A MATHEMATICAL MODEL OF THE 2014 OHIO MEASLES OUTBREAK TO ASSESS THE EFFECTIVENESS OF THE PUBLIC HEALTH RESPONSE

THESIS

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Measles is a highly contagious viral illness that was declared eliminated from the United States in 2000 after decades of focused vaccination campaigns. However, pockets of measles-susceptible individuals exist across the United States that are at high risk for a measles outbreak should the virus be imported. In early 2014, an Amish individual traveled to the Philippines for aid work and returned to the largely unvaccinated and susceptible Ohio Amish community infected with the measles virus. The resultant outbreak was the largest measles outbreak in the United States in 20 years. The Ohio Department of Health quickly set a mass vaccination campaign into motion with the goal of immunizing susceptible Amish individuals and stopping the virus in its tracks. Here we develop a mathematical model of the measles outbreak in Knox County, Ohio, using a susceptible-exposed-infectious-recovered (SEIR) model implemented with the stochastic Gillespie algorithm. Using this model, we investigate the effectiveness of the public health vaccination campaign. Model results suggest higher probabilities of worse outcomes in the form of more cases and longer outbreaks when vaccination is removed or delayed, suggesting the positive utility of vaccination as a public health intervention in the Knox County Amish community.
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Measles is a vaccine-preventable disease caused by the measles virus. The measles virus is highly infectious, and when introduced, spreads through a susceptible population like wildfire. In the pre-vaccination era, nearly everyone developed measles in childhood during cyclical, seasonal outbreaks, gaining lifelong immunity to the virus as a result of infection. However, high infectivity and transient virus-induced immunosuppression led to large numbers of cases with serious infectious complications of the lower respiratory tract and brain, ending in large numbers of deaths. The licensure of the highly effective live attenuated measles vaccine in 1963 brought the promise of elimination and even eradication of one of the world’s most common infectious diseases.

Measles remains an important cause of disease burden globally, but in the United States, successful two-dose vaccination campaigns helped the country reach its measles elimination goal in 2000. While vaccination rates are generally high across America, there remain pockets of susceptible individuals who are not vaccinated for a variety of reasons. North America is home to a significant, generally susceptible population in the form of the Amish community, whose population numbers in the hundreds of thousands across rural areas of the continent. While the Amish reject many aspects of modern life, immunization is not specifically one of them; instead, many Amish do not prioritize vaccination in their day-to-day life, especially when the disease is
not endemic and their children may not be at risk [21, 66]. However, the Amish are flexible regarding vaccination [42] and may choose to be vaccinated in the wake of outbreak in their community, especially when logistical barriers such as long-distance travel are reduced [35].

In the spring and summer of 2014, an outbreak of measles occurred in the central Ohio Amish community after an Amish individual returned from aid work in the Philippines infected with the measles virus. When the Ohio Department of Health was notified of the presence of measles in the world’s largest Amish community, local health departments initiated a mass vaccination campaign with the goal of quickly reducing the number of people at risk for infection by the virus. Over the course of four months, 382 people across nine Ohio counties became infected by the measles virus. The outbreak was declared ended after two incubation periods without a case, on September 4, 2014.

The simplicity of its well-studied biology and epidemiology make measles a popular disease for mathematical modeling. Mathematical modeling of epidemics is a useful tool that can help evaluate outbreaks of disease under different scenarios, such as various public health interventions. At the population level, measles is typically modeled using a susceptible-exposed-infectious-recovered (SEIR) epidemiological compartment model, which incorporates the disease’s long latent and infectious periods into model dynamics.

Here we report on mathematical modeling research conducted using Ohio Department of Health data from the 2014 measles outbreak. An SEIR model was constructed to model the measles outbreak and was implemented using the Gillespie algorithm, which takes the stochastic nature of disease in small populations into consideration. The model focused on the area of Knox County, Ohio, where the outbreak began and over half of the cases occurred. Demographic data of the Amish community was used
to determine the effective susceptible population size. The goal of the model was to determine the impact of the public health vaccination campaign on the course of the outbreak in Knox County by interpreting the summary statistics of final outbreak size and outbreak duration under different vaccination scenarios.
CHAPTER 2
BACKGROUND

2.1 Biology and Epidemiology of Measles

2.1.1 Measles Virus

Measles (rubeola) virus is a paramyxovirus in the genus Morbillivirus [14]. Like other viruses in the Paramyxoviridae family, measles has a monopartite, negative-sense, single-stranded RNA genome enclosed in a helical nucleocapsid surrounded by a bilayered lipid envelope. Measles virus envelope glycoprotein spikes facilitate cell attachment via the virus’s hemagglutinin (H) protein and membrane fusion via its fusion (F) protein.

The measles virus infects only humans and certain non-human primates [53, 54] through H protein attachment to the signaling lymphocyte activation molecule (SLAM, also called CD150) protein on the surface of many immune cells and an unknown receptor on endothelial, epithelial, and neural cells [57, 65]. SLAM proteins have the important function of conveying regulatory signals between immune cells. Many vaccine and lab-adapted strains have evolved to also utilize a ubiquitously expressed alternate receptor, CD46 [65]. A glycoprotein found on all nucleated cells, CD46 functions to bind the complement proteins C3b and C4b, which results in their degradation by serum proteases and prevention of the formation of the membrane attack complex (MAC) against uninfected cells [57]. The H protein does not agglutinate
human red blood cells because they lack CD46; however, H protein can agglutinate erythrocytes of animals, including sheep and monkeys [57].

**Replication Cycle**

Once the measles virus has attached to the host cell via the appropriate receptor, the measles F protein initiates pH-independent fusion with the cell membrane, allowing for insertion of the ribonucleoprotein (RNP) core into the cytoplasm of the host cell [57]. The RNP core consists of the viral polymerase (L protein), polymerase co-factor (P protein), and multiple copies of the RNA genome arranged in a helical structure with the support of the nucleocapsid (N) protein [40]. The viral polymerase then initiates transcription at the viral RNA promoter in order to produce positive-sense RNA transcripts that can be translated into viral proteins by host cell ribosomes [57]. Differential transcription results in a greater number of transcripts produced from genes located near the promoter (such as N), and fewer transcripts produced from genes farther away from the promoter (such as L) [57].

The host cell uses the positive-sense RNA transcripts to synthesize six virus structural proteins: nucleocapsid (N) protein, matrix (M) protein, fusion (F) protein, hemagglutinin (H), phosphoprotein (P), and large (L) protein, which is the RNA-dependent RNA polymerase that forms the transcription-replication complex along with the P protein [53]. The virus follows the “rule of six”: one N protein associates with six genomic ribonucleotides, effectively limiting the genome length to a multiple of six [57]. The N protein sheath helps condense the RNA into a smaller, more stable, easy-to-package form. The M protein functions to “bridge” the envelope (proteins) and the RNP complex, which stabilizes the virion structure and modulates membrane fusion [57].
The gene encoding the structural P protein also encodes the three nonstructural proteins C, R, and V through overlapping reading frames and ribosomal frameshift [32], [57]. Measles C and V proteins are important virulence factors with separate mechanisms of action during in vivo infection of laboratory animals [49]. The mechanism of their pathogenicity may be to antagonize the proper functioning of the innate interferon response, an important step in the activation of the adaptive immune system against viral infection [24, 32]. The C protein also helps regulate measles RNA transcription and genome replication [2]. The R protein is translated at very low levels, and little is known about its significance in vivo [55].

The viral RNA-dependent RNA polymerase also produces new copies of the measles virus genome [3]. First, the polymerase copies the full length of the genome into a positive-sense strand that is immediately encapsidated by N protein [3, 52]. The antigenome RNP template contains a strong promoter that drives excess production of negative-sense RNP genomes, the form included in the infectious virion as it exits the cell [52].

Following transcription, translation, and genome replication, the virus proteins assemble together to create new virions. The negative-sense RNP associates with P and L proteins [57]. The H and F proteins acquire membrane status in the endoplasmic reticulum, then undergo modification in the Golgi apparatus before being translocated to lipid rafts in the plasma membrane. Finally, M proteins aggregate the glycoprotein spikes and nucleocapsids together in preparation for viral budding. The entire replication cycle takes about 24 hours [59], and produces pleomorphic virions that range in size from 120-250 nanometers, with round, filamentous, or irregular shapes [57].
2.1.2 Clinical Disease

Measles virus enters the body through the upper respiratory tract or conjunctiva and causes an upper respiratory tract infection followed by replication in the draining lymph nodes and viremic dissemination via peripheral blood mononuclear cells [56, 57]. A secondary viremia occurs five to seven days after exposure, which causes infection of the skin and internal organs [51, 57]. Viremia dissipates as antibody production rises [59].

Disease caused by measles virus follows a typical course. The two- to four-day prodromal stage of infection consists of high fever, malaise, cough, coryza, conjunctivitis, and often photophobia [8, 14, 57]. The characteristic enanthem of Koplik spots (raised spots with white centers) appear on the oral mucosa near the second molars at the end of the prodromal stage, and last about 3 days [5, 57]. A maculopapular exanthem appears one to two days later, about 14 days after exposure to the virus, and begins on the head, then extends down the trunk, and finally reaches the extremities [14, 57]. This rash, initially blanching upon pressure, lasts five to six days and fades in order of rash appearance on the body [57, 59]. The patient shows rapid improvement in the form of fewer symptoms and decreased virus shedding from the height of the rash, unless complications occur [57]. Subclinical infections are rare [14, 6].

Multinucleated giant cells (syncytia) are often observed in affected organs, formed by the action of excess measles F protein fusing neighboring host cells together [57]. This is a quicker killer of cells than virus production. Cells affected by the rash and Koplik spots also display syncytia formation [59].

Measles virus is lymphotropic, infecting B and T cells as well as monocytes (especially late in infection) [57]. Immune cell infection causes generalized immunosuppression lasting one to four weeks [28]. Lymphopenia of B and T cells is observed during
typical measles infection [57]. This may be due to measles glycoproteins causing reduced interleukin-12 (IL-12) secretion by host cells, making dendritic cells ineffective at stimulating T cell activation [57]. But even uninfected lymphocytes recovered from measles patients fail to proliferate upon stimulation [55]. Immunosuppression may last for weeks after recovery, characterized by inhibition of delayed-type hypersensitivity responses and reduced lymphocyte proliferation in response to stimulation, even when the patient is no longer lymphopenic [57]. Immunosuppression and generalized damage to the respiratory tract make the patient vulnerable to secondary infections, which can cause serious complications [6, 51].

Measles virus infection is cleared by the cell-mediated immune system [57]. First, transient interleukin-2 (IL-2) and interferon-gamma (IFN-γ) cytokines are produced, followed by production of IL-4 [59]. These cytokines encourage the differentiation and activation of CD8+ cytotoxic T cells, which destroy virus-infected cells, and CD4+ helper T cells, which stimulate antibody production during rash onset. Interestingly, CD4+ T cells are simultaneously depleted in the week before and weeks following rash onset [59]. Children with agammaglobulinemia have normal measles disease, which suggests the importance of cell-mediated rather than humoral immunity in clearing the infection [36, 59]. The characteristic rash may never appear in patients with compromised cell-mediated immunity, as the exanthem is caused by damage to vascular walls due to the delayed-type hypersensitivity reaction [57].

Maternal IgG antibodies protect babies for the first months of life, even up to 1 year old [59]. Modified measles, with decreased symptomatology, occurs with measles exposure in infants with residual antibodies or those treated with anti-measles immunoglobulin (IG) or, occasionally, live vaccine failure [57, 59].
Complications

Measles virus-induced immunosuppression leads to (often superinfectious) complications in up to 40% of cases [36]. Complications can include diarrhea, otitis media, pneumonia (viral, bacterial, or giant cell), and encephalitis [36]. Complications are especially prominent in malnourished patients [5, 8].

The most common lethal complications of measles are pneumonitis, gastroenteritis, and secondary bacterial infections. In children, pneumonia is the leading cause of death by measles [5], while adults more frequently experience acute encephalitis [59]. Children under five and adults older than 20 are more likely to experience severe disease, complications, and death from measles [59]. More than 95% of measles deaths occur in low-income nations due to a variety of factors: less developed healthcare systems, lower vaccination rates, and malnutrition, among others [59].

Malnourished or immunosuppressed cases are more likely to have long-lasting (three to four weeks long) measles infection due to a weakened immune response, and high death rates among those who develop pneumonia [8] or measles inclusion-body encephalitis (MIBE) [59]. Such patients may not even display a rash, which is the result of a functional adaptive immune response [36]. Measles is severe in HIV-infected children, who have displayed up to 50% mortality rates [59]. Pregnant women infected with measles virus are at risk for premature labor, miscarriage, babies with low birth weight, stillbirth, and abortion, especially when the mother is infected during the first trimester [8, 47, 57, 59].

Occasionally, measles infects the brain and may cause a number of different brain diseases. Central nervous system (CNS) involvement is probably common even in uncomplicated measles, as evidenced by abnormal electroencephalogram (EEG) and reports of headache in 50% of patients [57]. The CNS is the only site with persistent measles virus infection [56].
Acute postinfectious measles encephalomyelitis (APME) is one CNS complication of measles. This complication usually occurs four to five days after rash onset, but may occur before or during the rash, or up to 3 weeks later [28, 57]. High mortality (10-40%) results, and over 50% of surviving cases report subsequent sequelae, including mental retardation, paraplegia, or ataxia [62]. No measles antigen or RNA is detected in the CNS, and only very rarely is measles virus detected in the cerebrospinal fluid (CSF); however, myelin basic protein (MBP) is often found in the CSF. This demyelination suggests an immunologically driven inflammatory process [28, 62]. The pathology of this CNS complication is similar to experimental autoimmune encephalomyelitis, which suggests that it may be caused by an autoimmune reaction. Infection of lymphocytes may disrupt regulation of self-reactive immune cells that are normally under control and allow for cell-mediated immune responses against host myelin [28], since no hyperimmune response to measles virus exists [56]. Alternatively, MBP and measles antigens may be similar enough such that antibodies to the virus may cross-react with MBP [62]. About 0.1% of cases are affected, with incidence lower in children under two years old [28].

Subacute measles encephalitis (or measles inclusion body encephalitis, MIBE) is considered an opportunistic measles infection of the brain, and occurs in immunocompromised patients [28]. The complication occurs one to six months after measles infection, usually involves localized seizures, and may last days to weeks, ultimately ending in coma and death [57]. Eosinophilic inclusion bodies are seen in neural cells of these patients. Measles antigen is detected and the virus is readily isolated from brain tissue culture, but no measles antibodies are detected in the CSF [28, 57]. Measles viruses that cause MIBE have many mutations along their genome, which drastically reduces glycoprotein production, preventing giant cell formation, and eliminates M protein synthesis [57].
Subacute sclerosing panencephalitis (SSPE) is a rare, fatal complication of the CNS that develops several (six to eight, but sometimes to 20-30) years after recovery from natural measles infection [57]. It is unknown where the virus persists during the incubation period [57]. After the onset of SSPE, four stages of mental deterioration take place over the course of months, affecting both the white and gray matter in the brain; death typically occurs within 3 years [28]. Temporary remission is common, but the disease is nearly always lethal [57]. While patients with SSPE do not show symptoms of acute infection, they do have extremely high serum and CSF measles antibody titers, except to the M protein [28, 56, 57], and many neural cells contain measles antigen and RNA and display characteristic intranuclear eosinophilic inclusion bodies [28]. Serum antibodies are polyclonal, but CSF antibodies are oligoclonal, suggesting that they are produced by a small population of plasma cells that migrated to the CSF in response to measles antigens located in the CNS [57].

Viruses recovered from SSPE patients display significant mutational change in their genomes, which helps the virus escape immune clearance but also causes loss of functionality for proteins on which little selection pressure exists, such as the M protein [56]. It is likely that a defective virus is required for SSPE development [62]. Interestingly, the SSPE virus is incapable of budding infectious virus particles from neural cells; nucleocapsids accumulate in the cytoplasm and nucleus, but the virus remains cell-associated, possibly due to the lack of the M protein which facilitates budding, or functional H and F proteins [28, 57]. In MIBE and SSPE, the virus’s ability to mature and bud is reduced or abolished, but it maintains the ability to transcribe and replicate its genome [56]. As such, SSPE virus can only be recovered when co-cultivated with non-neural cells, although it is not clear whether these recovered viruses are typical of SSPE brains, or if they have reverted to become
replication-competent again, or alternatively are laboratory cotaminants [56, 57]. The host immune response could play a role in SSPE development [57].

SSPE is a result of accidental persistent infection, not evolutionary selection [10]. This complication is caused by wild-type virus genotypes, and incidence of the disease has decreased drastically since introduction of the measles vaccine [57, 59]. SSPE occurs in about one per million children each year in unvaccinated populations [28]. SSPE typically manifests itself around age nine, although the range can be one to 35 years old. Males are affected more than three times as frequently as females, as are children who have been infected by measles before the age of two, and rural children.

Host susceptibility, including age and immune status, is likely the driving force in developing severe complications like SSPE, not the virulence of various virus genotypes [57]. An immature immune system, especially one supplemented by maternal, external, or cross-reactive antibodies, may explain the initiation or persistence of infection [28]. Cell-mediated immunity is often deficient in people with persistent measles virus infections of the CNS.

Recovery, Treatment, and Prevention

For most patients, the disease is uncomplicated: the immune system clears the infection, with CD8+ T cells destroying virus-infected cells and type 2 CD4+ T cells stimulating cytokine production and antibody development [8, 36, 59]. Immunoglobulin M (IgM), IgA, and IgG antibodies develop during first few days of rash (about 2 weeks after infection), and protective IgG antibodies persist at a low level for life [59]. Since the adaptive immune system is so important in resolving the infection, measles can be devastating in patients with a compromised adaptive immune system.

Cases with severe measles often have a vitamin A deficiency, which together with measles infection can lead to blindness. Therefore, vitamin A is essential in the
therapy of infants, immunosuppressed young children, or measles-affected children in countries associated with vitamin A deficiency [6, 59]. In fact, timely vitamin A administration can prevent up to 50% of measles deaths [47].

No antiviral therapy has been developed for measles. Many complications of measles are superinfections caused by bacteria, which may be treated with the appropriate antibiotics. Loss of fluids from gastroenteritis should be treated with oral rehydration solutions to prevent dehydration [47]. Administration of ribavirin (an RNA nucleoside inhibitor) or interferon may help reduce the severity of disease in immunocompromised patients [59].

Measles is primarily prevented through receipt of two doses of measles vaccine on an appropriate timeline. If exposed, infection may be averted by the administration of anti-measles immunoglobulin (IG) within six days of exposure, or measles-containing vaccine within 72 hours of exposure [5, 57, 59]. IG is typically only used if the patient has contraindications to vaccination, and while it may prevent infection and therefore spread of the virus, IG should only be used to prevent infection of at-risk patients who cannot be vaccinated [59].

Outside the cell, the virus is relatively easy to inactivate, and does not survive long on fomites [36]: its cell-derived lipid envelope makes it sensitive to detergents and other lipid solvents, and it is also inactivated by sunlight, pH extremes, and high heat [57, 59]. However, aerosolized virus may remain in the air and cause infection for several hours [43].

2.1.3 General Epidemiology

Measles virus is highly contagious, and it is very easily transmitted between people via respiratory droplets or aerosols, causing infection in up to 90% of those exposed [5, 6, 59]. The average incubation period of measles is 10 to 12 days, but symptoms
can appear as soon as seven days following infection, or up to 21 days later. Cases are considered infectious for eight to nine days: four days before rash onset, and four days after. Cases are most contagious during the prodrome, before the rash appears, but continue to be infectious for several days thereafter [59].

Humans are the only natural host of measles virus. Cotton rats are the only small mammals that permit infection and display realistic intranasal transmission routes and virus-induced immunosuppression, making them a good model for study of disease and pathogenesis [57]. Although non-human primates (NHP) can be experimentally infected with measles virus, the disease is not zoonotic, and transmission from NHP to humans is not an important route of infection [57]. However, a famous relative of the measles virus is rinderpest virus, the cattle and other even-toed ungulate pathogen that is one of only two biological agents ever to have been eradicated from animal populations [57]. Using phylogenetic modeling, it has recently been estimated that the measles virus diverged from its common ancestor with the rinderpest virus in the 11th century at the earliest [22]. Due to the critical community size of at least 250,000 people [31], it would make sense that measles only became a human pathogen of concern when humans organized society into dense urban centers in fairly recent centuries [8].

The highly infectious virus can survive outside the host in aerosolized form for several hours. For this reason, measles cases who visit the hospital should be isolated in negative-pressure rooms to prevent spread to sick or susceptible patients [34]. Rapid diagnosis of measles in a healthcare setting is of great import in order to ensure that susceptible—especially immunosuppressed—patients are not exposed.

Measles mortality is highest in children under two and in adults [57]. Measles mortality rates depend on living conditions and healthcare systems: in high-income regions, such as the United States when measles was endemic in the mid-20th century,
fewer than 1 in 1,000 measles-afflicted children (0.001%) die, while the case fatality rate in sub-Saharan Africa is estimated to be 5% [36]. In complex emergencies, such as refugee camps and famine, measles case fatality rates in children reach up to 30%.

Recovery from natural measles infection or receipt of two live attenuated measles vaccine doses, almost always induces lifelong immunity against the virus, which does not undergo significant antigenic drift over time [59].

**Molecular Epidemiology**

RNA viruses are known for their error-prone polymerases that create infidelity in genetic replication, but the measles virus genome appears to be fairly stable over time [53]. Genetic diversity does exist, however, and forms the basis for viral classification. Viral strains are currently grouped into eight clades and 23 genotypes [59] based on diversity of the gene sequence encoding the carboxylic acid end of the N protein gene [54]. Sequence variability at this point in the genome can be up to 12% between wild-type viruses. Strains similar in this region may be distinguished by variability in the H or F protein genes [53]. Five genotypes (E, F, G, D1, and C1) appear to be extinct or not circulating [53, 54].

Sequence diversity is insignificant at the immunological level: only one serotype exists, and infection with any genotype is enough to provide lifelong immunity to any of the other genotypes [57]. However, since different genotypes are predominant in certain geographic regions at certain times, sequence diversity is useful for identifying sources of outbreaks, understanding transmission patterns, and monitoring the effectiveness of surveillance and control programs [54]. In the rare event of measles symptoms following vaccination, or during an outbreak situation with a vaccination campaign response, molecular epidemiology can also help tease apart antibody responses to identify vaccine versus wild-type strains [53].
Diagnostic Tools

While measles presents a characteristic course of symptoms, many laboratory tests can confirm measles infection, especially where it is rare, such as regions where vaccination campaigns have eliminated the disease and physicians who have little experience with the virus may be prone to misdiagnosis [59]. Other diseases such as rubella (German measles), human herpes virus (HHV) 6, and dengue fever can be difficult to distinguish from measles on a clinical basis [36]. The use of molecular diagnostics is crucial to determine the disease agent and rapidly implement proper precautions for this very contagious pathogen [59].

Measles is commonly diagnosed by the presence of antibodies to the measles virus. Measles may be diagnosed if anti-measles IgG titers rise by more than four times between clinical samples, or if anti-measles IgM is detected [57]. Comparisons of IgG levels is usually performed using an enzyme-linked immunosorbent assay (ELISA); a rise in IgG levels may indicate re-infection or infection following vaccine failure. Anti-measles IgM antibody, detected with enzyme immunoassay (EIA) from a blood specimen, is the most common test to confirm first-time infection, and is most sensitive after three days following infection.

When desired (especially for genotype identification), measles virus may be cultured from throat washings, respiratory secretions, or blood from an infected case [5, 59], although the ability to isolate measles virus wanes soon after rash onset [36]. Otherwise, measles RNA can be extracted from several sites in the body, including the upper respiratory tract and urine [36]. Reverse-transcription polymerase chain reaction (RT-PCR) is necessary for sequencing the RNA genome, and in the US is conducted in approved laboratories such those of the Centers for Disease Control and Prevention (CDC).
2.2 Vaccination and Measles Elimination

2.2.1 The Measles Vaccine

Measles is a vaccine-preventable illness for which an extremely effective vaccine has existed for decades.

History

Goldberger and Anderson first recognized measles as an infectious agent in 1911, when the scientists successfully transmitted the infection from humans to monkeys [59]. The technical challenges of growing and isolating viruses delayed the laboratory cultivation of the measles virus until the 1930s, when it was described by Plotz and subsequently Rake and Shaffer in chick embryonic tissue [15]. However, it wasn’t until 1954 that the measles virus was definitively isolated by John Enders in human kidney cell culture, from patient David Edmonston [29]. Passages of the virus in kidney cells and subsequently human amnion cells cultivated a strain that displayed cytopathologic syncytia formation, and antibodies from measles patients reacted with the lab-grown strains in neutralization tests. Cynomologus macaques displayed a measles-like illness when infected with the lab-grown strains, providing further evidence for the isolation of the causative agent of measles.

Enders continued to passage the virus from human amnion cells into embryonated hens eggs and then into chick embryo tissue culture, paving the way toward the development of an attenuated strain of measles that could be used in a vaccine. Thirteen passages of the virus in chick embryo cells resulted in an attenuated virus that showed low virulence in measles-susceptible monkeys, but which was still capable of inducing protective antibodies against measles; the monkeys successfully resisted the challenge of infectious measles virus grown in human kidney cells [29]. This attenuated strain of measles virus was promising for use in a vaccine for humans.
The Enders lab members performed toxicity tests on themselves with the pure “Edmonston” vaccine strain and found acceptable results. With parental consent, the scientists tested the vaccine on measles-susceptible children in institutions for the developmentally delayed, which were vulnerable to large outbreaks of measles. Many vaccinees developed fevers or a transient rash, but otherwise appeared normal and developed neutralizing antibodies within a few weeks [29]. Injecting a small amount of human immunoglobulin (IG) along with the vaccine greatly reduced side effects of the vaccine, but this became unnecessary when the virus was passaged further in the lab for greater attenuation [59]. The product of this work was the first live attenuated measles vaccine, which was licensed in the United States in 1963 [29].

The formalin-inactivated, alum-precipitated measles vaccine was a second type of measles vaccine also licensed in 1963 for use in infants who should not generally receive live virus vaccines (Rauh and Schmidt 1965, [57, 59]. While the vaccine was derived from the same Edmonston strain, the killed virus was less immunogenic: vaccination required three doses to be effective, and yet immunity was not long-lasting [29]. Additionally, about 15% of people who received the inactivated vaccine and were later exposed to measles developed “atypical” measles, caused by antigen-immune complexes [29, 59]. The disease was typically more severe than natural measles, characterized by sudden high fever, a rash starting rather than ending at the extremities, and a lack of Koplik spots and infectivity [6, 8, 57, 59]. Atypical measles required hospitalization in 75% of cases, often due to pneumonia. Due to the poor immunogenicity of the vaccine and chance for serious complications upon re-exposure to wild type measles virus, the vaccine was discontinued after four years in 1967 [59]. Atypical measles rarely occurs after live virus vaccination [59].
Modern vaccines

Measles vaccine development has continued since the 1960s with the goal of reducing side effects and improving antibody affinity and titers. Vaccine virus strains are attenuated: they don’t cause disease in humans, but they do replicate in the body and induce protective antibody formation. The Schwartz (1965) and Moraten (1968) strains were attenuated from the Edmonston strain by passaging 85 and 40 times, respectively, in chick embryo cells at 32°C [59], and induce fewer side effects of fever. Today, the United States exclusively uses the Moraten strain, while countries such as Canada and Brazil use the Schwartz strain. A few strains not derived from the Edmonston strain are used in Russia, China, and Japan. All live attenuated vaccines are of genotype A and greatly reduce the risk of measles infection, but each generate different mean geometric mean antibody titers [53, 59]. Remarkably, vaccine strains derived from the Edmonston strain vary from each other by at most 0.6% in their F, H, N, and M genes [59]. Vaccine strains are sufficiently different from wild-type strains that they can be distinguished by their cytopathic effects on host cells, ability to grow in different cell types, plaque forms, and optimal temperatures for growth [59].

The measles-mumps-rubella (MMR) combination vaccine was licensed in 1971 and includes live attenuated forms of three viruses responsible for different diseases [59]. Most measles vaccine in the US is administered in this combination form, which stimulates good immunity to all three antigens, as good as if they were administered in separate vaccines. In 2005, a varicella vaccine component was added to the MMR combination, creating a new vaccine that also protected recipients against chickenpox caused by the varicella zoster virus (VZV). However, while the MMR vaccine may be administered to anyone older than six months, the MMR-varicella (MMRV)
vaccine is only licensed for use in children between 12 months and 12 years old. Additionally, vaccine side effects are more common after MMRV vaccination compared to simultaneous but separate MMR and varicella immunizations [59].

Live attenuated viruses require cold storage temperatures in order to prevent inactivation. A relatively heat-stable vaccine was produced in 1979, which was an important step forward for vaccine use in conditions without consistent electricity or refrigeration [59]. However, reconstituted MMR vaccine must still be used within eight hours if refrigerated, and sooner if not. MMRV vaccine is even more strict: it must be stored frozen and used within 30 minutes of reconstitution.

Side effects may be experienced several days after vaccination, including rash, fever, and joint pain, and sometimes febrile seizures [59]. However, none of these adverse events appear to have negative long-term effects. Adverse events occur more frequently in patients who are immunocompromised. When considering possible side effects, the risk of getting measles and its serious complications, or creating a susceptible pool in a highly vaccinated population through which measles may spread and threaten persons unable to be vaccinated, must be weighed against the risk of possible side effects.

**Immunization Schedule**

The US Centers for Disease Control and Prevention (CDC) recommends administration of the first dose of MMR vaccine at 12-15 months old, plus a booster dose given at 4-6 years old [20]. The MMR booster immunization may be administered at any time at least four weeks after the first dose, while the MMRV vaccine needs a minimum of three months between doses [20, 59]. Measles vaccines are generally not recommended for infants younger than 12 months due to interfering maternal antibodies that may neutralize the vaccine virus before it has a chance to replicate.
and stimulate an immune response [59]. Vaccine doses are currently administered subcutaneously, but aerosolized vaccine may be a promising alternative in the future [59]. Children may even be vaccinated when they are mildly ill, with similar rates of seroconversion as well children.

Since measles remains endemic in many countries, special vaccination recommendations are given in the event of international travel and outbreaks. Infants as young as six months who are traveling abroad or living in an outbreak-affected area may be vaccinated, but should still receive an additional two immunizations on the normal schedule [20]. Anyone older than 12 months who is traveling internationally should have received two doses of vaccine, with at least 4 weeks’ time between doses.

**Immune Response**

Measles vaccine is safe and extremely effective in inducing protective immunity [45]. Vaccine virus strains activate both humoral and cell-mediated immunity [59]. Similar to natural infection, cell-mediated immunity in the form of cutaneous delayed type hypersensitivity response is also suppressed with vaccination, but this does not appear to have serious consequences or allow for superinfection.

The different clades of measles virus all display one cross-reactive antigenic type on the H protein [14]. Although some antigenic sequence variation exists [53, 54], wild type viruses are all neutralized by polyclonal antiserum to the H protein of vaccine virus. Neutralizing antibodies typically target the H protein (and sometimes the F protein), preventing virus attachment to the host cell receptor [53, 57]. However, if a virus is present inside a cell before H antibodies develop, the virus may continue to spread between cells through the fusogenic activity of the F protein, and only antibodies to the F protein can stop viral spread [57].
Antibody responses begin to develop about two weeks following vaccination [59]. Anti-measles IgA is detected in nasal secretions, while IgM antibody builds up in the serum, then decreases over a short amount of time. IgG antibody persists for several years, and slowly declines over time. A boost effect in IgG antibodies is seen after re-exposure to wild-type or vaccine strain measles virus, similar to what occurs after re-exposure following natural infection. Overall antibody titers induced by vaccination are typically lower than for natural infection, but this does not appear to have a significant impact on the probability of getting infected following exposure. Maternal antibodies generated against the vaccine virus are also often lower in titer than natural measles-induced immunity [59]. The lower titers of vaccine-induced maternal antibodies may make infants susceptible at a younger age than in the pre-vaccine era, but may also make them responsive to vaccination at an earlier age [53, 59].

Whether the measles vaccine is protective against measles infection depends on seroconversion and antibody titer: higher titers are more protective, while a poor antibody response, even if it occurs, may not be protective and can result in vaccine failure [59]. Primary vaccine failure occurs when a patient is vaccinated but never seroconverts, while secondary vaccine failure occurs when a patient is vaccinated and seroconverts, but fails to be protected against disease upon exposure. Most vaccine strains successfully seroconvert more than 95% of vaccinees upon primary vaccination. A small percentage (5-15) of people display primary vaccine failure, often due to residual maternal antibodies or immunosuppression, but more than 97% show immunity after receiving a second dose [45]. Primary vaccine failure may also have a genetic component based on homozygosity between class I and II human leukocyte
antigen (HLA) alleles; however, people with these genes are often successfully sero-
converted with a second dose [59]. The vaccine efficacy is estimated to be 90-95% or
greater.

Contraindications

Immunocompromised patients and pregnant women should generally not receive
live vaccines, including measles-containing vaccine [45]. However, HIV-infected peo-
ple who don’t display severe immunosuppression should receive the MMR (but not
MMRV) vaccine, as measles can have severe consequences in HIV-affected individuals
[59]. If immunosuppressed patients do receive the vaccine, several weeks must pass
before getting tested with the tuberculin skin test, due to the ability of even the
vaccine virus to cause further immunosuppression [59].

Care should be taken when thrombocytopenic patients are given the vaccine, for
it can rarely cause mild idiopathic thrombocytopenic purpura in 1 per 25,000 doses
administered [59].

Even though the measles vaccine virus is grown in chicken embryo cells, people
with egg allergies can still receive the vaccine, as egg proteins are not detected in
the vaccine; people with allergic reactions to the vaccine actually react to the gelatin
or neomycin antibiotic in the vaccine [45, 59]. Anaphylactic and hypersensitivity
reactions are extremely rare, occurring in fewer than 10 per million doses [59].

To provide the highest level of safety for patients who cannot be vaccinated, their
close contacts and healthcare workers should be vaccinated appropriately [59].

2.2.2 Measles in the World

No society has escaped the measles virus. In the 10th century, Rhazes described
the disease as more feared than smallpox [8, 59]. In the pre-vaccine era, nearly all
children became infected with measles; its high infectivity and potential for severe complications caused an estimated 130 million cases and 2.5 million deaths every year, mainly in children [64, 59]. In fact, measles killed more people than polio [6]. Although people can only be infected once in their lifetimes, measles is an efficient pathogen, remaining endemic in populations above the critical community size that can support it (at least 250,000 people) [31, 57].

The epidemiology of pre-vaccine era measles differs markedly from contemporary transmission in countries with high vaccination rates. The maximum incidence of measles virus infection was in school-aged children (five to nine years old), and secondary cases usually arose in younger siblings of these children [57]. Ninety-nine percent of people were exposed by the age of 20. Then, the high population density of growing urban areas pushed the average age of infection to the pre-school age group [59]. Measles operated on a seasonal cycle, igniting outbreaks every 2-3 years in the winter or spring, whenever a new susceptible pool in the form of a birth cohort became large enough. Before major public health interventions, measles caused an estimated 30 million cases and one million deaths worldwide each year [36].

Today, teenagers are the most affected in areas with high vaccination rates, while children younger than four are most affected in regions with low vaccination rates [57]. In low-resource nations, children younger than two are most affected. Nearly all four-year-old children in certain areas in Africa have had measles [59]. This may be due to a variety of factors plaguing these areas: malnutrition, rapidly waning maternal antibodies, crowded living conditions, or early exposure of infants [59]. Measles is especially deadly in low-resource regions, with pneumonia and diarrhea exacerbating malnourishment and causing mortality rates of 2-15% [59]. As such, the World Health Organization recommends measles vaccination earlier in these areas, at nine months
of age [59]. Fortunately, seroconversion rates in malnourished children are just as good as in well-nourished children [59].

**Elimination**

Elimination of an infection is defined as the “reduction to zero of the incidence of a specific agent in a defined geographical area as the result of deliberate efforts” [13]. Because the disease may still be endemic in other geographical regions to which individuals might travel and pick up an infection, “continued efforts to prevent re-establishment of [local] transmission are required.” That is, even after elimination of local transmission, new generations of susceptibles must continue to be vaccinated to ensure that local transmission does not become re-established, should an infection be imported from another region. Unlike polio vaccine virus, measles vaccine virus is not transmitted between people following vaccination, so nearly everyone needs to be vaccinated or otherwise immune in order to interrupt transmission [45, 59]. Very high (92-95%) levels of population immunity are required to eliminate measles.

Measles has been eliminated in several geographic areas due to high vaccination rates. The Pan-American Health Organization (PAHO) initiated the catch-up, keep-up, follow-up program in 1994 in an effort to eliminate measles in the Americas [59]. The strategy began with a mass vaccination campaign to catch up children between 1 and 14 years, regardless of immunity status; keep up immunity levels at 90% by vaccinating new birth cohorts; and follow up with mass vaccination campaigns every few years to vaccinate children 1-5 years old, regardless of immunity status, who may have been missed in the previous two stages. The Western hemisphere was declared eliminated of measles in 2002, the largest world region ever to eliminate measles [59]. Notably, the European region has yet to eliminate measles [36].
While progress has been made toward elimination in several regions, measles is still an important global problem, especially for the world’s children. The United Nations (UN) Millennium Development Goals, adopted in 1990 and to be achieved by 2015, included a target goal to reduce under-five child mortality rates by two-thirds [38]. Addressing measles, the leading vaccine-preventable killer of children under five in 2000, was a major component of trying to achieve this goal [38, 59]. The World Health Organization (WHO), United Nations Children’s Fund (UNICEF), and others created a strategy to include a goal of greater than 90% measles vaccination coverage worldwide, opportunity to receive a second dose of vaccine, and administration of vitamin A [36]. This and other actions have led to a nearly 50% decrease in the under-five child mortality rate between 1990 and 2012, from 90 to 48 deaths per thousand live births [38]. The goal of reducing under-five mortality by two-thirds has been met in six UN regions, while the regions of Africa, Southern Asia, and Oceania have yet to meet this goal, experiencing moderately high to high rates of child mortality in 2014 [37].

In 2013, there were 179,864 cases of measles, over 43% of which occurred in the African region [48]. In the span of just one year, the geographic concentrations of measles changed drastically: the number of cases in the African region more than halved, while the number of cases in the Western Pacific region increased by over 300%, accounting for nearly 60% of the world’s 198,124 cases of measles in 2014. Fewer than 2,000 cases occurred in the Region of the Americas in 2014, but this was still an increase of 400% from 2013. Measles remains an important killer: an estimated 122,472 measles deaths occurred in 2012, over 89% of which occurred in sub-Saharan Africa and Southern Asia [38].

The numbers may appear dire, but this is great progress since 1981, when nearly 4.5 million measles cases were reported throughout the world. Then, the global
measles vaccination coverage rate was only about 20%. As vaccination rates steadily increased to an estimated 84% globally in 2013, measles case counts have concurrently dropped to only 4.4% of their previous level. Receipt of the measles vaccine increases overall survival, especially of children who are most affected by the disease [59]. In fact, since 2000, measles vaccination is estimated to have prevented 14 million deaths [39]. However, the global measles immunization rate has stalled at around 84% since 2009 [38], and the trends vary geographically: according to the United Nations, 94% of children in developed nations received at least one dose of measles vaccine at the appropriate age, while this occurred for only 71% of children in Oceania. Strong efforts must be kept up in order to realistically eliminate measles in more world regions.

**Eradication**

Eradication is the “permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts” such that public health intervention efforts are no longer required [13]. The biological and epidemiological properties of measles make it a promising target for global eradication: no animal reservoir exists, almost all cases display typical symptoms, and there is an effective vaccine available [6, 59]. However, the extreme contagiousness, long incubation period, infectious period beginning before the disease can be correctly diagnosed, earlier median age of infection, and older age required for vaccine effectiveness make measles much more difficult to eradicate than smallpox or polio [53, 59]. Smallpox is the only human disease to have been eradicated, which occurred in the late 1970s following decades of concentrated effort. Human society has changed since then, and societal factors may challenge measles eradication, including increasing population...
density requiring very high levels of vaccination, war, and increased frequency and ease of international travel [59].

2.2.3 Measles in the United States

Pre-vaccine Era

Measles, like many vaccine-preventable childhood diseases, was once endemic in the United States. In 1912-1922, the average reported incidence of measles was 289 per 100,000 people, and reached 310 per 100,000 people in the 1950s, likely with substantial underreporting [25]. In fact, only 500,000 cases were reported from an estimated four million cases every year [59]. Measles mortality rates in the US were as high as 21 deaths per 1,000 cases in 1912, and decreased more than 20-fold by 1962 due to improvements in nutrition and medical care, especially antibiotics that saved lives from bacterial superinfections [25, 36].

Outbreaks occurred with regular periodicity as children were born and entered the susceptible population. Large outbreaks continued to occur in the US until 1994, despite the fact that an effective vaccine had been licensed for over 30 years and elimination goals were declared in 1967, 1978, and 1993 [46].

Measles Resurgence

The persistence of measles in the US was due in part to a single-dose vaccination regimen, as well as not achieving an adequately high population vaccination level, especially in underserved urban areas [53, 59]. The gap in MMR vaccine coverage between white and non-white children was as high as 18% in 1970, and was estimated at 15% prior to the measles resurgence of 1989-1991 [26]. As a result, measles incidence in Native American, black, and Hispanic children was three to 16 times the incidence of measles in white children in 1991. The largest outbreaks during the
measles resurgence occurred among unvaccinated black and Hispanic populations in urban areas, such as New York City and Chicago, accounting for 46% of the resurgence cases while those populations only represented 17% of the US population at the time. Additionally, it became clear that a single dose of vaccine was not enough to interrupt transmission at the population level: even though only a small percentage of people experience primary vaccine failure, that susceptible pool, small as it was, made it impossible to eliminate measles [59]. The adoption of universal (second dose recommendation, increased funding for vaccine distribution) and targeted (discounted or free vaccines for uninsured or Medicaid patients, special campaigns in Spanish-speaking communities) public health interventions led to both the disappearance of a gap in vaccine coverage between racial groups and the elimination of measles in the United States [26].

**Elimination in the United States**

The US saw a 99.9% reduction of cases by 2005 compared to previous years, although this dramatic reduction was already seen earlier [59]. From 1992-1999, the US measles reproduction number (R), or number of new cases that can expect to be generated by an infected case in a partially immune population, was reported to be less than one [59]. By the late 1990s, the reported annual incidence of measles in the US was less than one case per 1 million people [46]. The US achieved measles elimination in 2000, when molecular and epidemiological surveillance data indicated that the US had met its goal of linking all measles cases to an imported case within two generations [30].

Vaccinations required for school entry are a result of the measles elimination strategy enacted in 1978 [59]. School entry vaccination requirements are an effective method to ensure that children are vaccinated in a timely manner, avoiding the
creation of a susceptible pool with new birth cohorts. In 2011, all 50 United States required children entering kindergarten to have received two doses of measles vaccine [19]. However, 48 of these states allowed for exemption from the school vaccination requirements due to religious and/or philosophical objection; only Mississippi and West Virginia disallowed such exemptions [18]. Geographic clustering of like-minded individuals who don’t vaccinate their children can lead to overall school vaccination rates that are much lower than state or national average, creating a risk for outbreaks [60]. Indeed, outbreaks of measles are possible even in populations where less than 10% of people are susceptible [36].

Even though measles was declared eliminated from the US in 2000, outbreaks continue to occur when introduced from foreign countries into susceptible pockets of the American population. A large number of outbreaks now occur in healthcare settings [59].

CDC guidelines for measles investigation in the post-elimination era include active surveillance of confirmed measles cases until two incubation periods following the date of the last confirmed case report; laboratory diagnosis of clinical specimens; rapid investigation of suspected cases; and frequent review and monitoring of surveillance systems and indicators [34].

2.3 The Amish

The Amish are a North American subculture descended from the religious divides of sixteenth-century Europe.

2.3.1 History

By the early 1500s, much of Europe had been spiritually united under the Catholic Church for more than a millennium, but growing food shortages, poverty, and state
corruption began to engender widespread discontent, especially among the newly-powerful merchant class. 1517 was the year it all changed: Martin Luther led the Protestant Reformation through his new ideas and interpretations of church doctrine, including “salvation by grace through faith alone”, decision-making based on Bible study, and worship service held in the common language of German [41]. Dissenters gathered in Zurich in support of the reformation began to realize that their concept of religion was even more extreme than that of other reformers: they wanted a non-violent church completely separate from the state, into which adult members chose to be baptized as a commitment of their faith, instead of every citizen automatically being baptized at birth as an infant. By 1525, they created their own religious sect, the Anabaptists (Latin for second baptism), by choosing to be baptized into their own church after having already been baptized into the state church as infants. Anabaptists believed that religion is the free choice to be made by an individual, not their family or country [12]. During the next century, Anabaptists faced severe persecution in the form of imprisonment, torture, and execution for their disobedience to the state church, which was seen as promoting anarchy in both society and politics [12, 41]. This persecution led to distrust in society and the government by Anabaptists, but also values of simplicity and humility [41]. Even under persecution, the Anabaptist movement continued to expand, moving to Germany and the Netherlands.

A split in the Anabaptist movement came when the former Dutch priest Menno Simons began to strongly advocate discipline in social avoidance of excommunicated Anabaptists, especially those who agreed with the violence that led to a 1534 battle against Catholics and Protestants in Munich. The Anabaptists from Switzerland and south Germany (“Swiss Brethren”) found the “Mennonite” social avoidance to be too harsh, but eventually accepted the idea of shunning unrepentant, excommunicated members. Facing continued government persecution in Switzerland, many
Mennonites migrated to more religiously tolerant neighboring areas of the Palatinate, Germany, and Alsace, France, after the end of the Thirty Years’ War, though they remained in close ties with Swiss Mennonites.

Another split arose when considering the sympathy of the True-Hearted people. These were state church citizens who nevertheless admired the model Christianity espoused by the Anabaptists and helped them out in times of trouble, yet continued to be members of and support the state church that was persecuting the Anabaptists. Swiss Brethren, who faced especially harsh persecution, believed that only God knew whether the True-Hearted were saved and that they could continue to rely on their support, while the Mennonites in Alsace and the Palatinate advocated the breaking of ties with the True-Hearted. This tension led to a complete break in the church 1693, when Jakob Amman broke off to form a new sect [12, 41]. The “Amish” defended extreme social avoidance of unrepentant excommunicated members and biannual (rather than annual) communion to encourage attention to the Christian life (and which included ritualistic footwashing), in contrast to their former Mennonite brethren [41]. The Amish grew their beards long and kept their linen clothes simple, keeping with the New Testament, and also criticized hierarchy and authoritarian methods of leadership.

However, the Amish remained religious outsiders, and were forced by state governments out of the areas where Anabaptists originated. Many moved to areas of Germany, Austria, and France where land-leasing nobles offered religious tolerance to loyal tenants who were dependent on the landowners for protection. Swiss Anabaptists (including Mennonites and the Amish) were literally exported to the Netherlands by the Swiss government. Others migrated farther to North America, attracted by the promise of economic possibilities and religious freedom, especially in Pennsylvania. From 1737 to 1767, 100 Amish families emigrated to the New World.
Amish in America

English-speaking Americans referred to the German-speaking immigrants moving into Pennsylvania as the “Pennsylvania Dutch”. The first definite Amish settlement was founded in Berks County, Pennsylvania, in 1737 [12, 41]. The Amish successfully raised funds prior to emigration and were able to buy land upon arrival in the New World and continue their main occupation of farming [41]. Mennonites also immigrated to the New World, but lacked relations with the Amish. Notably, the Amish did not own slaves, even though it was legal in Pennsylvania until 1780, probably due to a combination of simplicity and Christian humanitarianism. They did own redemptioners (indentured servants).

The Amish remained pacifist throughout several wars, including the American Revolution; in lieu of military service, they offered to fundraise for poor American families. Their refusal to support the patriots did not come without consequence: they lost the right to vote and were double-taxed and sometimes jailed. Meanwhile, the Amish in western Europe weathered the French revolution by paying extra taxes in lieu of fighting. But the rise of Napoleon Bonaparte led to the idea of equal citizens who were all accorded civil rights and duties, regardless of religious affiliation – which meant that the Amish would not be persecuted by the state, but were also no longer allowed to avoid military service. Fortunately for the Amish, this obligation was withdrawn when Napoleon was overthrown.

European Amish continued to immigrate to North America in the early 19th century, seeking better economic possibilities, good soil for sale, and an escape from conscription under various kings. They arrived when American Amish were beginning to move westward, so they, too, experimented with western settlements in Ohio, Indiana, Ontario, Iowa, and Missouri, generally welcomed by the existing Amish, and
sometimes taking land recently usurped from Native Americans. (There is little doc-
umentation of Amish interaction with Native Americans, but what exists is generally
positive.) Most Amish were able to avoid participating in the Civil War by paying a
commutation fee or hiring substitutes. Amish of all types followed the 19th century
American westward expansion, reaching states like Colorado and Oregon.

**Bifurcations in the Church**

The church did not remain static during these times. A growing change-minded
class, inspired by the refinement, individuality, and freedom of general American so-
ciety, started to disregard Amish tradition. The interpretation of the function and
changeability of the their rules of life (*ordnung*) led to the gradual split between
change-minded (“Amish Mennonite”) and tradition-minded (“Old Order Amish”)members in various locations in the mid- to late 1800s [12, 41]. The Amish Men-
nonite society continued to progress until they eventually combined with the various
American Mennonite groups in the early 20th century, a trend that continued as
recently as 1963 [41]. The Amish in Europe all followed a similar trend of join-
ing Mennonite groups; the Amish identity was completely lost from the European
continent by 1937.

**Amish in 20th Century America**

The group we think of today as Amish numbered only 5000 at the end of the
19th century, and were forced to endure hard times in modern society, such as war
and economic depression. While the First World War offered religious conscientious
objection and avoidance of the draft, many draftees were forced to report to training
camps anyway, with the goal of breaking them apart from their community. Some
Amishmen joined the ranks, but most refused to partake in any training; religious
prejudice resulted in tortuous camp conditions. The Amish refusal to join the US
army or buy war bonds, as well as their use of a German dialect, sparked ideas that they might be German sympathizers. Many Amish were even placed under the watch of the War Department’s Military Intelligence Division.

After the war, the Amish had to face national public education reform, which required pupils to attend school through the teen years and learn a variety of subjects required for modern life in a longer school year. The Amish believed that education should remain closely tied to the church, community, and vocational work, and that public education was useless for them and could threaten their way of life. The public school debate was put at a final end with the Supreme Court ruling in *Wisconsin v. Yoder* in 1972. Citing religious and parental freedom, the ruling legally allowed the Amish to operate their own schools or withdraw from public education after the eighth grade.

The Amish, like most other Americans, also had to endure the Great Depression, which hit the Amish and other farmers especially hard, and slowed the creation of new Amish settlements.

The Amish officially got out of military service in WWII; instead, they provided free labor to the government in national forests, hospitals, and social work programs, though some eventually joined the US military. They also refused to participate in the ration stamp program, instead providing their own food for themselves, acquiring the label of “model” citizens. The Korean War required conscientious objectors to partake in two-year work programs, in hospitals or non-profit agencies. Some Amish faced trial for resisting compulsory work, as it did not fall in line with being “of” the world but not “in” it, or maintaining strong community and religious ties. A resolution was finally reached in 1969, when the first Amish national committee negotiated with the government to allow managed farm labor as an alternative to conscription.
The dynamics of the church continued to change throughout the 20th century. The evangelistic Beachy Amish separated from the Old Order Amish when they adopted the use of automobiles and wired electricity in the home. In the 1960s, tension in Ohio led the to separation of the New Order Amish, who practiced youth meetings for Bible study and tolerated technology more than the Old Order Amish [12, 41]. However, the New Order Amish are so similar to the Old Order Amish in many traditions that they are considered a subset of the Old Order Amish [41]. Other, more conservative groups split off to form the Swartzentruber and Andy Weaver Amish sects [12].

As the church has evolved, so too has Amish society. The predominantly agricultural Amish workforce has shifted to partake in non-farming work, such as carpentry, assembly line factory work, and owning small businesses like grocery stores [12]. This occurred especially after 1970, and was due to urban sprawl and large families not having enough land for all their kids. In fact, farming is often a minority occupation today. Amish populations continue to grow at a very fast rate: Amish families are large (five or more children on average [17]), and children of Amish families are choosing to be baptized into the Amish church as adults at rates higher than ever. Such population expansion has stimulated migration to other parts of the US and Canada that have not historically been settled by many Amish, such as Kentucky, Missouri, Washington, and Maine. The quaint, humble lifestyle lived by the Amish has piqued outsider interest in the church, resulting in tourism to Amish areas, and films featuring the Amish as main characters.

2.3.2 Modern Amish

The 5,000 Amish in North America at the beginning of the 20th century have grown to a population of nearly 300,000 with a growth rate of 3.296% per year in 2010, making them one of the fastest growing subcultures in North America [17, 12, 11].
The Amish remain geographically isolated in church districts consisting of a few dozen families. Twice-monthly Sunday church services held in the rotating homes of church members are led by a bishop (chosen through lottery), deacon, and two ministers, who are all male and serve for life without pay [12]. At the service, men and women occupy opposite sides of the room, but together partake in a fellowship meal together following the conclusion of worship. No hierarchy exists above the church district level. In following the traditions of Jakob Amman, modern-day Amish continue to practice adult baptism (confirming the conscious commitment to the church and Amish society), twice yearly communion (including foot-washing), and shunning. The Amish lead a unique way of life in modern America, and want their children to learn in schools that reinforce their values. After legal battles over compulsory education, a 1972 Supreme Court decision allowed exemptions for the Amish so they don’t have mandatory schooling beyond the eighth grade. As church districts grow with immigration and expanding families, they become unmanageable to operate under the small-community mindset, so they split into two.

As their history shows, the Amish are members of a diverse group who follow similar yet distinct belief systems. However, Donnermeyer et al. [12] consider five characteristics that must be met in order to be considered Amish:

1. Pennsylvania Dutch is spoken during day-to-day conversation, while High German is spoken during religious services.
2. Church services are held at home, with the whole church district gathering in a large space (often a barn) on a baptized member’s property.
3. Amish have a distinctive style of dress (including use of plain colors only, and clothes without zippers or buttons).
4. Horsepower is used for farm work and transportation.
5. No telephones or electricity are available in the home.
The Amish are clearly distinct from contemporary American society, and have chosen to be. Each church district has their version of a set of “laws” (*ordnung*) by which members must abide to live in accordance with the Bible and Amish society. The *ordnung* is actively reviewed twice yearly in preparation for communion, and it is often modified to reflect new ways of life possible in light of modern technology. Included in the *ordnung* are rules for *meidung*, or the shunning of baptized adults who have been excommunicated. Shunning is typically not permanent, and will end when the excommunicated member joins another Christian congregation. Adultery and divorce are automatic reasons for excommunication, while other situations are reviewed and decided upon by the church.

Generally, the Amish make a conscious decision to maintain small, often rural communities (*gemeinde*) in the face of modernization by rejecting automobiles, which allow their members to travel far away from their community, and the ubiquitous urbanization of America [12]. But the changeability of the *ordnung* means that some church districts may allow automobile usage in special circumstances, such as medical care or long-distance travel, often with the stipulation that the automobile is operated by a non-Amish individual. The Amish community is a tight-knit unit that emphasizes neighborly collaboration, such as occurs with barn raising, farming, and quilting. The truly Amish doctrine of being “of this world but not in it” includes the rejection of utility lines connecting their communities to the outside world [12]. The ultimate reason for this is to maintain a community in which members help each other out and live their lives according to God. While the church is not hierarchical, separate church districts may be informed of general Amish happenings through popular news bulletins and periodicals.

However, the changeability of the local *ordnung* means that the Amish may be anywhere on a spectrum of tolerance for a number of modern innovations. Telephones
are often permitted on a property, but they must be inside a special telephone box instead of the home. Additionally, while Amish homes are not connected to power lines, they often utilize petroleum generators to generate electricity, and anything battery-operated is acceptable. At night, kerosene lamps illuminate the indoors. But farmers use machines if they can be pulled by horses, which helps to increase productivity but also keep things small-scale and family-centered. Outside the home, the Amish may use technology if they are employed by non-Amish, and sometimes even Amish, employer.

Amish children attend school through the eighth grade, often in Amish-built one-room schoolhouses. At school, Amish children are educated in accordance with the values of the home and church. The Amish guideline for behavior (*gelassenheit*) is taught from birth and is generally to be humble, place community before individuality, and live life by Christ’s teachings (this humility is a reason that the Amish generally avoid having their picture taken). School is also where Amish children first begin learning the English language, so that they may communicate with the others not from their community. Though some Amish children may experience contemporary American society and decide against baptism, over 85% of Amish young adults choose to be baptized into the Amish church [17]. After baptism, Amish members may marry each other; most Amish marry and have children. Men start growing their characteristic beards following marriage, and become the patriarchal leaders of the household. However, Amish women remain extremely important with their duties maintaining the household by mending clothes, growing, preserving, and cooking food, and raising children in the Amish faith.
2.3.3 Attitudes Toward Vaccination

During the 20th century, the Amish have gradually accepted and used modern medicine, which has resulted in reduced infant mortality and concurrent population growth [33]. Still, the Amish often utilize home remedies for medical conditions and wait until an illness becomes acute to visit a modern-trained physician [12]. When they do visit an English doctor, they prefer to visit local community doctors whom they know and trust.

Many Amish have complied with public health recommendations regarding immunization; the ideals of the Amish church do not specifically prohibit or encourage vaccination [66], but receiving vaccines free of charge may be against their acceptance of welfare from the government. Local health departments have found that the Amish will accept vaccination if it is offered vigorously [63]. But like other tools of modern technology, Amish attitudes toward and use of vaccination vary across church districts. In fact, they can be flexible regarding vaccination [42].

An outbreak of measles occurred among the Pennsylvania Amish in 1987-1988. A community survey of households with Amish children in Lebanon County, PA, indicated that about half of those children 1-14 years old had received the measles vaccine, while half had not received the vaccine [61]. The investigators noted that two vaccination clinics were held in Lebanon County but only 14 Amish were vaccinated, and vaccination did not halt transmission of the virus.

Following an outbreak of 274 rubella cases in the Ohio Amish community in 1990-91, 146 Amish residents of northeastern Ohio were queried as to their rubella vaccination status: only 3% of them had been vaccinated [27]. Vaccinations were offered free of charge at local clinics during the outbreak, but only five doses were administered. An Amish person from this region may have started a new rubella outbreak among an Amish community in Tennessee [4]. Only one person out of
383 about whom information was obtained had been vaccinated against rubella, and members of this community declined vaccination.

Following a cluster of invasive *Haemophilus influenzae* type B (Hib) cases amongst the Amish in Pennsylvania in 2000, Fry *et al.* found that less than 10% of respondents had their children fully immunized (as according to the the CDC) for their age in Amish community A, while Amish community B had rates of nearly 30% [21]. However, Amish community A had significantly a higher rate of polio vaccination in children (62%) compared to Amish community B (14%). Religion was not cited as a reason for lack of vaccination; instead, vaccination was not considered a priority compared to other activities of daily life. Philosophical objections, difficulty traveling, and lack of education about Hib or belief that children weren’t at risk for Hib disease were also common reasons. Over three-quarters of respondents indicated they would vaccinate their children if the vaccine were offered closer to or at home.

Yoder and Dworkin discovered that 84% of survey respondents with children in an Old Order Amish community had their children fully vaccinated [66], and 90% of respondents themselves had been vaccinated. This was influenced by past experience with vaccination and a growing acceptance of modern medical trends by young parents: parents who were vaccinated as children were more likely to have their children vaccinated, and younger parents were more likely to have their children vaccinated. Of respondents with unvaccinated children, most did not give religious reasons for lack of vaccination; instead, the most commonly cited reason was that vaccines are not safe, followed by being against their personal beliefs and not being effective to prevent disease in their children—who they believed may not have even been at risk.
CHAPTER 3

2014 OHIO MEASLES OUTBREAK

The Amish can become an island of susceptibles in a sea of herd immunity, and are especially at risk when a disease is introduced into the community [4]. This occurred during the measles outbreak that affected much of the Amish community in the state of Ohio in 2014. Ohio has the largest Amish population in the world at an estimated 67,230 members across 498 church districts, which are clustered together in many rural counties throughout the state [16].

3.1 Outbreak Description

The measles outbreak began in Knox County in March 2014. The index case developed a rash on March 24. The second case appeared two weeks after the index case, also in Knox County. Just one week later, measles had spread to Ashland and Coshocton counties. Another two weeks passed before cases appeared in Holmes and Richland counties. New cases started rapidly appearing beginning the week of April 13th, and the number of new cases increased each week for four weeks thereafter, reaching a maximum of 80 new cases during the week of May 11th (Figure 3.1). The weekly number of new cases generally stopped increasing after this week, but cases continued to be identified for 10 more weeks. The outbreak was declared officially over on September 4, 2014.
The outbreak lasted about four months, with 122 days passing between the rash onset of the first and last cases. Over half the cases had occurred by May 14th, 52 days into the outbreak. By the end of the epidemic, there were 382 confirmed cases in 178 females and 204 males, with no deaths. This was the largest outbreak in Ohio since the measles resurgence of the early 1990s, and the largest measles outbreak in the US endemic transmission ended in the early 1990s [23]. The outbreak spanned nine counties, eight of which were adjacent to each other in northeastern-central Ohio (Figure 3.2). About half the total cases occurred in Knox County, where the virus was introduced and the outbreak began (Table 3.1). The largest Amish community in Ohio, where nearly half the Ohio Amish community live—the Greater Holmes County settlement—was also affected by this outbreak [11]. Only a handful of cases appeared in Stark, Highland, Wayne, and Crawford counties, and they occurred during the height of the outbreak. The outbreak did not spread beyond Ohio.
Figure 3.2: Map of the affected region. Source of disease data: Ohio Disease Reporting System.
Table 3.1: Cases by county.

<table>
<thead>
<tr>
<th>County</th>
<th>Case count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knox</td>
<td>195</td>
</tr>
<tr>
<td>Holmes</td>
<td>64</td>
</tr>
<tr>
<td>Coshocton</td>
<td>48</td>
</tr>
<tr>
<td>Ashland</td>
<td>46</td>
</tr>
<tr>
<td>Richland</td>
<td>20</td>
</tr>
<tr>
<td>Stark</td>
<td>6</td>
</tr>
<tr>
<td>Crawford</td>
<td>1</td>
</tr>
<tr>
<td>Highland</td>
<td>1</td>
</tr>
<tr>
<td>Wayne</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>382</strong></td>
</tr>
</tbody>
</table>

The Ohio Department of Health (ODH) was notified of a possible case of measles on April 21, about a month after the index case began showing signs of the disease. In Ohio, measles is a Class A reportable disease that must be immediately reported by phone to a local public health department upon receipt of positive laboratory results. The *Columbus Dispatch* reported that the index case had been infected with measles while on a humanitarian aid trip to the Philippines and brought it back to the Ohio Amish community, where the disease was misdiagnosed as dengue fever, causing the delay in reporting [9]. Additionally, the traveler stated that he would have been vaccinated against measles had this been recommended by a physician. The Philippines experienced a large outbreak of measles in 2014, with 21,420 confirmed measles cases and nearly 60,000 additional suspected cases [44]. Molecular epidemiology confirmed the link: the outbreaks in both Ohio and the Philippines were caused by measles virus with genotype B3. The CDC officially confirmed measles in the state of Ohio on April 25, the same day that the first free vaccination clinics were held in Knox and Holmes Counties.
Cases were identified by the clinical case definition of generalized rash lasting three or more days; fever higher than 101.0 degrees Fahrenheit; and cough, coryza, or conjunctivitis. Confirmed cases were considered to be those cases with acute febrile rash illness and laboratory confirmation or epidemiological linkage to a laboratory-confirmed measles case [43]. The outbreak primarily affected the young: over half of the cases occurred in people under 15 years old, and the youngest case was only two weeks old (Figure 3.3). In isolated populations, measles often affects adults [59], which was seen in this outbreak—the oldest case was 53 years old. Estimates for the force of infection (the rate at which susceptibles become infectious) were also calculated for each age group by dividing the number of cases per age group by the Greater Holmes County settlement Amish population size per age group, who are assumed to be susceptible (Figure 3.4).

Figure 3.3: Case age distribution (n = 382 cases).
Figure 3.4: Force of infection for each age group.

If unvaccinated, large Amish families are expected to be entirely susceptible to measles, such that everyone in a family gets infected by the virus once the virus is introduced by one infected household member. Indeed, cases were mostly infected through household transmission routes and church services, which are held in the home (Figure 3.5). A full list of symptoms and complications reported by cases is presented in Table 3.2, while reported rash durations are given in Figure 3.6.
Table 3.2: Frequency of reported symptoms and complications of measles in the 2014 Ohio outbreak.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown/Blank (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>380 (99)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>380 (99)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cough</td>
<td>356 (93)</td>
<td>23 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>296 (77)</td>
<td>69 (18)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Coryza</td>
<td>277 (73)</td>
<td>84 (22)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>212 (56)</td>
<td>146 (38)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>92 (24)</td>
<td>255 (67)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (1.5)</td>
<td>231 (60.5)</td>
<td>145 (38)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (1.3)</td>
<td>189 (49.5)</td>
<td>188 (49.2)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (9)</td>
<td>220 (58)</td>
<td>128 (33)</td>
</tr>
</tbody>
</table>

Figure 3.5: Transmission settings reported for the 2014 Ohio measles outbreak (n = 327). 55 responses were blank. “Other” included close family and community locations, transportation, and events.
A majority (55%) of cases reported never having received the measles vaccine, of which 19 cases were too young to have been vaccinated according to accepted recommendations (ie, they were younger than 12 months old). Reasons provided for not having been vaccinated are detailed in Figure 3.7.

Few (21) cases were vaccinated more than 14 days (the average time from exposure to rash) before rash onset, indicating potential primary vaccine failure. A greater number of cases received MMR vaccine fewer than 14 days before rash onset. Thirteen cases were vaccinated 12-14 days before rash onset during the 72-hour window following exposure that post-exposure prophylactic (PEP) vaccination may effectively prevent measles disease; the development of measles in these cases potentially indicates PEP failure. A total of 86 cases were vaccinated within 14 days before rash onset, perhaps with the goal of protection against measles (if they were unknowingly infected) or PEP success (if they were known to be infected), or perhaps in order to gain protection against the other two vaccine-preventable diseases contained in the
MMR vaccine. Five cases were vaccinated after rash onset, likely to gain protection against mumps and rubella.

Figure 3.7: Reasons for not having received measles vaccination (n = 288). 94 responses were blank. Only one reason was given per case.

3.2 Public Health Response

Vaccination of susceptibles is a tool often used to control measles outbreaks [42]. Ohio’s two-dose MMR vaccination coverage rate is estimated at 96.2% among children enrolled in kindergarten during the 2013-2014 school year [58]. However, many Amish children do not attend public schools, and Amish schools do not require immunizations of their pupils prior to school entry. This and other reasons, such as
low prioritization of and logistical barriers to vaccination, led to the creation of a large pool of measles-susceptible individuals existing within the generally highly vaccinated Ohio population. ODH responded to the measles outbreak by ordering nearly 19,000 MMR doses for distribution throughout Ohio, while local health departments administered these vaccines in over 100 vaccination clinics. Over 11,000 doses were administered to residents of the measles-affected counties (Table 3.3). ODH also recommended quarantine of potentially exposed susceptible persons from schools and childcare centers for 21 days after the appearance of the last case [43].

Table 3.3: Cases and vaccine doses administered by county.

<table>
<thead>
<tr>
<th>County</th>
<th>Case count</th>
<th>Vaccine doses administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashland</td>
<td>46</td>
<td>678</td>
</tr>
<tr>
<td>Coshocton</td>
<td>48</td>
<td>646</td>
</tr>
<tr>
<td>Crawford</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Highland</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Holmes</td>
<td>64</td>
<td>5,182</td>
</tr>
<tr>
<td>Knox</td>
<td>195</td>
<td>1,700</td>
</tr>
<tr>
<td>Richland</td>
<td>20</td>
<td>951</td>
</tr>
<tr>
<td>Stark</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Wayne</td>
<td>1</td>
<td>1,812</td>
</tr>
<tr>
<td>Total</td>
<td>382</td>
<td>11,073</td>
</tr>
</tbody>
</table>

3.3 A Mathematical Model

Infectious disease outbreaks may be modeled mathematically using differential equations. Such so-called deterministic models divide the population of interest into several classes between which members of the population may transition. Any individual may only be in one class at a time, but individuals may change classes as the
outbreak progresses, depending on their infection status. Deterministic models utilize differential equations to describe the rate of change of movement into and out of each class, and when differential equations for each class are considered all together, a model of the entire outbreak is formed.

The biology of the infectious organism and epidemiology of the disease help inform model design. Much is known about the biology and epidemiology of measles, making it an attractive disease to model. A susceptible-exposed-infectious-removed (SEIR) model is a popular choice for measles modeling. The population of interest is divided into four compartments: individuals who are susceptible (not immune) to measles (the S class); individuals who have been exposed to and infected by measles, but who are not yet able to spread the virus (the E class); individuals who have incubated the virus long enough to become infectious, capable of spreading the virus to others (the I class); and individuals who have been removed from the outbreak, due to either virus- or vaccine-induced immunity (the R class). Since individuals may only be in one class at a time,

\[ S + E + I + R = N \]

where N is the total population size.

In our model, we consider a population that is almost entirely susceptible at the beginning of the outbreak, such that everyone is assumed begin in the susceptible class (save one or two index cases). Once the outbreak begins, individuals may become exposed to measles and move from the susceptible class to the exposed class, or become vaccinated and move from the susceptible class to the removed class (Figure 3.8). Exposed individuals incubate the virus and then move to the infectious class when they are contagious. Infectious individuals can spread the virus to susceptible individuals, but must move to the removed class when they have recovered from infection, developed immunity, and are no longer capable of spreading the disease.
Figure 3.8: Graphical depiction of the SEIR model.

For a measles outbreak in a susceptible pocket among a highly vaccinated community, the outbreak timespan is on the order of months, so the total population size is assumed to be constant: births, deaths, and immigration and emigration have no significant impact on the model dynamics and are ignored.

The rates at which individuals enter and exit different classes depend upon user-defined parameters in the ordinary differential equations (Equation 3.3.1). The model is unscaled, providing results in numbers of individuals.

\[
\begin{align*}
S' &= -\beta SI - v(t) \\
E' &= \beta SI - \sigma E \\
I' &= \sigma E - \gamma I \\
R' &= \gamma I + v(t)
\end{align*}
\] (3.3.1)

These parameters are key to translating empirical observations of measles dynamics into a mathematical form. The parameters for $\sigma$, the reciprocal of the average latent period (time between exposure and infectiousness), and $\gamma$, the reciprocal of the average infectious period, are taken from the past studies of measles epidemiology. The value for the susceptible-infective contact rate, $\beta$, is fitted to the stochastic
Table 3.4: Parameter values for the SEIR model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>Susceptible-infective contact rate</td>
<td>0.000217 contacts ( \times ) day(^{-1} )</td>
<td>Model fit</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Reciprocal of average latent period</td>
<td>( \frac{1}{9} ) day(^{-1} )</td>
<td>[1]</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>Reciprocal of average infectious period</td>
<td>( \frac{1}{7} ) day(^{-1} )</td>
<td>[1]</td>
</tr>
<tr>
<td>( v(t) )</td>
<td>Vaccination</td>
<td>Variable people ( \times ) day(^{-1} ) (see Equation 4.1.5)</td>
<td>ODH Data</td>
</tr>
</tbody>
</table>

model, while the value for the vaccination parameter is defined by vaccination data obtained during the outbreak (Table 3.4).

The susceptible-infective contact rate, \( \beta \), depends on the length of the infectious period and the basic reproduction number, \( R_0 \), for the pathogen. The basic reproduction number is a measure of how many new infections the average infective will produce at the beginning of an outbreak. If \( R_0 \) is less than one, an infective will spread the disease to less than one susceptible, on average, and the disease will eventually die out. If \( R_0 \) is greater than one, an infective will spread the disease to more than one person, on average, and an outbreak will be ignited. Measles is a very contagious, well-studied pathogen; it is estimated to have \( R_0 \) values in the range of 12.5-18 [1].

The SEIR model makes certain assumptions about population conditions. The population is assumed to be homogeneous and well-mixed: everyone has the same chance of interacting with each other, and space plays no role. In reality, these assumptions may not be met. Populations are stratified at different levels with different probabilities for interaction, such as the household, school, work, or town levels.
While outbreaks in large populations may be modeled deterministically, small populations are more vulnerable to the influences of chance. With a relatively small population, discrete numbers are preferable to continuous quantities (such as obtained through differential equation modeling) [50].

A disease may enter a small population in one infectious individual, but that person may not infect anyone else simply due to chance (whether it be not contacting anyone else for an extended period of time or not contacting anyone long enough to transmit the disease). If no one else gets infected and the originally infectious person recovers, the disease will die out in the population, and there will be no outbreak.

Since the susceptible population size and final size of the Ohio outbreak were relatively small (especially at the county level), and chance plays a significant role in small populations, a stochastic model based on SEIR dynamics was designed to reproduce the outbreak. It’s possible to see inherent process variability in a stochastic model.

3.3.1 The Gillespie Algorithm

The Gillespie Algorithm was created by Daniel T. Gillespie in 1976, in order to model stochastic chemical reactions over time. If reactions can be taken to mean transitions between epidemiological compartments, then the Gillespie algorithm can be used to model outbreaks of infectious diseases at the population level. The algorithm can be described by repeatedly iterating a series of three steps, an example of which is presented in Table 3.5 [50].
Table 3.5: Description of the Gillespie algorithm steps.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Determine a wait time until a transition occurs.</td>
<td>0.5 days</td>
</tr>
<tr>
<td>2</td>
<td>Determine which transition occurs.</td>
<td>$I \rightarrow R$</td>
</tr>
</tbody>
</table>
| 3    | Update the number of individuals in each compartment to reflect the transition that has just taken place. | $I(t_{n+1}) = I(t_n) - 1$  
|      |                                                                             | $R(t_{n+1}) = R(t_n) + 1$ |

The transition rates are derived from the SEIR model (Equation 3.3.1). An example of a transition rate is the transition from the I compartment to the R compartment: this occurs at a rate of $\gamma I dt$, where $dt$ is the time step plus a small error term.

The wait time between reactions is modeled by an exponential distribution whose mean is equal to the reciprocal of the sum of the transition rates; each wait time is chosen randomly from this distribution. A random number is generated before a transition occurs, which will indicate which transition occurs. The probability that a particular transition occurs is equal to the rate of that transition divided by the sum of all the transition rates. Transition rates depend on the total sizes of respective epidemiological compartments, so the probability of a particular transition occurring changes as the simulation progresses forward.
4.1 Methods

We investigate the outbreak that occurred in Knox County (Figure 4.3). We choose this county because it is where the outbreak began, it had over 50% of the total cases in the outbreak, we can ignore the impact of space, and we have a reasonable estimate for the size of the measles-susceptible population.

4.1.1 Population of Interest

According to Donnermeyer et al., Knox County had an Amish population of 2,257 people (baptized members and their children) across six settlements in 2010 [11]; with an annual growth rate of 3.296%, an estimated 2,570 Amish people lived in Knox County during the 2014 outbreak. However, we can safely assume that not all of these people are susceptible to measles; older members of the Amish population very likely had measles when it was still endemic in the United States, and since measles infection induces lifelong immunity, they are considered to be in the removed class at the start of the outbreak. For our purposes we can simply ignore them, and consider only the population that began the outbreak as susceptible.

How do we determine the susceptible population size in 2014? One of the ways to document immunity to measles is to have been born before 1957, when measles
was endemic in the United States. By this method, in an unvaccinated population surrounded by high levels of herd immunity, anyone under the age of 57 would be considered susceptible. While half of the cases were 15 years of age or younger, older cases ages were not uncommon (Figure 3.3): the oldest case was 53 years old. In light of these data, we assume the susceptible population to include all Amish people under the age of 55.

How many people in the Amish community were younger than 55 in 2014? The large size of Amish families and rapid population growth has resulted in a very young population (Figure 4.1). Demographic data gathered from the Greater Holmes County settlement indicates that 88% of the Amish community is under the age of 55 [7]. We assume that the age structure is similar across different Amish communities, such that 88% of the Amish population in a given location is susceptible to measles. In Knox County, we therefore assume that 2,269 of the 2,570 Amish were susceptible to measles at the beginning of the 2014 outbreak.

4.1.2 Vaccination

A time series of measles vaccination data was obtained from the Holmes County Health Department that delineated the number of doses given in mass vaccination and other clinics during the outbreak (Figure 4.2).

We did not have such specific vaccination distribution data for Knox County, so instead used the vaccination schedule in Holmes County and transformed it to fit the outbreak in Knox County. The rate of increase in cases was faster in Knox County, which indicates that virus swept through Knox County faster than in Holmes County; indeed, half the cases in Knox County occurred by day 45 of the outbreak, while it took until day 75 of the outbreak for half the cases to occur in Holmes County. In other words, time progressed “faster” in Knox County with regard to
Figure 4.1: Age structure of the Greater Holmes County Settlement Amish community [7]

Figure 4.2: Cumulative vaccination distribution in Holmes County over time.
case appearance; a day in Holmes County could be considered equivalent to more
than a day (for example, a day and a half) in Knox County. We incorporated this
faster time scale in Knox County by fitting the Holmes County vaccination data to
a Michaelis-Menten saturation curve, then stretching the curve to fit a more realistic
vaccination schedule for Knox County. A Michaelis-Menten curve is of the form

$$v(t) = \frac{kt}{a + t} \quad (4.1.1)$$

where $k$ is the saturation level of vaccine doses and $a$ is the time at which half the
vaccine doses have been administered. The Holmes County vaccination data were fit
to a Michaelis-Menten curve by optimizing the parameters $k$ and $a$ using a nonlinear
least squares optimization algorithm to minimize the difference in the observed vacc-
cination data and the Michael-Menten curve. The optimization algorithm gave the
optimized parameter values of $k_{Holmes} = 8613.6$ and $a_{Holmes} = 54.762$.

Once the parameters for the formula were optimized for Holmes County, they
were transformed to reflect the number of doses administered in Knox County and
the “faster” time scale.

$$k_{Knox} = k_{Holmes} \times \frac{\# Knox \text{ doses}}{\# Holmes \text{ doses}} \quad (4.1.2)$$

$$a_{Knox} = \frac{a_{Holmes}}{1.1} \quad (4.1.3)$$

The vaccination function used to move susceptibles to the removed compartment was
then:

$$v_{Knox}(t) = \frac{k_{Knox} t}{a_{Knox} + t} \quad (4.1.4)$$

$$= \frac{2825t}{49.7837 + t} \quad (4.1.5)$$
Figure 4.3: Cumulative case count over time in Knox County. Time indicates number of days since the outbreak began.

4.2 Results

4.2.1 Fitting the Basic Reproduction Number

We applied the parameters in Table 3.4 and Equation 4.1.5 to study how well the stochastic simulation modeled the outbreak in Knox County. We assumed that almost everyone was susceptible at the beginning of the outbreak, save for one individual incubating measles in the exposed class, and one individual capable of spreading measles in the infectious class (Table 4.1).

Table 4.1: Initial conditions for the model.

<table>
<thead>
<tr>
<th>Class</th>
<th>Initial value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S(t_0)$</td>
<td>$N - 2$</td>
</tr>
<tr>
<td>$E(t_0)$</td>
<td>1</td>
</tr>
<tr>
<td>$I(t_0)$</td>
<td>1</td>
</tr>
<tr>
<td>$R(t_0)$</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 4.2: Fitting $R_0$ to the observed data. FOS = final outbreak size (total number of cases), DUR = (outbreak) duration (days), IQR = interquartile range, n = 100 trials for each $R_0$ value.

<table>
<thead>
<tr>
<th>$R_0$</th>
<th>Average FOS</th>
<th>FOS Error</th>
<th>FOS IQR</th>
<th>Average DUR</th>
<th>DUR Error</th>
<th>DUR IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>149.62</td>
<td>-45.38</td>
<td>[16, 248]</td>
<td>81.57</td>
<td>1.57</td>
<td>[73.82, 100.31]</td>
</tr>
<tr>
<td>3.35</td>
<td>148.87</td>
<td>-46.13</td>
<td>[41, 222]</td>
<td>86.05</td>
<td>6.05</td>
<td>[79.41, 101.34]</td>
</tr>
<tr>
<td>3.4</td>
<td>174.41</td>
<td>-20.59</td>
<td>[77, 248]</td>
<td>89.16</td>
<td>9.16</td>
<td>[81.87, 100.92]</td>
</tr>
<tr>
<td>3.45</td>
<td>193.08</td>
<td>-1.92</td>
<td>[78, 250]</td>
<td>89.35</td>
<td>9.35</td>
<td>[84.62, 102.65]</td>
</tr>
<tr>
<td>3.5</td>
<td>186.84</td>
<td>-8.16</td>
<td>[40, 308]</td>
<td>84.21</td>
<td>4.21</td>
<td>[79.51, 100.65]</td>
</tr>
<tr>
<td>3.55</td>
<td>200.40</td>
<td>5.40</td>
<td>[58, 301]</td>
<td>88.46</td>
<td>8.46</td>
<td>[80.61, 103.14]</td>
</tr>
<tr>
<td>3.6</td>
<td>202.69</td>
<td>7.69</td>
<td>[48, 338]</td>
<td>87.86</td>
<td>7.86</td>
<td>[80.81, 101.54]</td>
</tr>
<tr>
<td>3.65</td>
<td>236.49</td>
<td>41.49</td>
<td>[77, 348]</td>
<td>89.40</td>
<td>9.40</td>
<td>[83.32, 105.37]</td>
</tr>
<tr>
<td>3.7</td>
<td>238.28</td>
<td>43.28</td>
<td>[93, 333]</td>
<td>95.59</td>
<td>15.59</td>
<td>[87.82, 104.90]</td>
</tr>
</tbody>
</table>

We determined the susceptible population to be 2,269 people; all that remained was to find a value for $R_0$ that would help the model fit the observed data. Classical $R_0$ values for measles are in the range of 12.5 to 18 [1]. However, these values were derived from data from comparatively modern big cities in the United States and United Kingdom with high population densities and patterns of social interaction and movement that are likely quite different from Amish society. We tested the model using different values for $R_0$ and obtained the model-predicted average final outbreak sizes and outbreak durations in Knox County for each $R_0$ value (Table 4.2).

By inspection, the error in final outbreak size is smallest when $R_0 = 3.45$. For our purposes it is more important to find a fitted $R_0$ value that minimizes the error in final outbreak size. Therefore we set $R_0 = 3.45$ for the following trials of our stochastic SEIR-Gillespie model, implemented in MATLAB.
4.2.2 Simulations of Public Health Interventions

In order to investigate the effectiveness of the vaccination campaign, we wish to see how the outbreak may have played out under different public health intervention scenarios.

Each simulation run will produce different dynamics due to the stochasticity of the model. In order to observe general trends, we run the model hundreds of times to create a large sample size of informative statistics, such as the final outbreak size and outbreak duration (Figure 4.4).

Scenario 1: Observed vaccination

While the virus had a month to spread before being reported to public health agencies, the vaccination response after notification was prompt and comprehensive.

With $R_0 = 3.45$, 500 trials of the stochastic simulation produced measles outbreaks in the range of one case to 934 cases, with an average of about 183 cases (Figure 4.4). In 13.2% of trials, the outbreaks were small in size (<10 cases). Although the range extended to over 900 cases, half of the trials produced outbreaks smaller in size than 151 cases.

The outbreak durations were much more concentrated, and had a mean of 87 days with a range of 1.8326 days to 140.94 days. Small outbreaks tended to have a wide range of outbreak durations, while large outbreaks typically had outbreak durations in the 75-125 day range (Figure 4.5).
Figure 4.4: Results of 500 trials of the stochastic simulation for Knox County with vaccination and $R_0 = 3.45$. Top: Distribution of final outbreak sizes, Bottom: Distribution of outbreak durations.
Scenario 2: No vaccination

If public health agencies were never notified of the outbreak, or the Amish were absolutely unreceptive to vaccination, we predict that the outbreak dynamics would have a very different trajectory. To determine the effect of this vaccination schedule, we ran the stochastic simulation 500 times using the exact same parameters as the observed outbreak, but completely eliminating the vaccination parameter such that \( v(t) = 0 \).

As Figure 4.6 shows, after 500 trials of the simulation with no vaccination and \( R_0 = 3.45 \), the final outbreak sizes are almost all greater than 2,000 cases. In fact, the average final outbreak size was about 1,990 cases. This is about a 900% increase in total number of cases compared to the observed outbreak in Knox County, which
only had 195 cases. A smaller percent of outbreaks were small: only 9% of the trials had fewer than 10 cases. While the range of final outbreak sizes was between 1 case and 2,216 cases, there really was no middle ground: either an outbreak is small, or an outbreak becomes extremely large in size. Indeed, over half the final outbreak sizes were larger than 2,186 cases. The correlation between final outbreak size and outbreak duration is similarly disparate: small outbreaks have outbreak durations of less than 100 days, while large outbreaks have outbreak durations exclusively (and often much) longer than 100 days.

Figure 4.6: Results of 500 trials of the stochastic simulation for Knox County with $R_0 = 3.45$ and without vaccination. Top: Distribution of final outbreak sizes, Bottom: Distribution of outbreak durations.
The outbreak durations were again more concentrated than the final outbreak sizes, but with a much wider range, from less than a day to 323.74 days. At 164.27 days, the average simulated outbreak duration was more than double the observed Knox County outbreak duration of 80 days.

![Figure 4.7: Final outbreak size vs. outbreak duration for Knox County without vaccination.](image)

**Scenario 3: Delayed vaccination**

What if the public health system was notified of the outbreak much later than observed, due to continued misdiagnosis or spread of misinformation? We add one month to the start time of vaccination; the vaccination data given by 4.1.5 remains the same, but vaccination begins on day 61 of the outbreak instead of day 33.
The results (Figure 4.8) appear somewhat in between those of Knox County with vaccination and Knox County without vaccination. Compared to Knox County with vaccination, the range in outbreak sizes is bigger, from one to 1,965 cases. At 1,068 cases, the mean final outbreak size with delayed vaccination is nearly 500% greater than with the observed vaccination schedule. The median is also much higher at 1,240 cases, and indeed, the “weight” of the final outbreak sizes appears to be shifting to the extreme of high case counts, as occurs when there is no vaccination (Figure 4.6).

![Figure 4.8: Results of 500 trials of the stochastic simulation for Knox County with \( R_0 = 3.45 \) and vaccination delayed by one month. Top: Distribution of final outbreak sizes, Bottom: Distribution of outbreak durations.](image)

The outbreaks are somewhat longer than Knox County with vaccination. The average duration is 123.69 days with a range of less than one day to 192 days long.
Outbreak durations are correlated to final outbreak sizes (Figure 4.9) in a similar manner as Knox County with observed vaccination (Figure 4.5).

Figure 4.9: Final outbreak size vs. outbreak duration for Knox County with delayed vaccination.

**Scenario 4: Immediate vaccination**

Perhaps the most interesting scenario is to use the model to predict what may have occurred if measles had not been misdiagnosed, and notification to public health agencies and the resultant vaccination campaign had not been delayed. To investigate this scenario, we take the observed vaccination data but begin vaccination on day 1 of the outbreak.

The results differ greatly from the other three scenarios considered (Figure 4.10). Outbreak sizes range from one to a maximum of only 26 cases (13% of the actual
outbreak size in Knox County), with half of outbreaks consisting of fewer than four cases. Over 90% of outbreaks are small, resulting in fewer than 10 cases.

Figure 4.10: Results of 500 trials of the stochastic simulation for Knox County with $R_0 = 3.45$ and immediate vaccination. Top: Distribution of final outbreak sizes, Bottom: Distribution of outbreak durations.

The outbreak durations are also shorter than for the other three scenarios: the maximum outbreak size is about 84 days, but half of the outbreaks are only about a month long, several months shorter than the observed outbreak length. The correlation between final outbreak size and outbreak duration is less obvious, if present (Figure 4.11). The stochasticity of the model likely plays a greater role in these smaller outbreaks.
Figure 4.11: Final outbreak size vs. outbreak duration for Knox County with immediate vaccination.
CHAPTER 5
DISCUSSION

As George E. P. Box wrote, “All models are wrong, but some models are useful.” The stochastic nature of Gillespie-SEIR model, as well as the ranges in parameter values and nontrivial task of accurately estimating the susceptible population size of isolated religious subcultures, makes it impossible to exactly match the data observed during the 2014 measles outbreak in Knox County. However, the observed final outbreak size was near the mean of 500 trials of the stochastic model with vaccination, indicating the model’s utility in understanding summary statistics (such as final size and duration) of the outbreak and evaluating intervention efficacy.

The model results suggest that in Knox County, the observed course of vaccination had a positive outcome on the outbreak trajectory with regard to final outbreak size and outbreak duration. Even with a relatively low $R_0$ value calculated to be 3.45, completely removing vaccination from the model led to over 80% of outbreaks having nearly the entire susceptible population become infected. The observed outbreak of 195 cases has essentially zero probability of occurring in the no-vaccination scenario: the outbreak either dies off by chance, or (much more frequently) consumes everyone. Additionally, the scenario of immediate vaccination with no reporting delay quantitatively informs how effective a quick mass vaccination response can be: the maximum predicted outbreak size of 26 cases pales in comparison to the observed 195 cases, and the outbreaks were predicted to be over much more quickly as well. With immediate
vaccination, the susceptible community would have been vaccinated quickly enough to prevent the observed outbreak from occurring.

This has real-world implications for clusters of undervaccinated communities such as the Amish: an outbreak has great potential to be controlled through mass vaccination clinics, whereas apathy toward vaccination or refusal to vaccinate could very likely result in an outbreak far greater in size and scope. The number of cases with serious complications increases as the total case count increases, such that it is much more likely for especially young children to develop pneumonia, encephalitis, or even die. The observed outbreak had a small number of complications and no deaths in part because spread of the virus was prevented through vaccination of susceptibles. With no vaccination, the final outbreak size and therefore morbidity and mortality likely would have been far greater. Additionally, the outbreak could have been far longer, with the longest simulated trial approaching an outbreak of a year in length. This model ignores the impact of space, but the virus surely would have spread to other Amish communities in that case, and perhaps even beyond Ohio’s borders into the large Amish settlements of Pennsylvania and Indiana.

Our model also allows us to compare the observed outbreak to the ones that could have occurred with a one-month delay in onset of the vaccination campaign. The observed outbreak size has a nonzero probability of occurring in the scenario of delayed vaccination, but the median final outbreak size is much higher at 1,240 cases, and by inspection the chance of only 195 cases occurring in this setting is rather small. While the chances of a larger outbreak are higher, it’s not the case of a small vs. large outbreak that completely wipes out the susceptible population, as with the scenario of no vaccination. The delayed vaccination still appears to have some positive effect on the outbreak trajectory, controlling the final size of the outbreak. However,
stochastic effects also play a big role in the outcome of an outbreak with delayed vaccination, as there are a wide range of predicted outbreak sizes and durations.

Results from the simulations with various vaccination scenarios highlight the need for surveillance of highly contagious, vaccine-preventable diseases in undervaccinated populations; education regarding travel to global areas where US-eliminated infectious diseases may be endemic; education of physicians in the diagnosis of US-eliminated diseases; and close investigations of suspected cases. The simulations also indicate the utility of a quick public health response in the form of a vaccination campaign that occurs as soon as possible after health department notification. As the Amish have historically shown, they are flexible regarding modern technology, and many are willing to be vaccinated when faced with a potentially deadly disease in their community.

This work has the potential to be extended in the future in several ways. One obvious way is to apply the model to the entire Ohio outbreak of 382 cases, which requires the nontrivial task of determining the effective population size of susceptible people in the areas affected by the outbreak. In this case it may also be useful to explore the impact of spatial dynamics with explicit movement of people between measles-impacted areas, or the implementation of quarantine or isolation procedures. Additionally, the nature of large Amish families and high reports of household transmission indicate that age structure may play an important role in the outbreak. However, with model complexity usually comes more unknown parameters, and it appears that a even this relatively simple model may help to understand the effectiveness of important public health decisions in the wake of an outbreak of the most contagious disease in history.


Ohio Department of Health. Measles (Rubeola), February 2015.

Western Pacific Regional Office. Measles-Rubella Bulletin. 9(1), January 2015.


