PSc_Sw_Awaiting_MMR)*aI_population_proportion)+((infectivity*PSc_sI_CR
        *PSc_Sw_Awaiting_MMR)*sI_population_proportion)
PSc_Sw_DR = PSc_Sw_Awaiting_MMR*PSc_f_DR
Ret_aI(t) = Ret_aI(t - dt) + (Ret_becoming_infectious + Ret_Index - Ret_SoR) * dt
INIT Ret_aI = 0
INFLOWS:
Ret_becoming_infectious = if(Total__Inf<1) then (Ret_Exposed_incubating)
else
(Ret_Exposed_incubating/Ts)
Ret_Index = PULSE((Ret_index_cases*Ret__Disease_switch),pulse__start,Ret_index_freq)
OUTFLOWS:
Ret_SoR = If (Total__Inf<1)
Then (Ret_aI)
Else (Ret_aI/Ta)
Ret_Exposed_incubating(t) = Ret_Exposed_incubating(t - dt) + (Ret_Sn_IR - Ret_becoming_infectious) *
        dt
INIT Ret_Exposed_incubating = 0
```

```
INFLOWS:
Ret_Sn_IR = if(Total__Inf<1) then (0)
else
((infectivity*Ret_aI_CR*Ret_Susceptible)*aI_population_proportion)+((infectivity*Ret_sI_CR*Ret_Susc
        eptible)*sI_population_proportion)
OUTFLOWS:
Ret_becoming_infectious = if(Total__Inf<1) then (Ret_Exposed_incubating)
else
(Ret_Exposed_incubating/Ts)
Ret_Imm(t) = Ret_Imm(t - dt) + (Wa_Imm_Aging - Ret_Imm_DR) * dt
INIT Ret_Imm = 11700
INFLOWS:
Wa_Imm_Aging = to_Ret_aging_switch*(Wa_Imm/Wa_aging_time)
OUTFLOWS:
Ret_Imm_DR = Ret_Imm*Ret__f_DR
Ret_R(t) = Ret_R(t - dt) + (Ret_RR + Wa_R_Aging - Ret_R_DR) * dt
INIT Ret_R = 0
INFLOWS:
Ret_RR = IF (Total__Inf<1)
Then (Ret_sI)
Else (Ret_sI/Td)
Wa_R_Aging = to_Ret_aging_switch*(Wa_R/Wa_aging_time)
OUTFLOWS:
Ret_R_DR = Ret_R*Ret__f_DR
Ret_sI(t) = Ret_sI(t - dt) + (Ret_SoR - Ret_RR - Ret_sI__DR) * dt
INIT Ret_sI = 0
INFLOWS:
Ret_SoR = If (Total__Inf<1)
Then (Ret_aI)
Else (Ret_aI/Ta)
OUTFLOWS:
Ret_RR = IF (Total__Inf<1)
Then (Ret_sI)
Else (Ret_sI/Td)
Ret_sI__DR = (Ret_sI*Ret__f_DR)+(Ret_sI*I__f_DR)
Ret_Susceptible(t) = Ret_Susceptible(t - dt) + (Wa_Sn_Aging - Ret_Sn__DR - Ret_Sn_IR) * dt
INIT Ret_Susceptible = 1300
INFLOWS:
Wa_Sn_Aging = to_Ret_aging_switch*(Wa_Susceptible/Wa_aging_time)
OUTFLOWS:
Ret_Sn__DR = Ret_Susceptible*Ret__f_DR
Ret_Sn_IR = if(Total__Inf<1) then (0)
else
((infectivity*Ret_aI_CR*Ret_Susceptible)*aI_population_proportion)+((infectivity*Ret_sI_CR*Ret_Susc
        eptible)*sI_population_proportion)
Sc_aI(t) = Sc_aI(t - dt) + (Sc_Index + Sc_becoming_infectious - Sc_SoR) * dt
INIT Sc_aI = 0
INFLOWS:
Sc_Index = PULSE((Sc__index_cases*Sc_Disease_switch),pulse__start,Sc_index_freq)
Sc_becoming_infectious = IF (Total__Inf<1) then (Sc_Exposed_incubating)
Else
(Sc_Exposed_incubating/Ts)
OUTFLOWS:
Sc_SoR = if (Total__Inf<1)
Then (Sc_aI)
Else (Sc_aI/Ta)
```

```
Sc_Exposed_incubating(t) = Sc_Exposed_incubating(t - dt) + (Sc_Sn_IR - Sc_becoming_infectious) * dt
INIT Sc_Exposed_incubating = 0
INFLOWS:
Sc_Sn_IR = if(Total__Inf<1) then (0)
else
((infectivity*Sc_aI_CR*Sc_Susceptible)*aI_population_proportion)+((infectivity*Sc_sI_CR*Sc_Suscepti
        ble)*sI_population_proportion)
OUTFLOWS:
Sc_becoming_infectious = IF (Total__Inf<1) then (Sc_Exposed_incubating)
Else
(Sc_Exposed_incubating/Ts)
Sc_Imm(t) = Sc_Imm(t - dt) + (PSc_Imm_Aging - Sc_Imm_DR - Sc_Imm_Aging) * dt
INIT Sc_Imm = 24660
INFLOWS:
PSc_Imm_Aging = to_Sc_aging_switch*(PSc_Imm/PSc_aging_time)
OUTFLOWS:
Sc_Imm_DR = Sc_Imm*Sc_f_DR
Sc_Imm_Aging = to_Wa_aging_switch*(Sc_Imm/Sc_aging_time)
Sc_R(t) = Sc_R(t - dt) + (Sc_RR + PSc_R_Aging - Sc_R_DR - Sc_R_Aging) * dt
INIT Sc_R = 0
INFLOWS:
Sc_RR = IF (Total__Inf<1)
Then (Sc_sI)
Else (Sc_sI/Td)
PSc_R_Aging = to_Sc_aging_switch*(PSc_R/PSc_aging_time)
OUTFLOWS:
Sc_R_DR = Sc_R*Sc_f_DR
Sc_R_Aging = to_Wa_aging_switch*(Sc_R/Sc_aging_time)
Sc_sI(t) = Sc_sI(t - dt) + (Sc_SoR - Sc_RR - Sc_sI__DR) * dt
INIT Sc_sI = 0
INFLOWS:
Sc_SoR = if (Total__Inf<1)
Then (Sc_aI)
Else (Sc_aI/Ta)
OUTFLOWS:
Sc_RR = IF (Total__Inf<1)
Then (Sc_sI)
Else (Sc_sI/Td)
Sc_sI__DR = (Sc_sI*Sc_f_DR)+(Sc_sI*I__f_DR)
Sc_Susceptible(t) = Sc_Susceptible(t - dt) + (PSc_Sn__Aging - Sc_Sn__DR - Sc_Sn_IR - Sc_Sn__Aging)
        * dt
INIT Sc_Susceptible = 2740
INFLOWS:
PSc_Sn__Aging = to_Sc_aging_switch*(PSc_Sn_Never__Immunized/PSc_aging_time)
OUTFLOWS:
Sc_Sn__DR = Sc_Susceptible*Sc_f_DR
Sc_Sn_IR = if(Total__Inf<1) then (0)
else
((infectivity*Sc_aI_CR*Sc_Susceptible)*aI_population_proportion)+((infectivity*Sc_sI_CR*Sc_Suscepti
        ble)*sI_population_proportion)
Sc_Sn__Aging = to_Wa_aging_switch*(Sc_Susceptible/Sc_aging_time)
Wa_aI(t) = Wa_aI(t - dt) + (Wa_becoming_infectious + Wa_Index - Wa_SoR) * dt
INIT Wa_aI = 0
INFLOWS:
Wa_becoming_infectious = if(Total__Inf<1) then (Wa_Exposed_incubating)
else
```

```
(Wa_Exposed_incubating/Ts)
Wa_Index = PULSE((Wa__index_cases*Wa__Disease_switch),pulse__start,Wa_index_freq)
OUTFLOWS:
Wa_SoR = if (Total__Inf<1)
Then (Wa_aI)
Else (Wa_aI/Ta)
Wa_Exposed_incubating(t) = Wa_Exposed_incubating(t - dt) + (Wa_Sn_IR - Wa_becoming_infectious) *
        dt
INIT Wa_Exposed_incubating = 0
INFLOWS:
Wa_Sn_IR = if(Total__Inf<1) then (0)
else
((infectivity*Wa_aI_CR*Wa_Susceptible)*aI_population_proportion)+((infectivity*Wa_sI_CR*Wa_Susc
        eptible)*sI_population_proportion)
OUTFLOWS:
Wa_becoming_infectious = if(Total__Inf<1) then (Wa_Exposed_incubating)
else
(Wa_Exposed_incubating/Ts)
Wa_Imm(t) = Wa_Imm(t - dt) + (Sc_Imm_Aging - Wa_Imm_Aging - Wa_Imm_DR) * dt
INIT Wa_Imm = 47700
INFLOWS:
Sc_Imm_Aging = to_Wa_aging_switch*(Sc_Imm/Sc_aging_time)
OUTFLOWS:
Wa_Imm_Aging = to_Ret_aging_switch*(Wa_Imm/Wa_aging_time)
Wa_Imm_DR = Wa_Imm*Wa_f_DR
Wa_R(t) = Wa_R(t - dt) + (Wa_RR + Sc_R_Aging - Wa_R_DR - Wa_R_Aging) * dt
INIT Wa_R = 0
INFLOWS:
Wa_RR = if (Total__Inf<1)
Then (Wa_sI)
Else (Wa_sI/Td)
Sc_R_Aging = to_Wa_aging_switch*(Sc_R/Sc_aging_time)
OUTFLOWS:
Wa_R_DR = Wa_R*Wa_f_DR
Wa_R_Aging = to_Ret_aging_switch*(Wa_R/Wa_aging_time)
Wa_sI(t) = Wa_sI(t - dt) + (Wa_SoR - Wa_RR - Wa_sI__DR) * dt
INIT Wa_sI = 0
INFLOWS:
Wa_SoR = if (Total__Inf<1)
Then (Wa_aI)
Else (Wa_aI/Ta)
OUTFLOWS:
Wa_RR = if (Total__Inf<1)
Then (Wa_sI)
Else (Wa_sI/Td)
Wa_sI__DR = (Wa_sI*Wa_f_DR)+(Wa_sI*I__f_DR)
Wa_Susceptible(t) = Wa_Susceptible(t - dt) + (Sc_Sn__Aging - Wa_Sn__DR - Wa_Sn_IR -
        Wa_Sn_Aging) * dt
INIT Wa_Susceptible = 5300
INFLOWS:
Sc_Sn__Aging = to_Wa_aging_switch*(Sc_Susceptible/Sc_aging_time)
OUTFLOWS:
Wa_Sn__DR = Wa_Susceptible*Wa_f_DR
Wa_Sn_IR = if(Total__Inf<1) then (0)
else
```

((infectivity*Wa_aI_CR*Wa_Susceptible)*aI_population_proportion)+((infectivity*Wa_sI_CR*Wa_Susc
eptible)*sI_population_proportion)
Wa_Sn_Aging = to_Ret_aging_switch*(Wa_Susceptible/Wa_aging_time)
aI_population_proportion = Total_aI/Total__Population
Annual_BR = 64.1
BR_switch = 1
Daily_Live_f_BR = ((Annual_BR*0.508)/1000)/365
days__until_S = 212
Fract_IMMUNE = (Total_Imm+Newborns+Total_R)/Total__Population
Fract_immunIZED = Total_Imm/(Total__Population-Newborns)
Fract_S = (Total_S-PSc_Sw_Awaiting_MMR)/(Total__Population-Newborns)
infectivity = 0.9
I__f_DR = 1/365
Neonatal__mortality = 4.18/1000/365
Never_Imm_fraction = 0.015
PSc_aging_time = 1642
PSc_aI_CR = 10
PSc_days__to_Imm = 28
PSc_f_DR = 3.920E-06
PSc_Imm_switch = 1
PSc_index_freq = 200
PSc_sI_CR = 3
PSc__Disease_switch = 0
PSc__Immunized = (PSc_Sw_Awaiting_MMR*Veff)*PSc_Imm_switch
PSc__index_cases = 0
PSc__Total_Inf = PSc_aI+PSc_sI
pulse__start = 0
Ret_aI_CR = 8
Ret_index_cases = 0
Ret_index_freq = 200
Ret_sI_CR = 3
Ret_Total_Inf = Ret_aI+Ret_sI
Ret__Disease_switch = 1
Ret__f_DR = 1.223E-04
Sc_aging_time = 4745
Sc_aI_CR = 15
Sc_childbearing_fraction = 0.515
Sc_Disease_switch = 1
Sc_f_DR = 1.127e-6
Sc_index_freq = 200
Sc_sI_CR = 3
Sc_Total_Inf = Sc_aI+Sc_sI
Sc__index_cases = 0
sI_population_proportion = Total_sI/Total__Population
Ta = 4
Td = 4
Total_aI = PSc_aI+Ret_aI+Sc_aI+Wa_aI
Total_E =
PSc_Exposed_incubating+Ret_Exposed_incubating+Sc_Exposed_incubating+Wa_Exposed_incu
bating
Total_Imm = PSc_Imm+Ret_Imm+Sc_Imm+Wa_Imm
Total_PSc_population =
PSc_aI+PSc_Exposed_incubating+PSc_Imm+PSc_R+PSc_sI+PSc_Sn_Never__Immunized+PSc_
Sw_Awaiting_MMR
Total_PSc__Susceptible = PSc_Sn_Never__Immunized+PSc_Sw_Awaiting_MMR
Total_R = PSc_R+Ret_R+Sc_R+Wa_R

Total_Ret_population = Ret_aI+Ret_Exposed_incubating+Ret_Imm+Ret_R+Ret_sI+Ret_Susceptible
Total_S =
    PSc_Sn_Never__Immunized+PSc_Sw_Awaiting_MMR+Ret_Susceptible+Sc_Susceptible+Wa_Susceptible
Total_Sc_of__child_bearing__age = Sc_childbearing_fraction*Total_Sc_population
Total_Sc_population = Sc_aI+Sc_Exposed_incubating+Sc_Imm+Sc_R+Sc_sI+Sc_Susceptible
Total_sI = PSc_sI+Ret_sI+Sc_sI+Wa_sI
Total_Wa_population = Wa_aI+Wa_Exposed_incubating+Wa_Imm+Wa_R+Wa_sI+Wa_Susceptible
Total__Inf = Total_aI+Total_sI
Total__Population =
    Newborns+Total_PSc_population+Total_Ret_population+Total_Sc_population+Total_Wa_population
to_PSc_aging_switch = 1
to_Ret_aging_switch = 1
to_Sc_aging_switch = 1
to_Wa_aging_switch = 1
Ts = 12
Vacc_fraction = 0.915
Veff = 1
Wa_aging_time = 14235
Wa_aI_CR = 12
Wa_f_DR = 1.015e-5
Wa_index_freq = 200
Wa_sI_CR = 3
Wa_Total_Inf = Wa_aI+Wa_sI
Wa__Disease_switch = 1
Wa__index_cases = 0

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