Using High-Resolution Measles Vaccination Coverage Data Improves Detection of Spatial Heterogeneity and Measles Outbreak Risk in the US and Africa

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Abstract

Measles outbreaks burden both low- and middle-income countries (LMICs) and high-income countries (HICs), including the United States. Although these outbreaks happen locally, usually due to pockets of low vaccination coverage, and though data is often collected locally, this data is often available to researchers only at an aggregated, low-resolution level. This diminishes the strength of spatial analyses, particularly those that determine heterogeneity and clustering. We collected and used high-resolution measles coverage data and performed spatial clustering and prediction analyses, as well as a longitudinal analysis on US school vaccination exemption law, to determine whether analyses using high-resolution data could perform well compared to those using the low-resolution data typically available. With Demographic and Health Surveys (DHS) data, we mapped clusters of low vaccination coverage in a 10-country area of East Africa and determined the covariates associated with low coverage. Using the Lexis Nexis database, we examined the effect of vaccination exemption law changes by state on coverage rates in the US over a six-year period. Finally, we created a database of publicly available high-resolution school vaccination coverage data and used this to create two models predicting counties at high risk for measles outbreak in the United States. Together, these papers show that high resolution data is better at finding areas of local, low-coverage clustering as well as predicting outbreak risk. Health departments and surveys often already collect this data; improved availability of high-resolution

data will create new opportunities to improve understanding of disease risk and to detect geographic communities at increased risk of outbreaks. This in turn will allow public health practitioners to improve efficiency of resource use by better targeting their efforts, decreasing the impact of possible outbreaks or preventing outbreaks altogether.

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1.0 Introduction

Vaccination coverage is on the rise worldwide, yet measles, declared eliminated from the US in 2000, outbreaks continue to increase in the US and Europe.[1] The US will lose its non-endemic status at the end of October 2019 unless cases from ongoing outbreaks in New York reach zero. Though many measles symptoms are mild, cases can result in pneumonia, encephalitis, and death.[2]

Outbreaks in high-income countries (HICs) are at least partially the result of vaccine exemptions, the rules for which vary from state to state in the US. In California, for example, vaccination is high statewide, but because of exemptions, especially for the measles-mumps-rubella (MMR) vaccine, small communities have low enough coverage to create risk of measles outbreaks.[3] In low and middle income countries (LMICs), measles cases remain high mostly because of lack of access to vaccines, rather than hesitancy.

Measles is one of the world's most contagious diseases, meaning an outbreak can spread rapidly.[4] Despite potential of rapid-growth outbreaks, researchers do not know exactly where many non-vaccinating communities are located, as local data that are needed to determine this are available only nationally, with local-level data locked away in local health departments. Some research to determine this has been conducted globally (particularly in Africa), but it has often been done on a country-by-country basis rather than at a larger, regional scale. This means that border communities, at risk for transmission, are often underpowered in analyses.

No equivalent to the Demographic and Health Surveys (DHS), which collect high-resolution, spatially-linked health data, used in the African studies, has been readily accessible in the US.[5] In many cases in the US, this data is already collected by schools and counties, but it is inaccessible to researchers. As a result, research examining local variation of vaccination coverage within the United States is sparse. We aim to rectify these gaps in our understanding of rates of vaccination coverage, locate the communities with low levels of vaccination coverage, and determine the factors associated with the development of these low-coverage communities. There is a critical need to determine areas in the US and internationally that may need additional support or intervention to prevent measles outbreak, as well as what factors may influence it.

1.1 Goals of This Research

This research examines spatial heterogeneity of vaccination coverage and relevant covariates. Vaccination coverage has long been measured by averages calculated at a low resolution, i.e. the national or state level. These, however, are not representative of the local level, where disease outbreaks usually occur. The long-term goal of this research is to reduce infectious disease outbreaks. Our overall objective is to characterize spatial heterogeneity in vaccination coverage rates, locate areas with low vaccination coverage, and identify socio-demographic predictors for low coverage. This will help to determine the benefits of collecting and examining vaccination data at the local level rather than state level to assess variation in coverage and determine the best method of calculating vaccination coverage. As such, we can better control epidemics based on high-resolution spatial information about vaccination coverage and its determinants at the local, rather than state or national level.

1.1.1 Public Health Significance

This research offers three major benefits to public health practitioners. First, determination of the impact of local-level data will reveal the best resolution to collect data nationally. Local-level data is time-consuming to collect and clean; it is easier to aggregate and release low-resolution (state or national) datasets. A demonstration of the usefulness of higher-resolution data can spur local health departments toward collecting and disseminating higher-resolution data. In the case of the data used in the third paper of this dissertation, that data is already collected, but not readily available as those that collect it may lack the resources to easily disseminate it to researchers. Second, by identifying the covariates associated with low vaccination coverage clustering and other risks of outbreak, we can facilitate the enaction of evidence-based policies. This includes evidence-based laws that target vaccination requirements, the focus of the second paper. Third, identifying high-risk clusters enables policymakers to channel public health interventions to more effectively target high risk areas. Resources are scarce, and knowing which areas are at high risk for outbreaks allows local health departments to channel these resources to the areas of high risk instead of areas of low risk, providing a significant improvement to public health investments.

1.2 Measles and MCV Coverage: US and International

This dissertation entirely focuses on measles and the vaccine that prevents it. This vaccine can be given as either a single-antigen vaccine or the combination measles-mumps-rubella vaccine (MMR).[2,6] These are collectively referred to as measles-containing vaccines (MCV).

1.2.1 An Overview to Herd Immunity

MMR is a highly safe and effective vaccine. The measles component of the MCV single-antigen measles vaccine is 99.6% effective after the standard two-dose cycle; this makes the measles vaccine on of the most effective vaccines on the market.[7] However, because measles is one of the most contagious and easily transmissible diseases, vaccination coverage also must be among the highest to prevent against outbreak. Measles is spread through respiratory droplet transmission through the CD147 (EMMPRIN) receptor, which leads to its uniquely high transmissibility.[6] It is infectious up to four days before onset of the characteristic rash (when many exhibit symptoms of a more generic illness), and can be transmitted by fomites for up to two hours.[2,6] Because of this, the basic reproduction rate for measles, or R0, is 15-20, among the highest of all known diseases.[4,8] This is the number of secondary cases each infection of measles will cause in a susceptible (unvaccinated) population. It is 10 times higher than influenza.[4]

Because the basic reproduction rate is so high, the critical vaccination fraction (CVF), or the percent of the population that must be vaccinated in order to prevent outbreak, is 95%, which is the highest for any vaccine preventable disease.[8] For comparison, the CVF for rubella is around 80%.[4] Because the CVF for measles is so high, even as the US reaches high levels of vaccination coverage nationwide, many states fall below the CVF. As more people in a population get vaccinated, the chance of outbreak decreases. A population that reaches the CVF has achieved herd immunity (also known as population immunity). In this population, unvaccinated people will be indirectly protected from disease by the vaccinated population because, since such a high percentage of a population is vaccinated, disease is unlikely to spread within the population and reach them.

MMR coverage in the US decreased slightly in the 2016-2017 schoolyear. 29 out of 50 states did not achieve the CVF, one more than the previous year; in those states, fewer than 95% of kindergartners received two doses of MMR.[9,10] The US median coverage was 94 percent, a slight decrease from 94.6 of the previous year, and again falling below the CVF. In 2009-2010, the earliest year for which records are available, the US median was 94.5 percent. In areas below the CVF for any given disease, outbreaks are possible.[10]

1.2.2 The Current State of Coverage in the US

Despite the high current measles vaccination coverage in the US, the US has still experienced large measles outbreaks. After the recommendation of a second dose of MMR in 1997, coverage and immunity increased; by 2000, the CDC declared measles eliminated from the US, meaning measles was no longer endemic to the country (but outbreaks can still be started from imported cases, as they continue to be).[11] Coverage has fluctuated between 94 and 94.6% for the last decade.[9,12] This coverage approaching 95% is attributed partially to compulsory school vaccination requirements.[13] All states require kindergartners to be vaccinated with MMR, though there are exemptions for this rule, and it is applied differently in different states.[14] Despite this rising coverage, between 2014-2015 there were 855 measles cases.[1] These included major outbreaks in Ohio and California (including the outbreak that originated in Disneyland).[1] Years since have seen a steady, though lesser, number of measles cases until the beginning of the current outbreak, which started in October 2018 in New York City. Along with a large outbreak in the Pacific Northwest, there have been 1,241 cases of measles as of September 1, 2019, with cases in 31 states.[1] This is the greatest number of cases since 1992.[1]

These cases are thought to be due to intentional under-vaccination; that is, parents who choose not to vaccinate their children, rather than those who lack the opportunity. In the US, this is partially attributable to increasing personal belief exemptions. Though states may require kindergartners to be vaccinated, all states allow at least one type of exemption from the law, and philosophic, religious, or personal belief exemptions (PBEs) have increased. From 1994 to 2009, PBEs grew from 0.6% of kindergartners to 2.3%, an increase of 9.2% (95% confidence interval 8.8-9.6) per year. Despite increasing outbreaks, many of which have received considerable media attention, PBEs did not decrease in a study conducted from 2012 to 2014.[15]

These exemptions have led to highly clustered refusal and geographic hotspots, or under-vaccinated communities; while the US as a whole has increased vaccination due to programs such as Vaccines for Children, intentional under-vaccination has resulted in small areas with low vaccination.[16,17] This in turn has led to resurging outbreaks.[1,18]

1.2.3 The Current State of Coverage in Low-Income Countries

African countries are disproportionately affected by measles, as most cases occur in LMICs. Measles affected seven million people globally in 2016, causing 89,780 deaths, with the majority in low-income countries.[19] Though the measles vaccine, either as single-antigen MCV or combination MMR/MMRV, is available to most countries for free or subsidized through programs with WHO or GAVI (the Global Vaccine Alliance), coverage still lags behind the US in much of the continent.[20] The US achieved 94% MCV coverage in 2017, compared to 75% in Africa.[20] In addition, second-dose MCV coverage in Africa was only 25%.[20]

Because vaccines can prevent so many deaths, they figure prominently into WHO and CDC prevention strategies. The WHO coined the 2011 to 2020 decade as the Decade of Vaccines, and with their strategic partners, GAVI, UNICEF, the Bill and Melinda Gates Foundation, and the US National Institute of Allergies and Infectious Diseases, developed the Global Vaccine Action Plan (GVAP).[21] It was endorsed by the 194 member states of the World Health Assembly in 2012.[21] The GVAP seeks to increase accessibility and coverage of vaccines and sets ambitious goals, including eventual regional elimination of measles.[21]

Along with the GVAP, the Measles and Rubella Initiative is a partnership with UNICEF, the US CDC, the Red Cross, the United Nations Foundation, and the WHO. The Measles and Rubella Initiative seeks to eliminate measles and rubella in five of the six WHO regions by 2020.[22] This goal has not been revised in light of the impending deadline.

Vaccination coverage is highly variable globally. In 2016, 20.8 million children did not receive a measles vaccination; more than half of these children came from just six countries, all in Africa or Asia: Nigeria (3.3 million), India (2.9), Pakistan (2.0), Indonesia (1.1), Ethiopia (0.9), and the Democratic Republic of the Congo (0.7).[22] Very low coverage is seen in some African countries, including Angola (42%), Chad (37%), Equatorial Guinea (30%), and Nigeria (42%).[20] Others, however, are among the highest reported and well above the 95% CVF (and the US coverage rate), including Morocco (99%), Tunisia (98%), and Zambia (96%).

1.3 Causes of Under-vaccination Globally

Low vaccination can be caused by lack of access or a lack of willingness to vaccinate. Lack of access is most often seen in LMICs, where vaccines can be expensive and difficult to access because of distance, lack of availability of healthcare, and conflict. HICs see under-vaccination more often by choice (vaccine hesitancy), though in countries, such as the US, with high inequality, access issues can also be to blame for a smaller portion of under-vaccination in some areas. There are some exceptions to this, however, with vaccine hesitancy on the rise in LMICs and lack of availability an issue in geographic pockets of many HICs.

1.3.1 Vaccine Access

In Africa, like many LMICs, lack of access keeps vaccination rates lower than in HICs. As such, the highest vaccination coverage is seen in middle income countries and countries with strong, stable, and often nationalized healthcare systems (such as Rwanda).[20]

The most obvious reason for lower vaccination rates is cost. Studies have shown family income is positively associated with vaccination coverage.[23] Lower socioeconomic status has also been associated with lower vaccination coverage in India.[24] Income, however, is not often included in regression analysis in studies of LMICs, so there are not many studies that examine parental income. For most children in LMICs, vaccines are provided free via the WHO and GAVI. While the per capital gross domestic product (GDP) of the country is a factor, the family's income is not.

However, even when vaccines are free, getting a child vaccinated has additional, non-monetary costs. A mother taking a one child for a vaccination must find childcare for her other children. They must postpone their other activities.[25] Some of these persist in HICs as well, as children of working mothers in Japan had lower vaccination coverage rates than children of non-working mothers.[26]

The relationship between vaccination coverage and distance is unclear. Several studies have shown that mothers consistently cite distance as a barrier to vaccination of their children, including in Turkey, Pakistan, Mozambique, and Cameroon.[25,27–29] However some studies have shown no association between vaccination coverage with distance.[30] Most notably, it has been shown to be a factor when studied spatially (rather than by survey via mothers, which is subject to recall bias).[31] This may be due to the role of supplemental immunization activities (SIAs), which are short-term immunization campaigns to improve coverage in a specific population but do not necessarily improve overall immunization infrastructure.

Lack of knowledge / education about the vaccination and/or additional doses is also often cited as a reason for lower coverage rates or attrition. This has included studies in Pakistan, Ethiopia, Cameroon, where vaccine-specific education was positively associated with coverage.[23,25,29,32] In Turkey, India, and Mozambique, overall parental education was positively associated with vaccination status of the child.[24,27,28]

Vaccination programs are especially difficult to implement in areas with high migrant populations.[33] Effective vaccination programs rely on accurate measurements of local population, especially of children (in the case of childhood vaccinations like diphtheria-tetanus-pertussis (DTP) and measles), and areas with variable populations may underestimate the number of susceptible individuals.[33] A high migrant population also increases the risk of bringing a new disease into the population, putting the non-migrant population at greater risk with all things considered equal.[34]

1.3.1.1 Supplemental Immunization Programs

Supplemental Immunization Programs (SIAs) have also long been a well-utilized intervention to target unintentional under-vaccination, and they can and do increase vaccination coverage. Unfortunately, SIAs are temporary and do not always reach all areas of need; while they are highly effective in the short-term, it is difficult to maintain targeted elimination with SIAs alone in the absence of an effective childhood vaccination program.[35] In a study in Burkina Faso, the two biggest reasons for lack of vaccination during an SIA were lack of knowledge about the campaign (40%) and absence of either the child or the caregiver (18%).[36] They are especially difficult to implement in areas of high conflict, recent crisis (such as post-Ebola), or with high migrant populations.[33,37,38] As such, measles outbreaks continue to occur, especially in countries with high poverty, weak healthcare infrastructure, or conflict.[20]

1.3.2 Vaccine Hesitancy

In the US, essential childhood vaccines are provided free of charge through the Vaccines for Children program.[9] Though the US may still experience some healthcare challenges, it does not experience the infrastructure challenges of Africa. Vaccination coverage below the CVF has been attributed at least partially to intentional under-vaccination, and this low coverage increases outbreak risk. Though some under-vaccination may be attributable to access, increasingly in the US some is intentional, and creates risk of outbreak. This intentional under-vaccination has its roots in the anti-vaccine movement.

The US has targeted access-driven under-vaccination with programs like the Vaccines for Children program and wider healthcare programs like the Affordable Care Act (ACA) and the Children's Health Insurance Program, but during this same time, anti-vaccination efforts have become increasingly organized, limiting progression on vaccination coverage rates in some areas of the country.[39] A review of all recent outbreak data found the majority of measles cases in recent outbreaks were the result of intentional under-vaccination, rather than access-driven or age-restricted (or vaccine failure).[17] Indications show that there is a geographic trend with intentional under-vaccination, and if these communities continue to cluster, risks will continue to increase.[3]

1.3.2.1 History of Vaccination Law

Opposition to vaccines goes back as far as vaccines, to Edward Jenner and the original cowpox vaccine. With the introduction of the cowpox, and then smallpox, vaccines, multiple organizations sprung up in the late 19th century opposing vaccination, including the Anti Vaccination Society of America (1879), New England Anti Compulsory Vaccination League (1882), and the Anti-Vaccination League of New York City (1885).[40]

The case law establishing precedent for compulsory vaccination comes from this time, as well. In 1902, Cambridge, MA passed a law requiring compulsory smallpox vaccination. One resident (Henning Jacobson) refused, claiming it would cause “great and extreme suffering,” and that the vaccine was “an invasion of his liberty”.[40] The battle continued up to the Supreme Court. In the decision *Jacobson v. Massachusetts*, the Court ruled that that "the state may be justified in restricting individual liberty... under the pressure of great dangers" to the safety of the general public.[41]

The decision galvanized the anti-vaccine movement, but was reaffirmed in in *Zucht v King* (1922) which found that a school could refuse admission to unvaccinated students.[42] The case law has thus established that compulsory school requirements are legal in the United States.

1.4 Heterogeneity of Vaccination Coverage

The critical vaccination threshold (CVF) is the number used to guide vaccination programs to determine how many children must be vaccination to stop the spread of disease, and thus, what areas are highest risk and where resources should be allocated. For measles, the CVF is high; 95% of individuals in a community must be vaccinated or otherwise immune.[2] The CVF is based on the

R0, or the number of persons an individual can infect. The R0 of a disease assumes random mixing; i.e., that for a given population, the infected individual has an equal likelihood of encountering any other individual. This, however, is not true. The First Law of Geography tells us that clustering is everywhere: individuals interact within their community with individuals like themselves. Likewise, unvaccinated individuals cluster, making it more likely that an infected individual (who is more likely to be unvaccinated) would meet an unvaccinated individual.

Spatial heterogeneity is a relatively unexplored field with real-world data, but studies that examined coverage have shown that under-vaccinated communities cluster.[3,43] This means that R0 and the CVF, which depend on random mixing, cannot be random at that level of resolution; even something as simple as living on the coast can lead to a breakdown of the random mixing assumption.[44] Studies of outbreak risk have showed the effect of spatial heterogeneity on rubella and influenza, as well as vector-borne diseases such as malaria, which in each instance it has increased the R0.[45–47] Spatial heterogeneity has been well-studied with modeling; these studies focusing on measles, as well as other infectious diseases including influenza, have found similar results to those with real-world data.[48–50]

1.4.1 In the US: Intentional Under-vaccination

The greatest differences in measles vaccination coverage are seen within, rather than between, states, and in small often demographically homogenous communities that intentionally under-vaccinate. In the US, reasons for intentional under-vaccination vary from concern about the safety (including fears over autism), religious / philosophical beliefs, and desire for more information.[51] Because of limited data, only a few of these communities have been studied. They have either been discovered as a result of outbreaks or have been studied in California, where high-resolution (school-level) vaccination data is made publicly available.[52] Several studies on the California data have located under-vaccinating communities in San Diego and among certain types of schools, with the San Diego community responsible for a large outbreak in 2008.[3,14,48,50] Our preliminary analysis has also located communities in Northern California, which appears to have much lower coverage than surrounding areas in the state. Several of the existing studies used modeling rather than real-world data to simulate outbreaks in different conditions of spatial heterogeneity. In Ohio, an Amish community that did not vaccinate for measles came to light during a 2014 outbreak.[53] Like two of the California studies, this outbreak was also examined with modeling (due to limited data, case-control only). Though not in the US, some additional analysis can be gained on the basis of European studies, particularly in the Netherlands, which has struggled with geographically clustered intentionally under-vaccinating communities that refused the MMR based on their Protestant religious beliefs.[54] However, these are all either responsive studies or studies of convenience (due to data availability). In Ohio and the Netherlands, the studies occurred in response to an outbreak in order to elucidate its cause. The California studies, which included both case-control studies examining outbreaks and retrospective studies, are of limited geographic scope. Additional studies are needed to expand the scope beyond California and outbreak-specific case-control studies.

Though these intentionally under-vaccinating communities may differ from their region or state, they usually share similar religious, school, or income characteristics. Often, these clusters are private school communities. A 2009-2010 study found exemption rates in all private schools were 4.25% compared to 1.91% in public schools; personal belief exemptions (PBE) were even higher, at 6.1% (compared to 2.79%).[55] From 1994 to 2009, PBEs were 1.77 times greater (95% CI 1.55-2.01) in private schools.[56] Over the study period, the annual increase rose faster as well, 10.1% as compared to 8.8% for public schools. The differences are even starker for certain types of private schools.[55] Among alternative schools, PBEs were 8.7% compared to 2.1% for public.[57] Waldorf schools had the highest PBE rate, at 45.1% (IRR 19.1 when compared to public schools).[57] Montessori schools had the highest annual increase in PBEs (8.8%).[57] Though the studies on exemptions in public and private schools are thorough, they are somewhat limited by data availability (as are all studies currently), and are slightly out of date, as exemption laws changed in two states in 2018 and continue to change in response to the ongoing measles outbreak.[1,58,59]

While the clustering effect of private schools has been well-studied, less well studied are other covariates, such as wealth, rural/urban location, religion, and race. Schools charging tuition over $10,000 annually are twice as likely to have PBEs over 20% and had higher rates of conditional admissions (students not up-to-date on vaccines at the start of school).[60] However, parental wealth itself has not been directly studied. One study has examined rurality, finding that rural areas had 1.66 times greater PBEs (95% CI 1.26-2.08) than urban areas, but this was in California and this longitudinal study ended in 2009.[56] Because urbanism can be a significantly predictor of disease spread (due to contact patterns), this is important covariate to study. Religion has been studied at the school but not individual level. In one study, PBEs greater than 20% were seen among secular and Christian kindergartners but not Jewish, Catholic or Islamic schools; however this was a small study, and it is not clear how well the school religion correlated with pupil religion.[60]

1.4.1.1 Major Recent Measles Outbreaks

Many of the recent US measles outbreaks have originated in these communities. Though no study has set out to specifically predict high risk areas, many of the recent US measles outbreaks have originated in areas similar to those described in the literature. These areas exist often in states with overall high vaccination coverage but may have low coverage themselves: a hot spot. In modeling studies, outbreak risk is predicting using the total number of nonvaccinated individuals and heterogeneity (including these hot spots).[48] The Disneyland outbreak (2014-2015), the outbreak in an Ohio Amish community (2014), and the outbreak in a Texas Christian church (2013) exhibit this idea.[1,53,61] In all three cases, the state had coverage >90%, but the community, due to intentional under-vaccination, exhibited coverage far below. Another classic example is the outbreaks seen in the late 1980s and early 1990s, including the large (and deadly) outbreak in a nonvaccinating Philadelphia religious community. During this time, though coverage was increasing nationally, it lagged in urban areas, and combined with a non-vaccinating (and urban-residing) community, created one of the largest outbreaks since mass MMR vaccination.[62–64]

1.5 Concluding Remarks

None of these approaches has yet seen their project to completion, or been without flaw, but each has demonstrated the need for high resolution data and the viability of collecting said data. High resolution data exists for both the US (school records) and Africa (DHS and WHO data). It is a matter of transforming that data into something useful for research.

Our overarching aim is to make use of current existing high-resolution measles vaccination data in the United States and Africa. Internationally, this includes DHS surveys. In the US, we have worked to free up existing, underutilized data from schools and health departments, data currently inaccessible to researchers. We have used each data source to locate intentionally under-vaccinating communities, specifically focusing on measles-containing vaccine, using spatial epidemiological methods to locate and analyze clusters of where vaccination coverage is far below the CVF and address some of the covariates associated with these clusters.

2.0 Spatial Clustering of Measles Vaccination Coverage Among Children in Eastern Africa

2.1 Abstract

Note: This paper has been previously published in BMC Public Heath, which is an open-access journal.[65] It is preprinted here with minor additions.

During the past two decades, vaccination programs have greatly reduced global morbidity and mortality due to measles, but recently this progress has stalled. Even in countries that report high coverage rates, transmission has continued, particularly in spatially clustered subpopulations with low vaccination coverage. We examined the spatial heterogeneity of measles vaccination coverage among children aged 12-23 months in ten East African countries. We used the Anselin Local Moran's I to estimate clustering of vaccination coverage based on data from Demographic and Health Surveys conducted between 2008 and 2013. We also examined the role of sociodemographic factors to explain clustering of low vaccination. We detected 477 spatial clusters with low vaccination coverage, many of which were located in countries with relatively high nationwide vaccination coverage rates such as Zambia and Malawi. We also found clusters in border areas with transient populations. Clustering of low vaccination coverage was related to low health education and limited access to healthcare. Systematically monitoring clustered populations with low vaccination coverage can inform targeted catch-up campaigns towards attaining herd immunity. In addition to average statistics, metrics of spatial heterogeneity should be used to determine the success of immunization programs and the risk of disease persistence.

2.2 Introduction

Measles is a highly contagious viral disease and is one of the leading causes of death among children in low-income countries, accounting for 114,900 deaths globally in 2014 of which 73,914 (63%) occurred in Africa.[19,66] Measles also continues to cause epidemics in high-income countries, despite the availability of a safe and highly efficacious vaccine.[7,67]

The Measles-Rubella Initiative, spearheaded by the American Red Cross, the US Centers for Disease Control, the World Health Organization (WHO), and others, has targeted the measles virus for global elimination. This initiative aims to reduce annual measles incidence rates (IRs) to less than five cases per million, requiring >90% coverage of the first dose of measles containing vaccine (MCV) by the end of 2015 and >95% coverage by 2020 in all countries.[68] Improvement in vaccination coverage has decreased measles deaths from over half a million globally in 2000 to 114,900 in 2014.[66] Since 2010, however, progress has stalled.[66] The 2015 vaccination goal was not met and IRs remained relatively unchanged between 2013 and 2014.[66]

Measles elimination is complicated by the high transmission rate of the measles virus. This transmission rate can be expressed as the basic reproductive rate (R_0), defined as the number of infections caused, on average, by one infectious person in a fully susceptible population.[4] The R_0 for measles ranges from 15 to 20 infections, which is one of the highest among all infectious diseases (e.g., influenza has an R_0 around 1.5-2.0).[8] This high R_0 leads to the very high critical vaccination fraction (CVF) for measles of 95%, i.e., the vaccination coverage needed for herd immunity.[69] This CVF assumes that vaccination coverage and population mixing are distributed homogeneously throughout a country.[70] This assumption of homogeneity is not always realistic, as recently found in Mozambique[71] and Malawi.[72] Spatial heterogeneity of vaccination coverage can increase the CVF required for herd immunity to a level exceeding the 95% coverage goal set by the Measles-Rubella Initiative.[49,73]

Continued measles outbreaks, even in countries with high average nationwide vaccination coverage rates, have illustrated how spatial heterogeneity of vaccination coverage can delay disease elimination.[61,74] Timely detection and specific targeting of low-coverage population clusters by SIA can lead to protective herd immunity and accelerate disease elimination, as demonstrated in the Americas.[75] We used publicly available microdata from the Demographic and Health Surveys (DHS) to identify clustered subpopulations with low vaccination coverage among 10 countries in Eastern Africa.

2.3 Methods

2.3.1 Clustering Algorithm

We collected measles vaccination coverage data from the most recent DHS conducted in ten countries: Burundi in 2010; the Democratic Republic of the Congo (DRC) in 2013; Kenya in 2008; Madagascar in 2008; Malawi in 2010; Mozambique in 2011; Rwanda in 2010; Tanzania in 2010; Zambia in 2013-14; and Zimbabwe in 2010-11.[76] These countries were selected based on their contiguity and data availability.

DHS surveys are nationwide surveys that are representative of the population.[5] They are performed using a two-stage cluster sampling design: In the first stage, the DHS selects a random sample of clusters (groups of possible sample households in close proximity to each other) from an already existing sample frame (e.g., a population census); in the second stage, a random sample of households is selected within each cluster. While each country has the final control over survey management, with the guidance of the DHS organization, we carefully examined each survey methodology and found them to fit DHS standards and comparable to one another. Because DHS sample households are often selected with unequal probabilities to ensure that specific subpopulations are captured, sample weights are published that should be used to correctly compute average statistics.[77] We extracted, from DHS surveys, the vaccination status of children aged 12-23 months measured from sampled households in each cluster, not differentiating between vaccine doses received from routine immunization or immunization campaigns. Information on vaccination status was derived from vaccination cards where possible and otherwise from mothers' reports.[77] We calculated the cluster-level vaccination coverage rate as the median of the weighted household-level vaccination coverage rates.

We estimated the spatial association of MCV coverage rates among DHS clusters using the Global Moran's I and Anselin Local Moran's I statistics. The Global Moran's I ranges from -1 to 1 and is a single estimate of spatial association among all DHS clusters (spatial autocorrelation). Values close to zero indicate the absence of a spatial association, i.e., a random distribution, values close to negative one indicate strong spatial dispersion, and values close to positive one indicate strong clustering (autocorrelation). The Anselin Local Moran's I estimates the association of vaccination coverage rates between a DHS cluster and its neighboring clusters within a specified geographical area (inter-cluster variation). The Anselin Local Moran's I has been used previously for similar analyses, e.g., to locate pockets of childhood stunting in Nigeria.[78] We used the Anselin Local Moran's I to estimate spatial clustering of low (<75%), high (≥75%), or mixed (low near high or vice versa) weighted vaccination coverage. We considered Moran's I statistics with p-values <0.05 to be statistically significant.

2.3.2 Determinants of Low-Vaccination Clusters

We explored possible determinants for clustering of low-vaccination using additional information from country DHS surveys: (1) child in possession of a health card or not (H_c); (2) mother had heard of oral rehydration salts (ORS) or not (O); (3) mother is literate or not (T); (4) mother visited a health facility in the last 12 months or not (H_f); (5) mother mentioned that money had been a barrier to seeking healthcare in the past or not (M). We calculated the cluster-level percent children with a health card as the median of the weighted household-level percentages of children with a health card. From the other household-level variables, we computed the cluster-level equivalents as the percent of mothers (households) that answered each question affirmatively.

We used a logistic regression model to estimate the association between the odds for a DHS cluster being part of a low-vaccination spatial cluster and the aforementioned explanatory factors. We adjusted for spatial autocorrelation (inter-cluster variation) of vaccination status among clusters with a queen contiguity weights matrix based on spatial lags. Queen contiguity calculates spatial autocorrelation of the outcome variable among all contiguous neighbors (i.e., all DHS sites that share a common border with a reference DHS site).[79] This queen contiguity matrix reflects our spatial dependency assumption and is commonly used for spatial lag models of cluster data.[80] Our model took the following form:

$$\ln\left(\frac{L(x)}{1-L(x)}\right) = \rho W \ln\left(\frac{L(x)}{1-L(x)}\right) + \beta_0 + \beta_1 H_c + \beta_2 O + \beta_3 T + \beta_4 H_f + \beta_5 M + \varepsilon$$

where $\left(\frac{L(x)}{1-L(x)}\right)$ represented the odds of being in a low-vaccination spatial cluster, ρ represented the spatial autoregressive coefficient for the log odds of being in a low-vaccination spatial cluster, W represented the queen contiguity matrix, $\beta_{1\text{-}5}$ represented the regression coefficients for aforementioned covariates, and ε represented the error term.

We used SAS version 9.4 and ArcGIS version 10.4 for this analysis.

2.4 Results

2.4.1 Country-Level Vaccination Coverage

We included a total of 5,458 DHS clusters containing 70,092 households across all ten countries (Figure 1, Table 1). This sample is representative of a total population of 214,339,000 people. Nationwide MCV coverage among children aged 12-23 months was below the measles critical vaccination fraction of 95% for nine out of the ten countries and ranged from a low of 69.6% for Madagascar to a high of 95% for Rwanda. The average MCV coverage for all 10 countries, weighted by population size, was 83.6%.

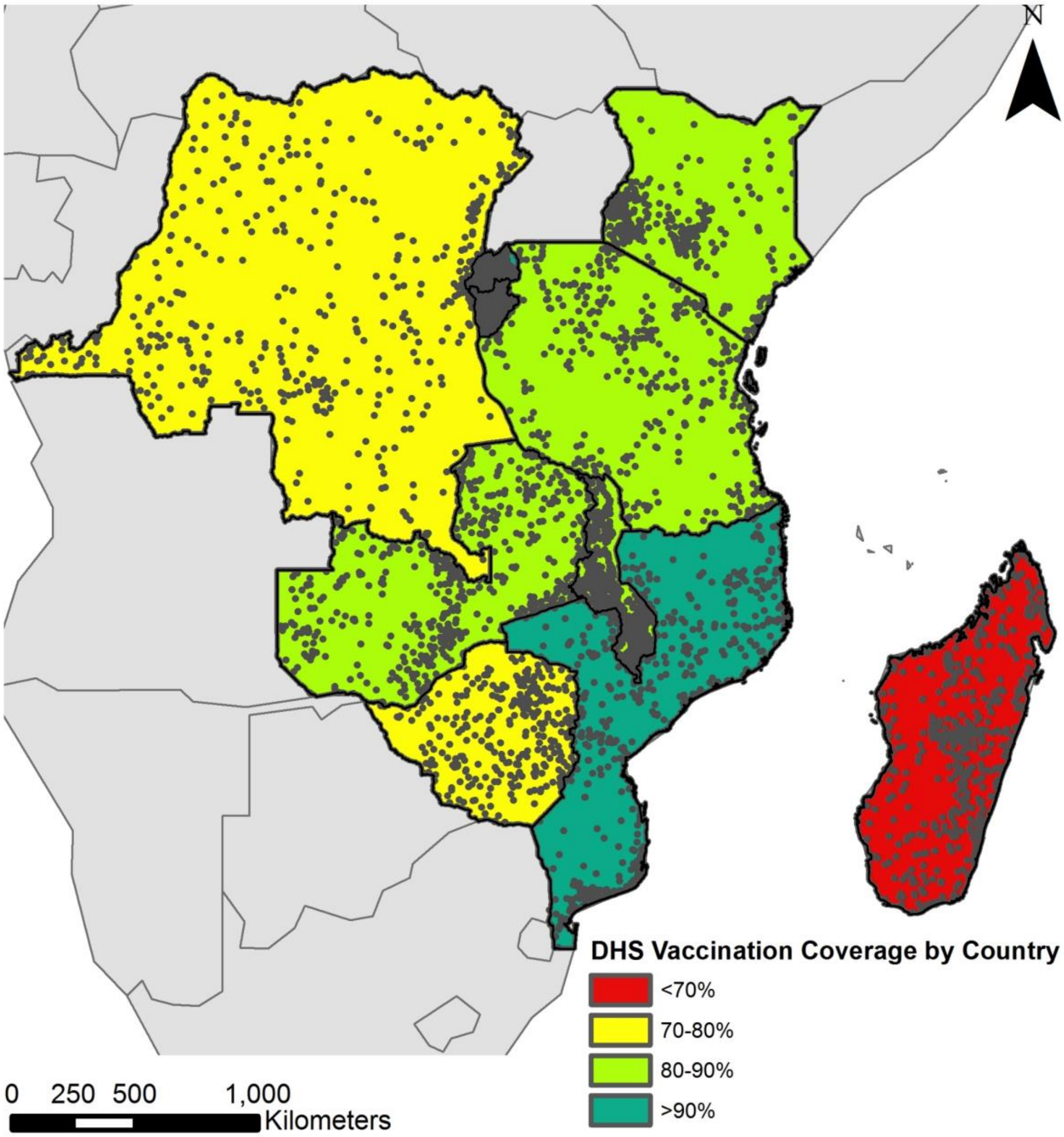

Figure 1: DHS vaccination coverage by country

Figure 1 shows vaccination coverage and DHS clusters in the study area. The location of each DHS cluster is depicted as a grey circle. We computed the average vaccination coverage rate for each country from DHS cluster-level data. Both maps were created by study investigators using open access data sources

Table 1: DHS survey populations by country

Country	Survey year	Clusters	House-holds	Population[a] in sampled households	Population in all households (1000's)	MCV[b] coverage (%)
Burundi	2010	376	4662	7742	9233	94.3
DRC	2013–2014	536	10,023	18,716	67,514	71.6
Kenya	2008–2009	398	3864	6079	3877	85.0
Madagascar	2008–2009	595	8151	12,448	19,927	69.6
Malawi	2010	849	12,889	19,967	15,014	93.0
Mozambique	2011	610	6882	11,102	24,581	81.5
Rwanda	2010	492	6019	9002	10,837	95.0
Tanzania	2010	475	4862	8023	44,973	84.5
Zambia	2013–2014	721	8692	13,457	14,539	84.9
Zimbabwe	2010–2011	406	4048	5564	13,077	79.1
Total		5458	70,092	112,100	214,339	83.6

Legend: [a]children 12–23 months of age, [b]Measles containing vaccine

2.4.2 Clustering of Low Vaccination Coverage Rates

We found strong spatial heterogeneity in measles vaccination coverage across the entire ten-country region (Global Moran's I of 0.388, $p < 0.001$). Based on the Anselin Local Moran's I, we identified statistically significant spatial correlation of low vaccination coverage (<75%)

between 477 DHS clusters, of mixed coverage between 148 clusters, and of high coverage (≥75%) between 645 clusters (Figure 2a). The DRC had the second-lowest nationwide vaccination coverage rate in our study region and had clustering of low coverage throughout the country. We found clustering of high coverage almost uniformly throughout Rwanda and Burundi, two countries with the highest nationwide average vaccination coverage in our sample. In other countries, clustering of low-coverage was concentrated in specific geographic areas: e.g., East Kenya, North Malawi, North Zambia, South Zimbabwe, and South Mozambique. Madagascar had the lowest average nationwide MCV coverage in our sample and had clustering of low-coverage throughout the country except in the capital region. We also found clustering of low coverage across country borders: e.g., across the Kenya-Tanzania and the Malawi-Zambia borders.

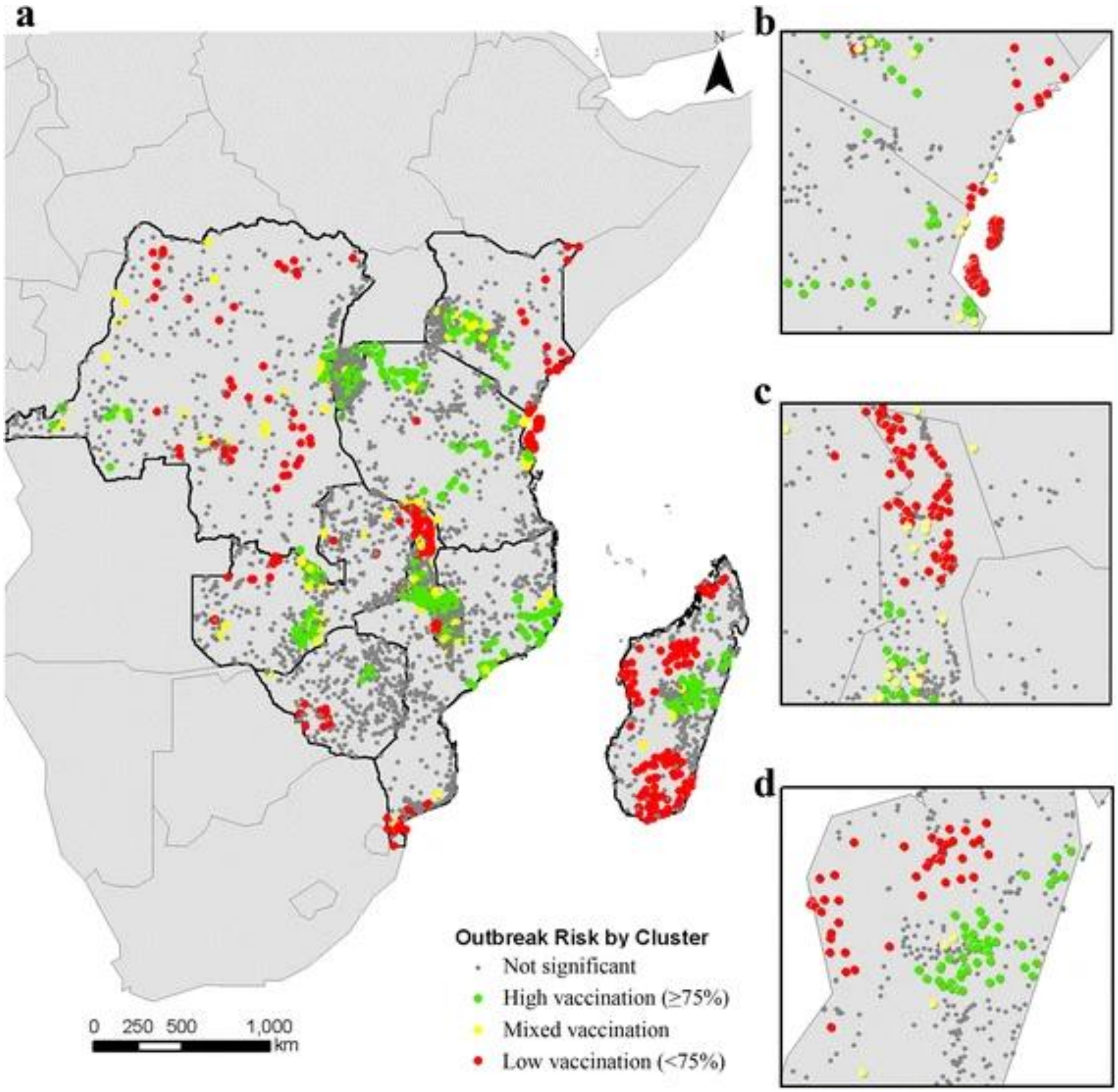

Figure 2: Spatial clustering of vaccination coverage in DHS clusters

Using the Anselin Local Moran's I, we classified each DHS cluster as being part of a spatial cluster with low-vaccination, high-vaccination, or mixed vaccination coverage (low-vaccination near high-vaccination or vice versa). Grey circles indicate that vaccination coverage for a DHS cluster was not statistically significantly clustered. **a)** We detected clustering of low, mixed, and high vaccination coverage in all countries. Vaccination coverage in some spatial clusters contrasted nationwide vaccination coverage rates: e.g., **b)** in the Zanzibar/Pemba islands and the Kenya-Tanzania border population (low vaccination vs. high nationwide); **c)** in Northern Malawi (low vaccination vs. high nationwide); and **d**) in the Madagascar capital region (high vaccination vs. low nationwide)

We found three areas with clustering of vaccination coverage that contrasted nationwide average rates: (1) the Zanzibar/Pemba island population in Kenya-Tanzania had clustering of low coverage while nationwide rates were relatively high (Figure 2b); (2) the Madagascar capital region had clustering of high coverage while the nationwide rates were low (Figure 2c); and (3) the Northern Malawi region had clustering of low vaccine coverage compared to high nationwide coverage (Figure 2d). Each of these areas has distinctive geological features that separated them from the surrounding area: Zanzibar and Pemba are Tanzanian island-populations with semi-autonomous governments; the Madagascar capital region of Antananarivo is located in the mountainous Hauts Plateaux region, separated from the rest of the country; and Northern Malawi includes most of Lake Malawi and areas of higher elevation compared to the South of the country that includes the river Shire.

2.4.3 Determinants of Low-Vaccination

We explored possible determinants for clustering of low vaccination coverage using a spatial regression model (Table 2). Clustering of low vaccination coverage was associated with children not having a health card and mothers not having knowledge of ORS. Clustering of low vaccination was 4.6% less likely for each percentage point increase in children with a health card (95% CI: -0.066, -0.026, $p<0.01$) and 1.7% less likely for each percentage point increase in mothers with knowledge of ORS (95% CI: -0.033, -0.001, $p<0.05$). In addition, clustering of low coverage was inversely related to having financial restrictions to healthcare, i.e., 1.6% less likely per percentage point increase in mothers listing financial barriers to seeking healthcare (95% CI: -0.029, -0.003, $p<0.05$). Maternal literacy rates and a maternal history of visiting a health clinic were not statistically significantly associated with clustering of low vaccination coverage.

Table 2: Spatial regression predictor of outbreak risk

Variable	Coefficient (95% C.I.)
Health card	-0.046 (-0.066, -0.026)**
Money/Barrier	-0.016 (-0.029, -0.003)†
Heard ORS	-0.017 (-0.033, -0.001)†
Literacy	-0.0012 (-0.0163, 0.014)
Health visit	-0.0025 (-0.021, 0.016)

Legend: †indicates significance at p<0.05; *indicates significance at p<0.01

2.5 Discussion

Using publicly available DHS data from 10 countries, we found 477 geographical clusters of low measles vaccination coverage spread across East Africa, many of which contrasted relatively high nationwide average vaccination coverage rates. Similar analyses have been performed on DHS data in single-country analyses.[81–83] These clusters can weaken herd immunity, cause inequity in disease risk, and delay elimination programs. Indeed, recent measles outbreaks have occurred in high-risk subpopulations with low immunization rates, both in low- and high-income settings.[54,71] Zambia had an average MCV coverage of 84.9%, and Malawi of 93%, but both countries experienced a large measles outbreak in 2010-2011.[84] This outbreak spread from high-risk subpopulations in South Africa to Zambia, Malawi, and to high-risk subpopulations in Tanzania consistent with the clusters that we identified.[20,85] The persistence of virus transmission due to highly connected, clustered, unimmunized subpopulations has also been demonstrated by mathematical models based on metapopulation theory.[86–88] These models can be used to compute vaccination coverage goals that take into account spatial clustering of low vaccination.

We found that clustering of low vaccination coverage was more likely in populations with low health education and limited access to healthcare. Previous studies have found similar risk factors for low immunization rates.[29,72,89] We also found that financial barriers to healthcare were associated with better vaccination rates, which seems counterintuitive. One possibility for this observed relationship may be that vaccination is often free of charge and may not be affected by financial barriers. In Malawi, for example, high vaccine uptake was observed despite significant cost and travel time, possibly related to high levels of trust in the effectiveness of the vaccine to prevent serious disease.[90]

While we would have liked to perform this analysis for the entirety of the African continent, our method was limited by the availability of recent DHS survey data and the contiguity of the available data. Because this is a geographic analysis examining clusters which might span borders and cross-border risk, we only performed the analysis on countries which shared borders. Though Madagascar does not share a land border with the surrounding country of Mozambique, trade and travel happen across the Mozambique channel similar to other borders in our analyses. Our analysis also spans several years. Though a single-year analysis would be ideal, data is not available for such a study, as DHS surveys are conducted on a rolling basis, with each study repeated every 5 years. Thus, we examined WHO MCV data during our study period for signs of instability as an exclusion criterion. Though it is possible there are within-country fluctuations during the 2008-2013 period, all countries included had fairly stable vaccination data during this period, increasing our confidence our ability to take data from this period. Finally, we used geographic (GPS) data from the DHS surveys. Each cluster is slightly displaced to product the anonymity of study participants. This is a common practice in geographic surveys with human subjects. The DHS, urban clusters may be displaced between 0 to 2 km; rural cluster may be displaced 0 to 5km, with 1 percent of these clusters displaced up to 10km.[5] This amount of error is small, and highly unlikely to be significant for the largely area we have analyzed.

Subpopulations with low vaccination coverage across country borders are a particular concern because these transient populations are often not covered by national immunization programs.[71,75] We found such subpopulations at the Kenya-Tanzania border and the Malawi-Zambia border. The Kenya-Tanzania border area includes the famous Serengeti and Kilimanjaro national parks and is inhabited by the nomadic Maasai people.[91] The Malawi-Zambia border is crossed frequently by the Chewa people that reside in both countries.[92] Trans-border populations with low vaccination coverage can be especially vulnerable to disease importations from one country into another. Such importations occurred during the 2010-2011 measles outbreak that spread from Malawi into Zambia.[84] Coordination of immunization activities between countries will be essential to increase coverage and eliminate measles in these cross-border populations.[75]

Most countries in our sample had vaccination coverage rates well below the measles CVF and have already been identified by the Measles-Rubella Initiative as high priority areas for continued activities to increase immunization rates.[22] We found strong spatial heterogeneity of vaccination coverage in some of these countries, indicating that the vaccination coverage target of 95% set by the Measles-Rubella Initiative may not lead to herd immunity, but that targeted SIA will be necessary to reach particularly vulnerable populations. It is important to note that while the Measles-Rubella Initiative sets national goals, as mentioned in this paper, they do also track sub-national targets, as well, as we advocate here. This is done at the district level, which is a lower resolution than the small communities sampled in the data used in our analyses. The methodology performed in this paper can help supplement their current efforts.

Clustering of low vaccination coverage demonstrates that unimmunized people tend to live near other unimmunized people, leading to an inequitable distribution of disease risk. A recent study in 35 countries found that improvements in average measles vaccination coverage also reduced inequity.[93] Despite these improvements, we found that many clusters of low vaccination coverage still exist, mostly in populations with limited health education and access.

2.6 Conclusions

Systematically identifying and monitoring the low vaccination sub-populations identified in this paper can inform SIA towards attaining herd immunity among vulnerable populations in East Africa. In addition to average coverage statistics, metrics of spatial heterogeneity of vaccination coverage should be used to determine the success of immunization programs and the risk of disease persistence. Targeted SIA and sub-national risk assessments are currently performed, and the methods shown in this analysis can supplement existing strategies and increase their rate of success.

3.0 Heterogeneity in Vaccine Legislation Among States and the Effects of Recent Law Changes on Exemption Rates

3.1 Abstract

To examine the heterogeneity in exemption laws in the United States over a longitudinal period, we reviewed vaccine-related legislation for each state for the 2010-2018 period and characterized the difficulty for parents to use medical, religious, and philosophical exemptions. We also compared state legislation to vaccine exemption rates and to coverage rates of the measles-mumps-rubella (MMR) vaccine provided by CDC VaxView survey data of kindergarteners.

We found great diversity among state vaccination exemption laws. In 2018, all states allowed medical exemptions, 47 states permitted religious exemptions, and 18 states philosophical exemptions. Non-medical exemptions are the most difficult to receive in Vermont, where only religious exemptions are recognized, and parents must complete an education module overseen by an arbitrator. Exemptions are the easiest to obtain in Arizona, Minnesota, and Pennsylvania, where both types of non-medical exemptions are recognized with only a written statement required from parents. We found that generally, exemption rates are lower in states where they are difficult to obtain. While eliminating exemptions leads to the greatest decrease in usage, other methods of increasing difficulty also decrease usage and may positively affect coverage.

State policy makers should be aware of the impact of legislation, beyond allowing or disallowing exemptions, on vaccine exemptions and coverage, and thereby on the risk of infectious disease outbreaks. When lacking the political capital to eliminate exemptions, state lawmakers should consider other methods of increasing exemption difficulty in order to decrease usage.

3.2 Introduction

Measles vaccination has prevented millions of measles cases and saved billions of dollars.[94,95] Measles was declared eliminated from the US in 2000 following recommendation of a second dose of measles-mumps-rubella (MMR) vaccine in 1989.[11] The success of the measles vaccination program is partially attributed to compulsory vaccination with one dose of MMR before school entry (recommended at 12-18 months) and a second dose recommended at 4-6 years.[13] Vaccination requirements are determined by state law, but all states allow certain exemptions to these requirements. Exemptions are given for medical conditions, philosophic, or religious objections.

The percent of children whose parents exercise philosophical exemptions has increased during the last decade in states that allow these exemptions (from 2.5% in 2004 to 3.7% in 2015).[14] This increase is related to parental concerns about vaccine safety, efficacy, and timing of vaccine doses.[96–98] Increased exemptions have led to a reduction in vaccine uptake and an increased risk of measles outbreaks.[14,17,99,100] Eighteen measles outbreaks have occurred in the US since elimination was declared; 57% of children in these outbreaks were not vaccinated, and 71% of these were based on non-medical exemptions.[17] In 2018-2019, the US has experienced an ongoing measles outbreak in Washington and Oregon, with potential to spread nationwide due to non-vaccinating communities; additional outbreaks exist in New York and New Jersey.[1] Continued outbreaks in the US could reverse measles elimination in the Americas, after almost two decades of elimination.

While disallowing non-medical exemptions is clearly associated with lower exemptions rates, there are more subtle differences in vaccine exemption laws between states. This legislation also determines the steps required from parents for obtaining each type of exemption; these steps can range from simply writing a statement to taking an online course to signing an affidavit in court. States vary as to how exemptions can be obtained and who is authorized to approve or reject a request. Requirements for exemption can also vary among the type of exemptions within the same state.

In response to the continued measles outbreaks and the risk of declining vaccination coverage levels, some states are currently considering changes to exemption laws and rejecting proposals to weaken exemptions. New York and Maine have both banned all nonmedical exemptions.[101,102] They join California, Mississippi, and West Virginia as the only states to not allow religious and/or philosophical exemptions. The New York law went into place at the start of the 2019 school year; after the 15 school-day “catch up” period, unvaccinated children without a valid medical exemption were banned from school on September 23.[101]

Other states have proposed similar bills, but these have failed or stalled. In February, Iowa did not pass a bill out of sub-committee that would create a philosophical exemption.[103] The New Jersey legislature is debating a bill to tighten restrictions on religious exemptions (it stalled in general committee), a Maine lawmaker is planning to introduce a bill to eliminate nonmedical exemptions in the next legislative session, and, in response to their outbreak, Washington lawmakers have introduced a bill to ban nonmedical exemptions, which has, as of February 2019, passed out of the House committee.[104–106] FDA Commissioner Scott Gottlieb said in February 2019 that “too many states have lax laws,” suggesting that in the absence of state-level change, the federal government may become involved.[107]

3.3 Methods

3.3.1 State Vaccine Legislation

We reviewed current state vaccination law using the LexisNexis database for the 2010-2018 period. If any law had changed since 2010, we also extracted information about the previous law. For each type of exemption (medical, religious, and philosophical), two reviewers extracted information about: (1) the level of evidence required to request an exemption; and (2) the arbitrator of the exemption request. Based on the extracted information, we characterized whether the exemption was available (yes/no), the level of evidence required for an exemption (classified in five categories), and arbitration requirements (yes/no) for each state.

3.3.2 Vaccination Exemption and Coverage Rates

We obtained downloaded report data for vaccination exemption and coverage rate for MMR, DTP, and varicella (1 and 2) from the US Centers for Disease Control and Prevention Database of State vaccination coverage surveys (VaxView) for the 2011-2018 period.[10] We also compiled vaccination coverage data from additional publications in the Morbidity and Mortality Weekly Report (MMWR) to calculate religious and philosophical exemptions and used MMWR rates for states without data in VaxView.[9,12,108] Vaccination exemption and coverage rates provided by VaxView and MMWR are collected by annual surveys administered by schools, aggregated at the state level by state health departments.

Additional sources report on vaccination coverage in the US, such as the Behavioral Risk Factor Surveillance Survey and the National Immunization Survey (Table 3). We used information from school surveys reported by VaxView and MMWR since these include school-age children.

Table 3: Vaccination data availability

Survey	Year	Source	Age range	Vaccines
National Immunization Survey	1996-2017	CDC	19-35 mos.	DTaP, polio, MMR, HiB, HepB, Varicella, PCV, Hep A, Rotavirus, Combined 3-, 4-, 5-, 6-, and 7-vaccine series
VaxView (school)	2009-2010, 2011-2018	CDC	Kindergarten	MMR, DT/DTaP/ DTP, 1- or 2-dose varicella, HepB, Polio
State surveys	Varies (1972 (MA)-2018)	State Health Departments	Varies (usually Kindergarten or 1st + 7th)	Varies (by year and state)
NIS-teen	2008-2017	CDC	13-15 years	HPV, TD or TDaP, MenACWY, MMR, Varicella, HepB

3.4 Analysis

We determined exemption change in states with relevant law changes by calculating rate of change of exemption rate in the year after the law went into effect as compared to the year before the law was passed. All analysis was performed, and figures created in R version 3.5.1.

3.5 Results

Information about state vaccination exemption laws was available for all 50 states. Several states have changed their exemption laws – most becoming stricter – over our 2010-2018 study period (Table 4).

A major change occurred in 2016, when California discontinued both philosophical and religious exemptions and Vermont removed philosophical exemptions. We also noted several other changes in state vaccine exemption laws during our study period, as outlined in Table 4.

Table 4: Selected exemption law changes

State	Year Passed	Year Enacted	Law	Changes
California	2015	2016	Cal Health & Saf Code § 120370[109]	Eliminates philosophical and religious exemptions
Colorado	2016	2016	C.R.S. 25-4-903[110]	Allows physician assistants to give medical exemptions (new addition)
Hawaii	2014	2014	HRS § 325-34[111]	Allows advanced practice registered nurse to give medical exemptions (new addition)
Michigan	2014	2015		Requires education for philosophical and religious exemptions (new addition); requires use of standard form for exemptions
Nevada	2017	2018	Nev. Rev. Stat. Ann. § 432A.250[58]	Allows advanced practice registered nurse to give medical exemptions (new addition)
Oregon	2013	2013	ORS § 433.267[112]	Requires education for philosophical and religious exemptions (new addition)
Utah	2017	2018	H.B. 308[59]	Requires education module to receive exemption form (new addition)
Vermont	2016	2016	18 V.S.A. § 1122[113]	Eliminates philosophical exemptions
Washington	2011	2011	Rev. Code Wash. (ARCW) § 28A.210.090[114]	Requires education from healthcare provider if requesting exemption (new addition)

We noted several trends occurring with law changes during this period. First was the expansion of medical exemption privileges to advanced practice registered nurses (Hawaii and Nevada, and similarly, physician assistants in Colorado). Another was the requirement for increasing education (often, replacing a written form only) to philosophical and/or religious exemptions (Oregon, Michigan, and Washington). A third was the complete elimination of exemption types (California and Vermont). We did a thorough inventory of current laws. In the 2017-2018 school year, all states allowed medical exemptions, 47 states (94%) allowed religious exemptions, and 18 (36%) allowed philosophical exemptions (Figure 3). All states that allowed philosophical exemptions also allowed religious exemptions.

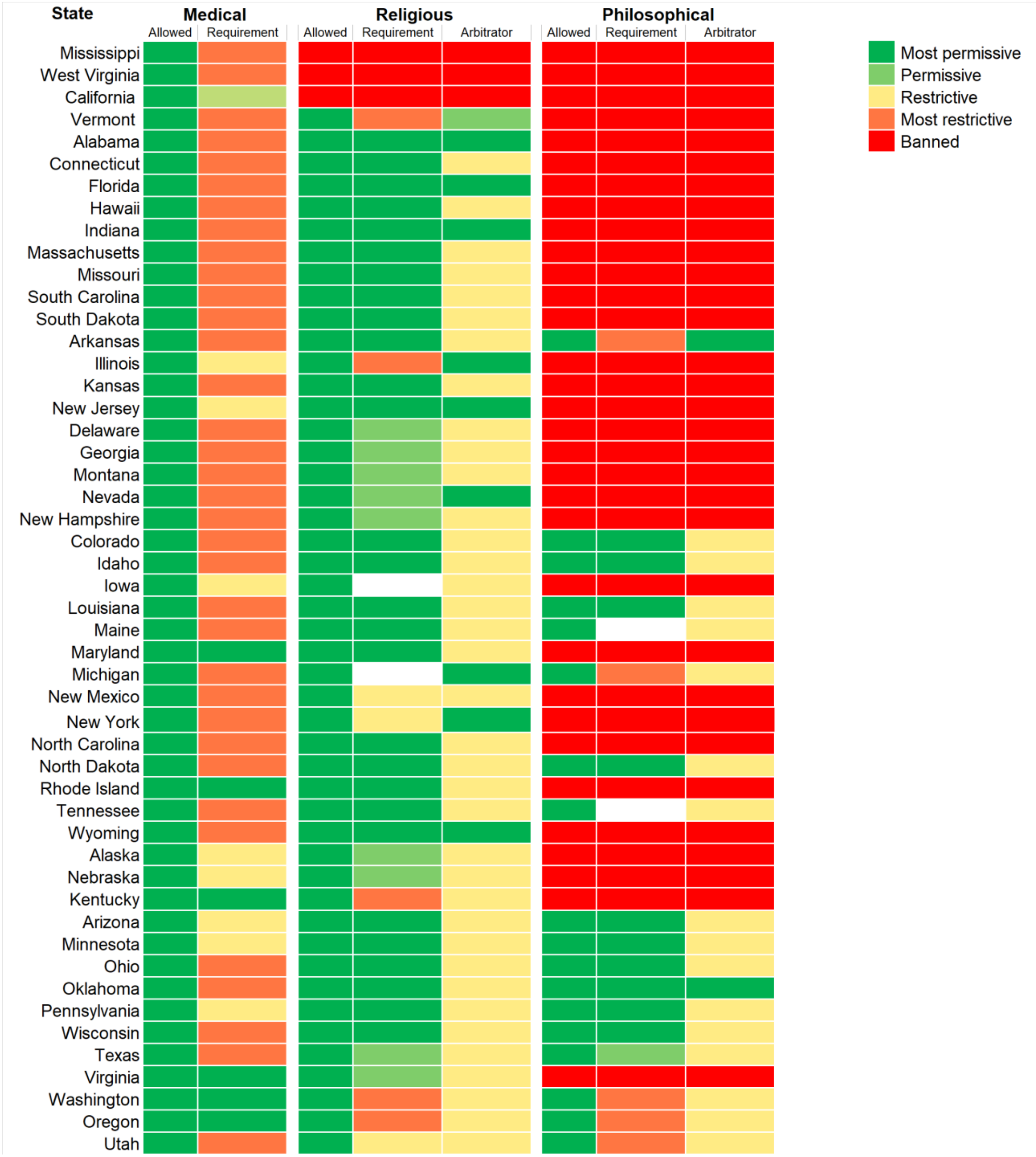

Figure 3: Coding of state exemption laws, 2017-2018 school year

We have coded exemption laws by difficulty of obtaining / permissiveness. Missing data (where we could not find data on how to obtain the specific exemption) are represented in white.

We found great diversity among state vaccination exemption laws. In 2018, all states allowed medical exemptions, 47 states religious, and 18 states philosophical exemptions. Nonmedical exemptions are the most difficult to get in Vermont where only religious exemptions are recognized, and parents must complete an education module which is overseen by an arbitrator. Exemptions are the easiest to obtain in Arizona, Minnesota, and Pennsylvania, where both types of non-medical exemptions are recognized, with only a written statement required from parents. Unexpectedly, all three states have more stringent requirements for medical exemptions (requiring approval of a physical, advanced practice registered nurse, or physician assistant) than do states that prohibit philosophical exemptions such as Maryland, Rhode Island, Virginia, and Kentucky.

Some states were restrictive for one exemption while permissive for others. Pennsylvania, for example, had moderately restrictive medical exemption requirements (requiring approval from a nurse practitioner or physician's assistant), but a religious and philosophical exemption could be easily obtained (written statement). Conversely, medical exemptions were easily obtained in Maryland and Washington (i.e., chiropractors and naturopaths were permitted to grant these exemptions), while philosophical exemptions were not available in Maryland, and Washington required parents to participate in an education module before approving either a religious or philosophical exemption.

State laws (2017-18) on medical exemptions varied concerning the type of practitioner that can give this exemption, ranging from physicians-only (36 states, 72%) to a broad range of practitioners including naturopaths and chiropractors (six states, 12%). For religious exemptions, 28 states (56%) required only a written statement from parents; seven (14%) required completion of an education module; and three (6%) required supporting documents from a religious institution. For philosophical exemptions, 11 states (22%) only required a written statement, and five (Oregon, Washington, Arkansas, Utah, Michigan;10%) required completion of an education module.

3.5.1 Exemptions, Coverage, and Laws Exhibit Heterogeneity Nationally

Coverage at the state resolution was high overall, though many states continue to fall below the Healthy People 2020 goal and CVF of 95%. Coverage during our study period ranged from a low of 81.7% (Colorado, 2013-2014) to Mississippi (99.9%, 2012-2013). For the 2017-2018 school year, coverage ranged from 88.7% (Colorado) to 99.4% (Mississippi). While there was movement in the coverage ranking of states during the study period, states with low relative coverage in 2011-2012 generally had low relative coverage in 2017-2018, and vise-versa. The exception to this was states with law changes. California, for example, increased from 92.3% to 97.3% coverage during our study period.

In states where philosophical exemptions were legal and easy to obtain, this was the most common exemption type, followed by religious, then medical. Medical exemptions were the preferred exemption type only in states where the other exemptions were not available. States with the majority of exemptions for philosophical reasons also had the highest proportions of the population exempt, followed by states where the majority of exemptions were for religious reasons.

We also saw a shift in exemptions in states with major law changes (

Table 5, Figure 4). During our study period, exemption rates decreased in states that increased the difficulty of obtaining an exemption. Between the 2014-2015 and 2016-2017 school years, philosophical exemptions in Vermont decreased from 5.8% to 0. In California, philosophical exemptions decreased from 2.0% and religious exemptions decreased from 0.52% to 0. However, though the overall exemption has still decreased (6.1% to 3.9% in Vermont and 2.7% to 1.1% in California), the usage of other exemptions has increased. Religious exemptions in Vermont have increased from 0.13% to 3.7% and medical exemptions in California have increased from 0.2% to 0.5%. We also found that California's exemptions began falling before implementation of the vaccination law; they reached their peak of 3.14% in the 2013-14 school year.

Coverage and exemptions varied during the 2017-2018 school year. Several states had medical exemption rates of 0.1%, while Alaska had medical exemptions of 0.8% and Nebraska, California (which prohibits non-medical exemptions), and Washington had rates of 0.7%. In states that allowed them, religious exemptions ranged from 0.04% (Utah and Maine, which also allow philosophical exemptions) to 5.6% (Alaska, which prohibits them). In states that allowed them, philosophical exemptions ranged from 0.9% to over 5% with highs in Utah (5.1%), Wisconsin (4.7%), Maine (4.6%) and lows in 0.9% (Louisiana) and 1.0% (Arkansas).

States that increased the difficulty of their exemptions by requiring education saw their exemptions fall compared to the national average, which nearly doubled during our study period (

Table 5, Figure 4). Hawaii, which allowed advanced practice registered nurses or physician assistants to give medical exemptions, saw exemptions fall; insufficient data is available to calculate the effects of Colorado's law change (no exemption data is available for 2016-2018). Nevada and Utah law changes went into effect for the 2018-2019 school year; data is not yet available to calculate the effects of these laws.

Table 5: Changes in exemption rate in selected states

Policy	State	Comparison Years		Pre-change rate (%)	Post-change rate (%)	State change (%)	National change (%)
		Pre-change	Post-change				
Removal of exemption types*	Vermont	2014-15	2016-17	6.1	3.9	-36.07	+17.65
	California	2014-15	2016-17	2.7	1.1	-59.26	+17.65
Allowing advanced practice RN/PA to administer medical exemptions	Hawaii	2014-15	2016-17	3.3	2.8	-15.15	+17.65
Increasing education requirements for non-medical exemptions	Michigan	2012-13	2016-17	5.9	3.7	-37.29	+11.11
	Oregon	2011-12	2016-17	5.9	6.2	+5.08	+42.85
	Washington	2009-10	2016-17	6.2	1.2	-80.62	+81.81

Rates are taken from before and after law change, with the closest available data years available for pre-law change and 2016-17 for post-law change in order to maximize follow-up years included in the dataset. We examined the same period to calculate the national rate change, then used these two numbers to calculate the percent relative effect of state law change. (*) Vermont removed philosophical exemptions, whereas California removed all non-medical exemptions.

In some states, exemptions continued to rise following changes to laws (Oregon) or remained high (Washington), but at a rate lower than would be expected based on the national average (Figure 4). This data and the national trends can also be seen, by law change type, in Appendix Figure 15.

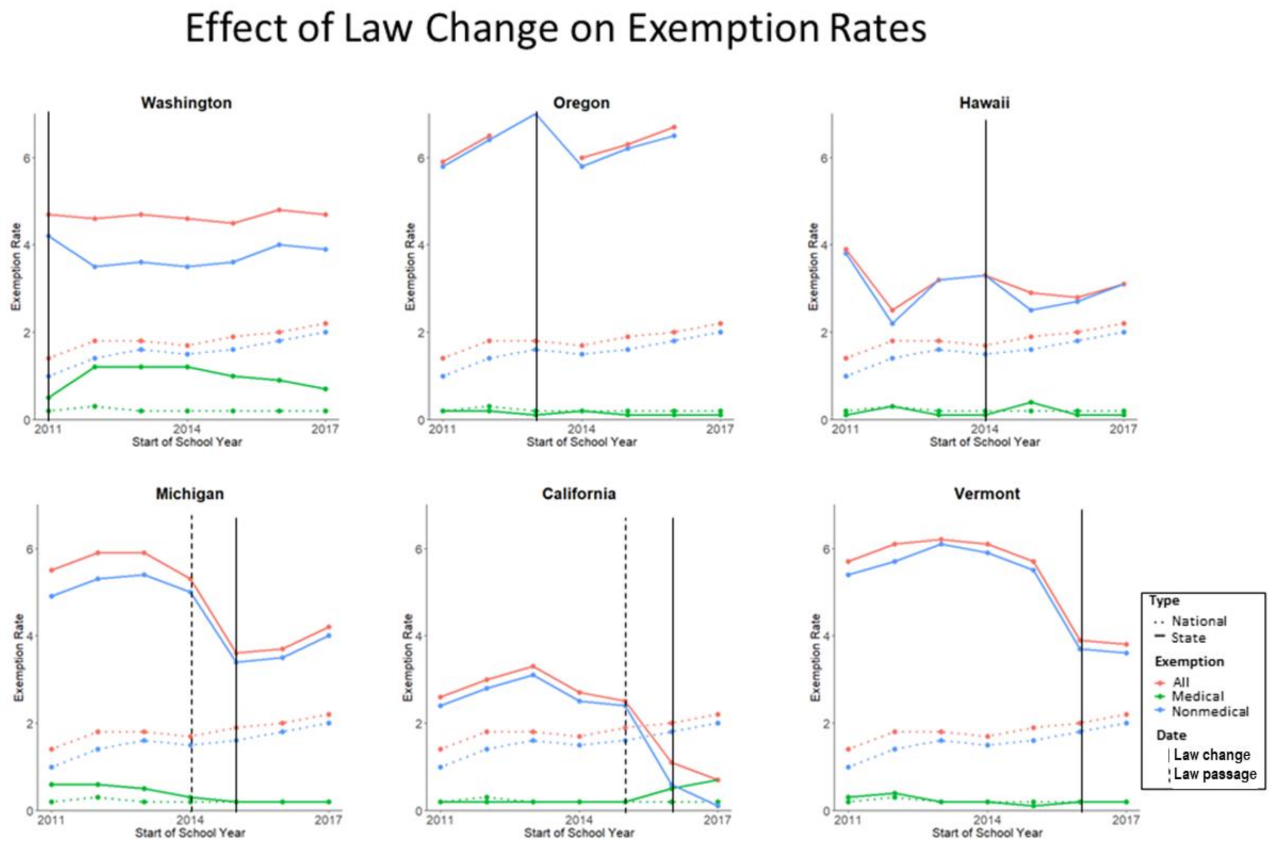

Figure 4: Effect of law change on exemption rates

Six states had both major law changes and available data before and after the law change. We have shown all, medical, and non-medical exemption rates for the national data (dashed line) and state (solid line) as well as the date of the law passage (solid line) and law change (dashed line). In states where these years are not the same (MI and CA), exemption rates fall following the passage of the law, before the law goes into effect. However, we do not have enough data to know whether the pending law change is a deterrent to exemptions or if this is unmeasured confounding. One state, California, experienced a large outbreak during this period (2014-2015).

Overall, all laws we highlighted had positive effects at lowering exemptions below expectations, with removal of exemption categories (Vermont and California) the most successful (Figure 4). In some states, however (Oregon, Hawaii, and Michigan), exemptions climbed again following an initial decrease after the passage of the law. In several states (Vermont, California, Michigan), exemption rates fell in advance of the law change. In California, while nonmedical exemptions (now outlawed) have fallen, medical exemptions have climbed following the law change, a marked departure from national trends. While nonmedical exemptions have now fallen to 0 in Vermont, which did not disallow religious exemptions, nonmedical exemptions have levelled off following an initial drop.

3.6 Discussion

Compulsory vaccination requirements for school entry and vaccination exemptions are regulated by state law, resulting in different policies across the country. We performed a small-scale longitudinal analysis to examine law changes during the 2011-2018 period, highlighting states where laws were changed during this period. Ideally, a long-term study would be conducted to examine the effect of changes to exemption law on exemption rates, coverage rates, and measles outbreaks. Data availability, however, is currently limited, and the 2011-2018 period represents the longest period of continuous data for most states available from a single source. Several states are missing data for exemption rates on the downloaded report available via the CDC VaxView site; because of sampling and reporting differences, these are reported in the VaxView Dashboard but not the downloaded report data. Law data is available for most states, going back almost indefinitely, and several states make their vaccination coverage data and/or exemption data available much farther back than does the CDC. This is, in most cases, the same data that is reported to the CDC and is available on VaxView. We found eight states with relevant major exemption law changes during the period of data availability, limiting our sample size; many more, however, had changed their laws since the 1970s. Because no single repository exists going back farther than the 2009-2010 school year (or farther back than 2011, continually), this limits the ability to perform a larger longitudinal analysis.

Except for a few cities, this data from the CDC is only currently available nationally at the state resolution level. Some states (such as California and Colorado) do choose to make their own high-resolution data available on state website. These two in particular have easy-to-access, parent-friendly websites. Others (such as Massachusetts) have ample data stretching back far beyond our analysis. However, no such data is collected nationally and no national repository for such data exists.

Over our study period, 2011-2018, we noted several trends to these law changes, with most states that changed their laws increasing restrictions on vaccination exemptions. These include mandatory education for parents taking philosophical and religious exemptions, requiring specific forms (with no alternatives), and eliminating exemption types entirely. California has discontinued religious and philosophical exemptions through Senate Bill 277 and Vermont has discontinued philosophical exemptions through House Bill 98, both effective July 1, 2016.[109,113] Previous to these changes philosophical exemptions comprised 68% and 95% of all exemptions used in each state, respectively. Following the law change, total exemption rates in both states fell dramatically (

Table 5). Though our analysis does not track individual parents, the rising rates of the remaining exemptions in the states indicates that parents who may have obtained one of the now outlawed exemptions are now switching to the exemptions that remain legal. Further restrictions may be required to stem further increases in these rates, and movements have been made to reexamine (not remove) medical exemptions in California.[115] Despite this, however, these changes represent the most successful attempts to decrease exemptions. Studies have found that states with both philosophical and religious exemptions (vs. only religious exemptions) have 2.41 times the exemption rates (95% confidence interval, 1.71-3.48), and we found states with only medical exemptions have among the lowest exemption rate in the US.[116]

Exceptions to the trend of increasing difficulty to obtaining exemptions are the law changes in Colorado, Hawaii, and Oregon, which allow additional healthcare professionals to give medical exemptions. We believe this has more to do with the larger nationwide trend of expanding practicing rights to advanced practice registered nurses and physician assistants than it does with medical exemptions or vaccine exemptions.[117,118] Recently, several states have passed or discussed laws that expand the ability of these groups to practice medicine in order to deal with primary care shortages; in all three states, multiple bills to this end have been passed.[118] This did not appear to have much impact on the overall exemption rates in these states compared to the national average.

Several states (including Pennsylvania) passed laws during this period shortening the period during which children have to become up-to-date on required vaccines. As this affects children who do not obtain an exemption and occurs before data is reported to the CDC, we did not include these laws in our study. We had no way to quantify the effect of these laws on exemption rates, as data is collected after the catch-up period has generally concluded; however, these fit into the general trend of increasing strictness of vaccination law.

The US experienced three major measles outbreaks during the 2011-2017 period: Ohio, California, and Minnesota. These took place in different communities: the Amish in Ohio, a non-vaccinating multi-state community in California, and Somali immigrants, mostly preschool age, in Minnesota. Currently, the US is experiencing measles outbreaks in New Jersey, Connecticut, and New York, as well as the most recent, and potentially largest, in the Pacific Northwest, which has exhibited signs of spreading nationally.[1] Measles, like all infectious diseases, is transmitted locally. Our analysis looks at state-level data, as that is the resolution collected and analyzed by the CDC. Exemptions, however, have led to highly clustered refusal and geographic hot spots, or under-vaccinated communities; while the US as a whole has increased vaccination due to programs such as Vaccines for Children, intentional under-vaccination has resulted in small areas with low vaccination.[16,17] This in turn has led to increased local risk and outbreaks.[1,18] A review of all recent outbreak data found the majority of measles cases in recent outbreaks were the result of intentional under-vaccination, rather than access-driven or age-restricted (or vaccine failure)[17]. Indications show that there is a geographic trend with intentional under-vaccination, and if these communities continue to cluster, risks will continue to increase.[3]

Studies that examine coverage have shown that under-vaccinated communities cluster, but real-world local level measles data is not available nationally.[3,43] Several groups have attempted to collect this data. Kluberg et. al. (2017) collected data at the county level, but even with a FOIA request could not gather the data for all 50 states.[119] The group at the University of Georgia used healthcare data to collect vaccination coverage data for the coverage area, but that only covered areas covered by that insurer.[120] A team at Baylor used publicly-available data to map county-level non-medical exemption rates for 14 states.[121] In light of these recent papers, pushes from local citizen groups, and the success of easy-to-use websites that allow parents to look up the status of their child's school (such as those in California and Colorado), more states are making school- or district-level vaccination data available. We found school-level data for 15 states, and sub-state data for 25 states in total.

Because state data is poorly representative of coverage levels of a given area, expanding tools such as VaxView is a crucial step. A national, easy-to-use, easy-to-access repository for high resolution vaccination coverage data can provide a valuable tool to researchers and policymakers. This additional data is not only advantageous to researchers but is useful to parents in selecting or improving their child's school. State websites may include information on coverage (overall or vaccine-specific), exemptions, and non-compliance.

Additional sources report on vaccination coverage in the US, such as the Behavioral Risk Factor Surveillance Survey and the National Immunization Survey (Table 3). We used information from school surveys reported by VaxView and MMWR since these include school-age children. High resolution incidence data does not exist. Finally, our analysis indicates that eliminating philosophical or religious exemptions, as expected, decreases overall exemption rates. However, this may need to be done in conjunction with other policy initiatives as anti-vaccination parents shift to medical exemptions which cannot be eliminated for reasons of safety. A true pro-vaccination policy should not only address exemption availability but also difficulty.

3.7 Public Health Implications

Heterogeneity in state vaccine exemption laws can lead to varying vaccination coverage and disease risk across the country. State legislators have an opportunity to influence vaccination coverage and the risk of disease through vaccine legislation. While eliminating nonmedical exemptions is the strongest response to decreasing exemptions, in states where lawmakers may lack the political capital to do so, other responses that increase the difficulty of obtaining an exemption (such as requiring an education module) may assist in this goal as well. Vaccine exemption policies should not be reviewed as a binary but a complex system that can be understood with detailed, high-resolution information about exemption, vaccination coverage, and disease rates.

4.0 A High-Resolution School-Based Coverage Data Model to Predict Measles Outbreaks in US Counties

4.1 Abstract

Despite most states achieving coverage levels above 90%, the US is currently in the middle of the largest measles outbreak since measles was declared non-endemic 19 years ago. While state coverage may be high, small communities may have pockets of low coverage. These same communities have experienced measles outbreaks in recent years. Coverage data, however, is often only available to researchers at the state and national level, obscuring these communities that may fall below coverage goals. We collected school-level measles vaccination coverage data and outbreak data, as well as covariates including distance from the nearest large airport and number of airline passengers per year. Using the data from four large measles outbreaks (California 2014-5, Minnesota 2017, New York 2018-19, and Washington 2018-19), we predicted county outbreak risk in seven states. We created two models, one maximized for PPV, and another, a compromise model, for high PPV and sensitivity. These models found five (max PPV) and eight (compromise) counties at high risk of outbreak across four states. This research underscores the need for researchers to have access to high-resolution coverage data, which in most states is already collected but has not been made publicly available.

4.2 Introduction

Current measles vaccination coverage in the US is high, but despite this, pockets of under-vaccination have resulted in large outbreaks. After the recommendation of a second dose of MMR in 1997, coverage and immunity increased; by 2000, the CDC declared measles eliminated from the US, meaning measles was no longer endemic to the country.[11] However, 2019 will likely see a return of endemic measles to the United States. 28 states have experience outbreaks to date this year, totaling 1,022 cases, the most since measles was declared eliminated in 2000.[1] These outbreaks originate in small communities; several of the past years have seen small local measles outbreaks rise to national prominence: Minnesota (2016), Disneyland (2014-5, the previous largest recent outbreak, with 855 cases), Ohio (2014), and Texas (2013); current outbreaks originating in New York and Washington state have spread throughout the US.[1]

Though these outbreaks are localized, US research databases such as the CDC VaxView and National Immunization Survey analyze vaccination coverage data, including measles, on a national scale.[10,122] Though local health departments have access to local-level data, including school-level, or for surveys, census-tract level data, this data is often not shared with researchers or other, sometimes bordering health departments. Local-level analyses performed by researchers would help inform targeted approaches to prevent future outbreaks, but no central repository for local-level data of vaccine preventable diseases exists, making research to examine local-level patterns of under-vaccination extremely difficult. This approach obscures local heterogeneities with respect to intentionally and non-intentionally under-vaccinating communities which may have higher risk of outbreak.

Previous studies have attempted to collect or model high-resolution school-level coverage data.[119,120] Two additional studies have attempted to create models to estimate measles risk using county-level data.[121,123] No study, however, has combined high-resolution school-level data with a measles outbreak model. In this paper, we attempt to use publicly available high-resolution data to predict counties at highest risk of future measles outbreaks.

4.3 Methods

4.3.1 Data Collection

We collected data over a four-year period (2015-2019) by performing continually updated internet searches for publicly available data as well as checking likely sources (state health department websites, Departments of Education) and previous sources for updates. Pennsylvania data was obtained with a special partnership with the Department of Health; all other data is publicly available.

Table 11 (Appendix) represents all collected data as of August 1, 2019. CDC survey design gives an idea of whether school data is collected. In addition to survey design, the CDC also provides numbers for percentage of respondents. For census designs, these surveys reach 87-100% of the target population. Other designs, such as voluntary response surveys and convenience samples, fail to reach large portions of the population. For example, the most recent Wisconsin survey (a stratified 2-stage cluster design) reached just 1.7 percent of the population.[10] While this may be enough to calculate coverage for the state, it is insufficient to provide the high-resolution data.

4.3.2 Data Cleaning Process

Because this data is not in any central repository or collected and processed by any organization, each state is responsible for its own data. As a result, each data set contains a distinct set of coverage variables, covariates, location data (or lack thereof), and school information.

4.3.2.1 Original Datasets

Most datasets contain vaccination coverage data (usually percentage of students vaccinated for each vaccine) and school name, with no location data provided. The CDC also provides state-level exemption data. Table 11 (appendix) lists years where coverage data is available. Missingness is significantly more for exemption data, especially for personal belief and religious exemptions.

4.3.2.2 Matching / Geocoding

In order to provide spatial coordinates for schools, we have geocoded addresses or available location data. Where an entire address is not provided, we have created a unique identifier using provided information such as a relatively unique school name, district, county, and state. We were able to geocode school by with this information and geocode using the Bing Maps Geocoder. For the few schools that this method does not work for, or yields incorrect coordinates, we found address information by hand, and then use this information to geocode.

4.3.3 Spatial Statistics

We used two different methods of calculating clustering, Global Moran's I and Anselin Moran's I.

4.3.3.1 Global Moran's I

In order to estimate global clustering (i.e., if schools with low coverage are near other schools with low coverage), we used the Global Moran's I. This measure ranges from −1 to 1, with 0 indicating a random distribution, -1 a perfect spatial dispersion, and 1 a perfect clustering (autocorrelation).

4.3.3.2 Anselin Moran's I

We used the Anselin Local Moran's I to estimate the association of MMR coverage rates between a specific school and neighboring schools within a given geographical area. We considered Moran's I statistics with p-values < 0.05 to be statistically significant. In order to incorporate this measure into the model, we calculated the number of low vaccination coverage clusters (schools with <90% coverage and statistically significant clustering with the Anselin Moran's I test) in a county.

4.3.3.3 Washington State Analysis

We ran a separate, small analysis on Washington State to examine the effect of spatial resolution of measles coverage data on clustering. This was performed with the Washington State 2017-2018 Kindergarten Data.[124]

4.3.4 Model

4.3.4.1 Inclusion / Exclusion Criteria

Outbreak states

We divided states into outbreak and prediction data based on outbreak status. States with available, high-resolution school measles vaccination data that had experienced major outbreaks (a year with unusually high activity of >20 cases before July 1, 2019) were used to create our model. Additional inclusion criteria included: high-resolution school measles or MMR coverage data for kindergarten or first grade for the year of the outbreak, or one year adjacent; school location data for public and private school (at least 85% of counties); available county-level measles cases data for outbreak period. California, Minnesota, Washington, and New York (not including New York City) made up the states in the training data set. We were unable to include New York City because while the city is made up of five counties, measles case data reported by the Health Department does not distinguish among these. New York also reports only aggregate data for public schools. For each of these states, we matched data to the year of the outbreak.

Prediction states

States were included in our prediction dataset if they met the following criteria: no or low measles activity (n<10 cases) in 2018; high-resolution school measles or MMR coverage data for kindergarten or first grade, 2017-2018 or 2018-2019; school location data for public and private school (at least 85% of counties). States with available, high-resolution school data with limited measles activity included Arizona, Massachusetts, Colorado, Maine, Pennsylvania, and Vermont. Because the Minnesota outbreak was several years ago, we also used the most recent Minnesota data within this data set. For each of these states we used the most current available data. We also have high-resolution data for California, but with 22 cases reported in 2018, the state did not fit our inclusion criteria for low measles activity.[125]

4.3.4.2 Outcome

Our model outcomes were number of measles cases (per county) and probability of an outcome occurring. Because we have a year mis-match (measles cases are given by the calendar year, whereas vaccination coverage is by the school year), we used the majority school year to match with measles cases, i.e.: 2017-2018 data matched to 2018 measles cases, as six of the nine months of this school are in the year of the case data. New York state has reported the current measles cases for the entire outbreak (which began in October 2018); since these are not separated by month, we have used this time period for this state only. We log-transformed the number of measles cases to achieve a normal distribution. We determined a county's outbreak status in our outbreak states dataset by whether a given county had experienced one or more cases during the outbreak period.

We obtained measles case counts from publicly available reports from the state Department of Health websites and the CDC.

4.3.4.3 Covariates

Clusters: This is the number of low-low clusters of schools with vaccination coverage <90% per county as obtained by the Anselin Local Moran's I test. Vaccination coverage was measured on kindergartener coverage of MMR (measles-only for NY state). This is the number of low-coverage schools which neighbor a statistically significant number of other low-coverage schools and use it as a measure of outbreak risk. We log-transformed this variable to achieve a normal distribution.

Airports: We obtained data from the Bureau of Transportation Statistics and matched to outbreak year.[126] We selected for airports with >2.5 million enplaned passengers; this included the top 59 largest airports by total passengers. We geocoded these airports and performed a Near Analysis of airport centroid in ArcMap. Included covariates were distance from population-weighted county centroid (obtained from Census Data) to the nearest airport and airport size by total enplaned passengers.[127] Airport location can and size can be seen in Appendix Figure 18.

4.3.4.4 Model Selection:

Our initial model also included population density (2010 Census).[127] We also examined county-level MMR vaccination coverage data, where available in our original data, but did not include this because of significant collinearity with our clustering metric, which performed better in the model. We tested for six models (Figure 5), three linear regression models for outbreak size (number of cases) and three logistic regression models of whether a given county experienced an outbreak. We selected the two models (one linear, one logistic) that performed best on the model selection criteria of R^2 and AIC. Model 2 was selected in both cases. A Poisson regression did not improve diagnostics for the predicted cases model.

	Predicted Cases #1	Predicted Cases #2	Predicted Cases #3	Outbreak Logistic #1	Outbreak Logistic #2	Outbreak Logistic #3
Intercept	0.2054	0.2337	0.3968*	-0.3628	-0.4292	-0.3316
	(0.1245)	(0.1243)	(0.1954)	(0.7406)	(0.7298)	(0.9423)
Log Transformed LL Clusters (Log (x+1))	0.2384***	0.2465***	0.2399***	0.4603*	0.4518*	0.4513*
	(0.0449)	(0.0450)	(0.0454)	(0.2023)	(0.2017)	(0.2023)
Distance of the Nearest Airport to the Population Weighted Centroid of the County	-0.1772***	-0.1996***	-0.2995**	-2.6728***	-2.5424***	-2.6964*
	(0.0404)	(0.0390)	(0.1003)	(0.5978)	(0.5483)	(1.1024)
Population Density (# of People per 100 Square Miles)	0.0000			-0.0000		
	(0.0000)			(0.0000)		
Number of Travellers (in millions)	0.0142*	0.0165**	0.0068	0.0482	0.0424	0.0356
	(0.0064)	(0.0063)	(0.0110)	(0.0333)	(0.0319)	(0.0520)
Airport Distance * International Travellers			0.0058			0.0108
			(0.0053)			(0.0660)
R^2	0.2299	0.2176	0.2215			
Adj. R^2	0.2168	0.2077	0.2082			
Num. obs.	240	240	240	240	240	240
RMSE	0.7307	0.7349	0.7347			
AIC				114.5904	113.0137	114.9869
BIC				131.9936	126.9363	132.3901
Log Likelihood				-52.2952	-52.5069	-52.4934
Deviance				104.5904	105.0137	104.9869

Model 1 included Population Density, Model 2 omitted Population Density, Model 3 omitted Population Density but included interaction between distance to the nearest airport and the population weighted centroid of the county

Statistical models

Figure 5: Model selection

Predicted Cases #2 performs best among the cases models. Outbreak Logistic #2 performs well and is an equivalent model to our cases model. Clusters and distance to airport are significant in both models; number of travelers is significant in our cases model only. Population density is not significant. The interaction term is not significant in either model.

4.3.4.5 Model Training

These two regression models were then used on the four outbreak states to test performance. We used this to generate cutoff points as well as to calculate model performance (PPV, sensitivity) at those cutoff points before running the model on the prediction dataset.

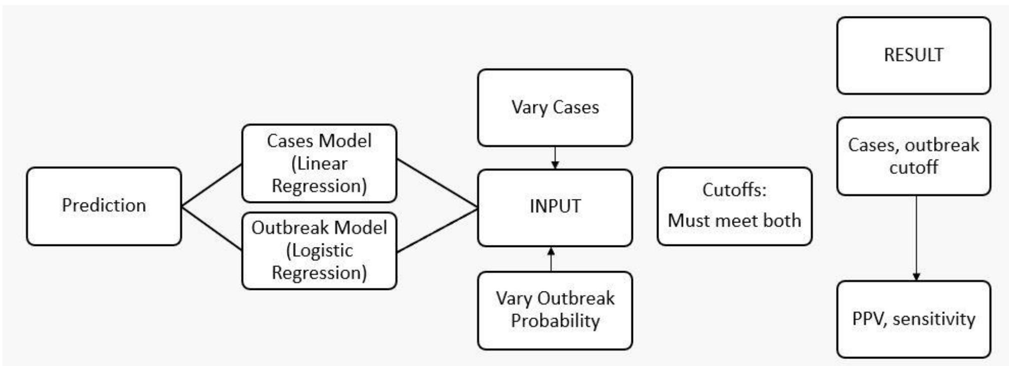

Figure 6: Model cutoff selection process

We used the two models (outbreak and cases) in combination. This means that we would predict a county to have a measles outbreak only if the cutoff points for both models are met. For example, if the cutoff points for the cases model and the outbreak model are 1 and 0.6 respectively, we would only predict a county will have a measles outbreak if the cases model result is greater than 1 and the outbreak probability is greater than 0.6. Appendix Table 12 walks through an example of this process.

To select the most appropriate cutoffs, we conducted an uncertainty analysis by varying the two cutoff points sequentially and testing for outcomes including positive predictive value (PPV), negative predictive (NPV), sensitivity, and specificity (Figure 8 and Figure 8). For the cases model, we specified a range of 0-2.5 and ran intervals of 0.05. For the outbreak model, we specified a range of 0.3-0.75 with intervals of 0.005. This resulted in 4641 iterations.

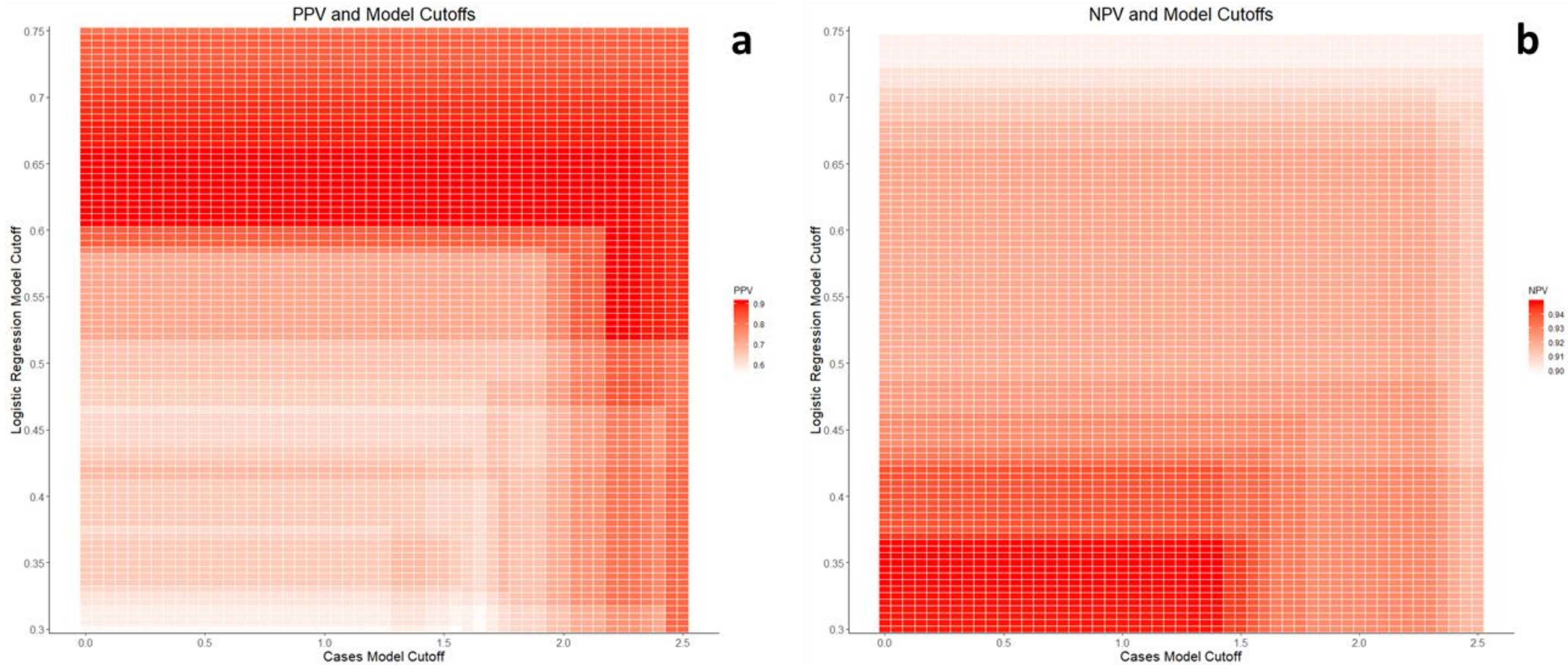

Figure 7: Selecting for a) PPV and b) NPV cutoffs

As the shade in the figures darkens, PPV (left) or NPV (right) increases with each combination of our cutoff values. We find higher NPV for lower cutoff values and higher PPV for higher cutoff values.

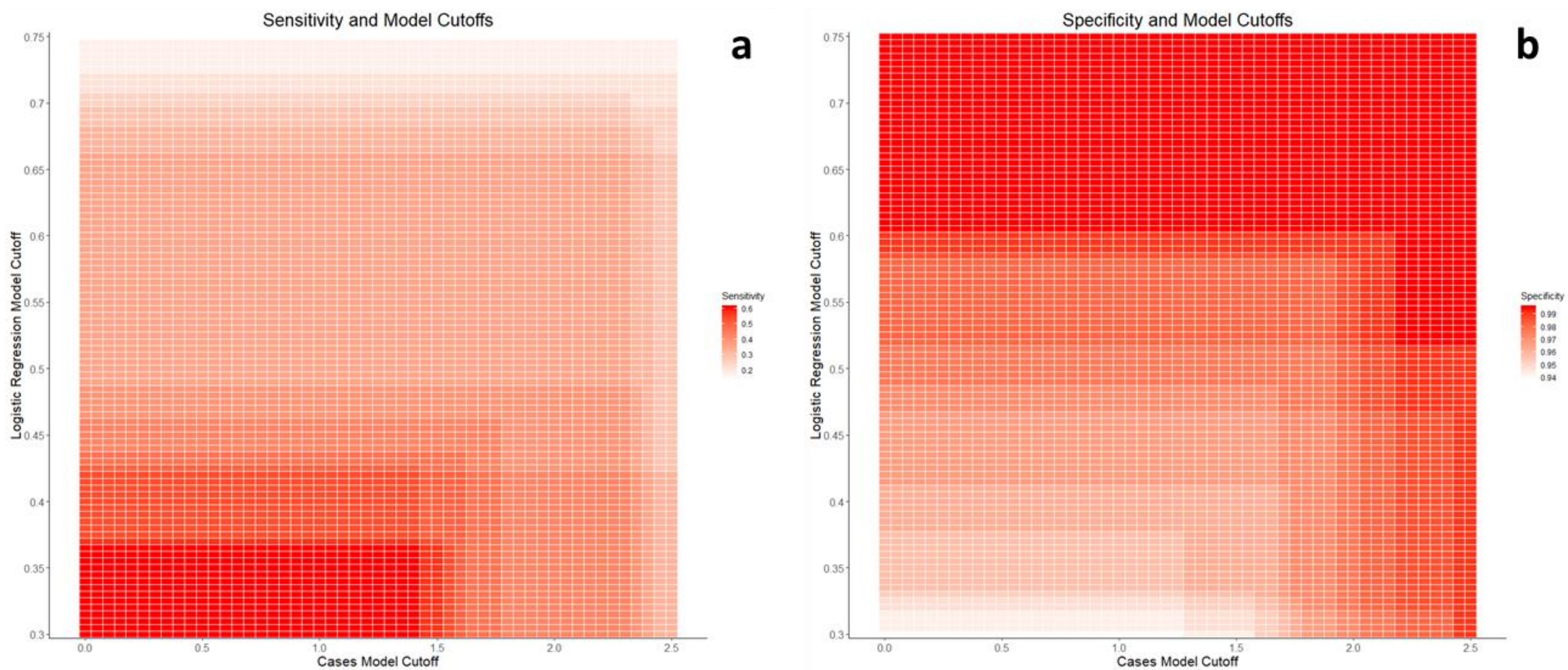

Figure 8: Selecting for a) Sensitivity and b) Specificity cutoffs

As the shade in the figure darkens, sensitivity (left) or specificity (right) increases with each combination of our cutoff values. We find higher sensitivity for lower cutoff values and higher specificity for higher cutoff values.

To select the best model, we created a Pareto Frontier to optimize for both sensitivity and PPV (Figure 9).

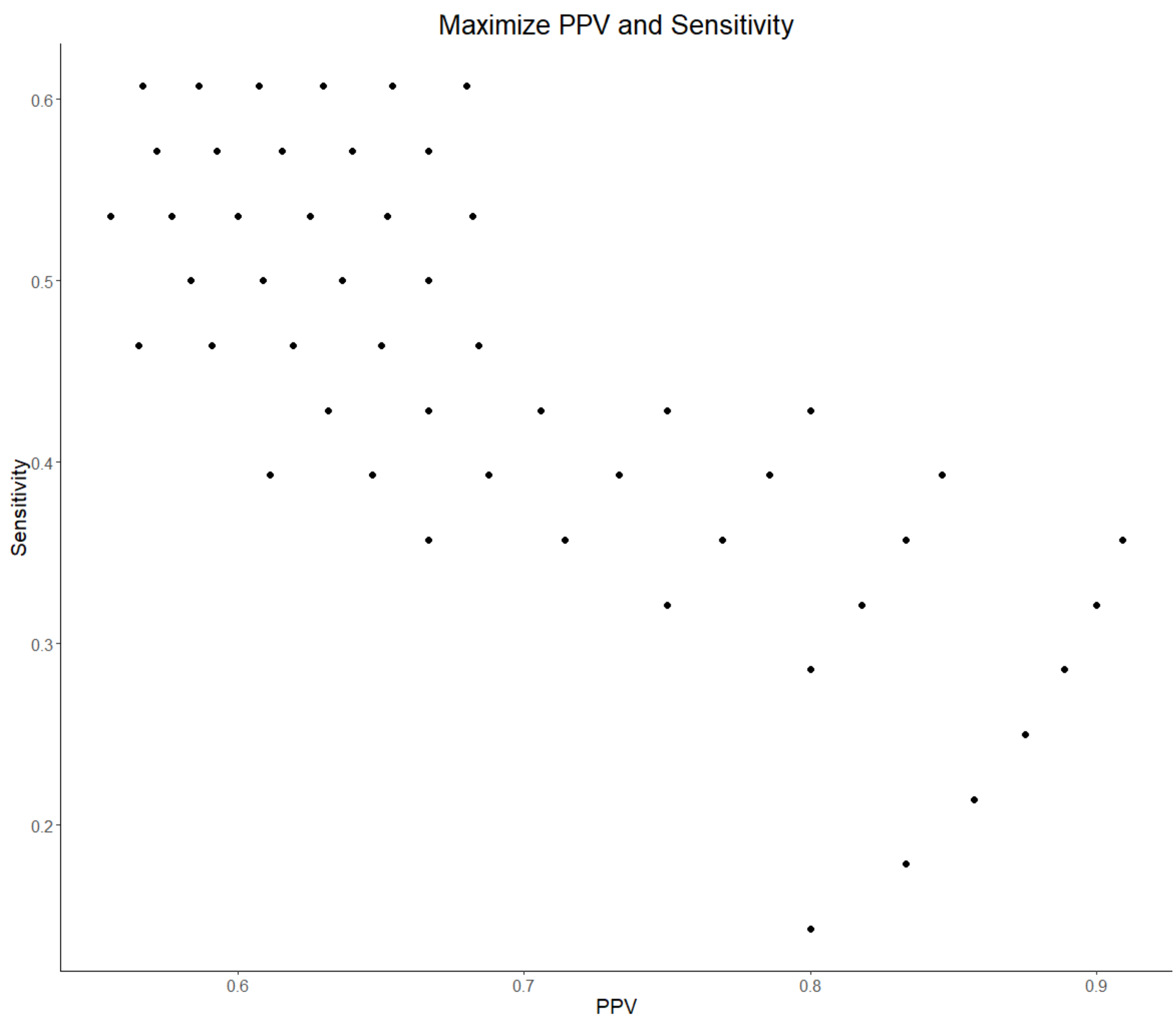

Figure 9: Pareto Frontier

The points on the pareto frontier denote model cutoff points where it is impossible to improve either sensitivity or PPV without making the corresponding metric worse off.

We selected two models: a conservative model maximized for PPV and a compromise model with >/=80% PPV and >40% sensitivity. The values for the models are in Table 6:

Table 6: Model cutoffs, conservative and compromise

Model	Cases parameter	Outbreak parameter	PPV	NPV	Sensitivity	Specificity
Conservative	0	0.605	0.9091	0.921	0.3571	0.9953
Compromise	2.2	0.32	0.8	0.929	0.4285	0.986

4.3.5 Prediction

The resultant models were then used on our low-activity prediction dataset to calculate areas of likely high future measles risk.

All figures were generated in R version 3.3.2. All maps were generated in ArcGIS version 10.6.1.

4.4 Results

4.4.1 Data Resolution: Washington Example

We examined data at 3 levels of data resolution for Washington State, Kindergarten MMR coverage, 2017-2018.

Moran's I results for the three levels of spatial resolution is in Table 7:

Table 7: Washington clustering results

Resolution	Global Moran's I	Local Moran's I
County	Index: 0.17	Figure 10
	Z-Score: 1.795	
	P-Value: 0.073	
District	Index: 0.099	Figure 11
	Z- Score: 4.59	
	P-Value = 0.000005	
School	Index: 1.40	Figure 12
	Z-Score: 10.93	
	P-Value < 0.000005	

The increasing index and Z-scores and decreasing P-values indicates increasing statistically significant clustering of MMR coverage. Because the underlying data is the same – simply aggregated for the district, and further aggregated at the county levels – this would indicate that aggregation of data decreases the ability to detect this clustering.

Maps (Figure 11, Figure 12, and Figure 12) show the movement and ability to detect clusters changes with the changing spatial resolution. Again, the underlying data does not change; this is the same data set from Washington State Department of Health aggregated to the district and county levels from the original school data.

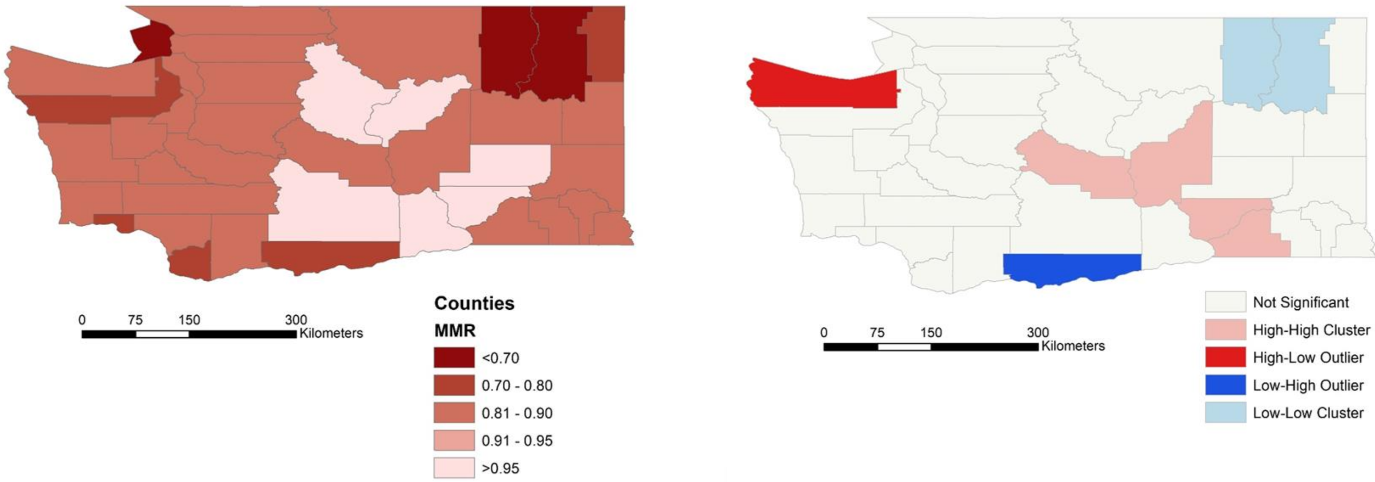

Figure 10: Washington State, Local Moran's I clustering (county)

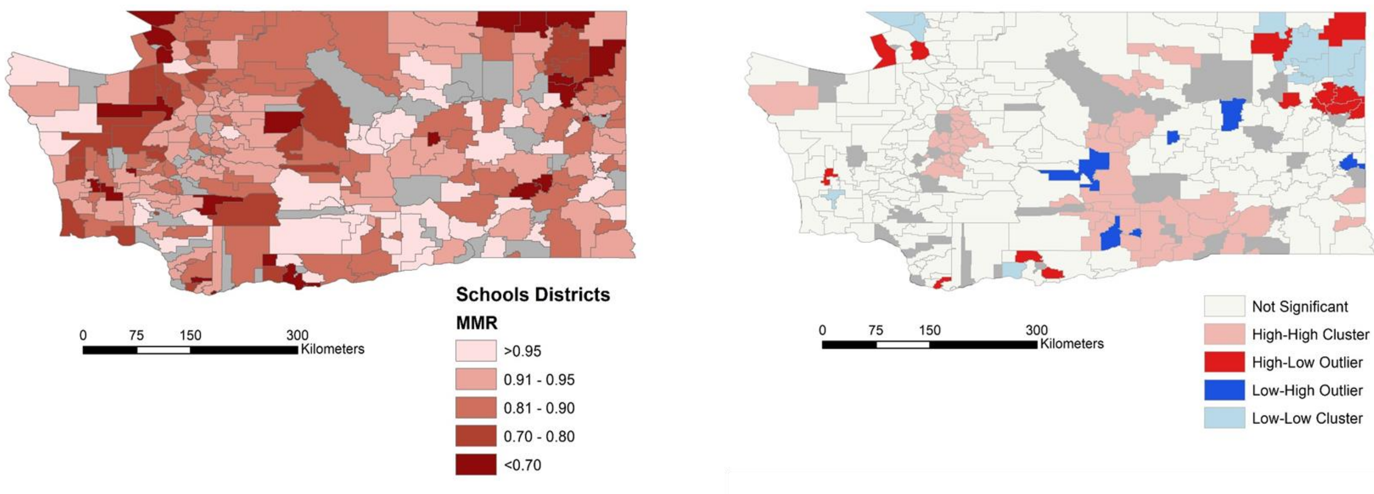

Figure 11: Washington State, Local Moran's I clustering (district)

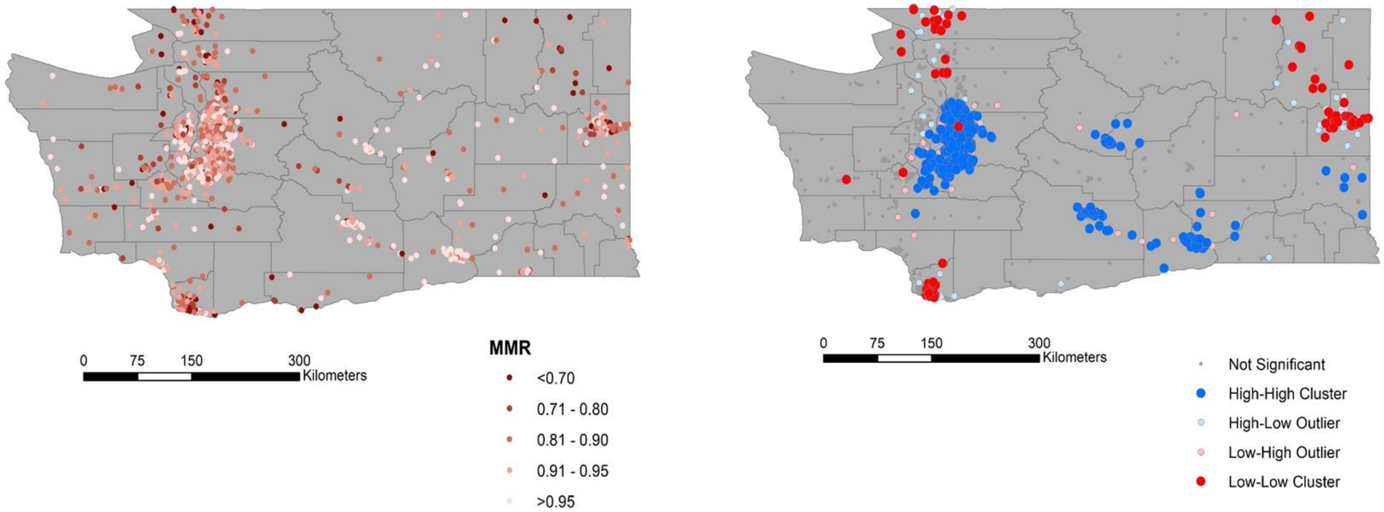

Figure 12: Washington State, Local Moran's I clustering (school)

Figure 10 - Figure 12 show autocorrelation (clustering) change as spatial resolution increases in Washington state. In the first of these, we find four counties with high-high (light pink) clusters: counties with high coverage rates surrounded by similar high-coverage counties. Two low-low (light blue) counties are found in the Northeast. These have low coverage and are neighbored by other low-coverage counties (as seen on the left-hand coverage map). As the resolution increases, the district map (Figure 11) reveals outlier regions in both of these areas, as well as additional low-low (light blue) clusters in the Southwest and Northwest. In the final Figure 12, school-level) map, we see are large area of low-low (red) clusters in the Southwest, near Clark county, the site of the 2019 measles outbreak. This area is not visible on the county-level map.

On these maps, we see relatively low ability to detect low-low and high-high clusters with the county data. Though these clusters remain (in the eastern and central parts of the state) in the district resolution map, we pick up on additional clusters in the western part of the state and the south. The school-level map shows an entirely different set of clusters, with high-high clusters becoming predominant in the central west (with one low-low cluster), the low-low clusters remaining in the east, and a large group of low-low clusters in the south (the same county responsible for the majority of the cases of the current outbreak).

4.4.2 Clustering

Table 8: Outbreak states

State	Global Moran's I	Count (LL cluster / schools)	Range (MMR / cluster)	Range (MMR / school)	No. Counties
California (2013-4)	Index: 0.076 Z-Score: 24.83 P-Value < 0.000005	753 / 6960	0.11 – 0.90	0.0 – 1.0	58
Minnesota (2016-7)	Index: 0.195 ZScore: 18.5 P-Value < 0.000005	85 / 1108	0.33 – 0.9	0 – 1	87 (86 have school data)
New York (2017-8)	Index: 9.07 ZScore: 418.26 P-Value < 0.000005	169 / 4688	0 – 0.897	0 – 1.0	57 (Without NYC)
Washington (2017-8)	Index: 1.40 Z-Score: 10.93 P-Value < 0.000005	91 / 1430	0 – 0.87	0 – 1.0	39

Table 9: Prediction states

State	Global Moran's I	Count (LL clusters / total schools)	Range (MMR / Cluster)	Range (MMR / School)	No. Counties
Arizona (2017-2018)	Index: 0.219 Z-Score: 1.827 P-Value: 0.676	94 / 1072	0.54 – 0.9	0.15 – 1	15
Colorado (2016-2017)	Index: 0.297 Z-Score: 4.612 P-Value: 0.000004	149 / 1792	0.31 -0.9	0.31 – 1.04	64 (61 have school data)
Maine (2017-2018)	Index: 0.024 Z-Score: 1.779 P-Value: 0.075	7 / 330	0.54 - 0.9	0.38 – 1	16 (14 have school data)
Massachusetts (2017-18)	Index: 0.336 Z-Score: 15.09 P-Value < 0.000005	20 / 777	0.59 – 0.9	0.48 – 1	14
Minnesota (2017-18)	Index: 0.152 Z-Score: 26.62 P-Value: < 0.000005	123 / 1099	0.36 – 0.9	0 – 1	87 (83 have school data)
Pennsylvania (2017-18)	Index: 0.288 Z-Score: 2.98 P-Value: 0.003	21 / 1633	0.6 – 0.9	0.43 -1	67 (65 have school data)
Vermont (2017-2018)	Index: -0.016 Z-Score: -1.23 P-Value: 0.219	0 / 402	NA	0 – 1	14

4.4.3 Prediction Model

The two results of the prediction models are shown in Figure 13 and Figure 14:

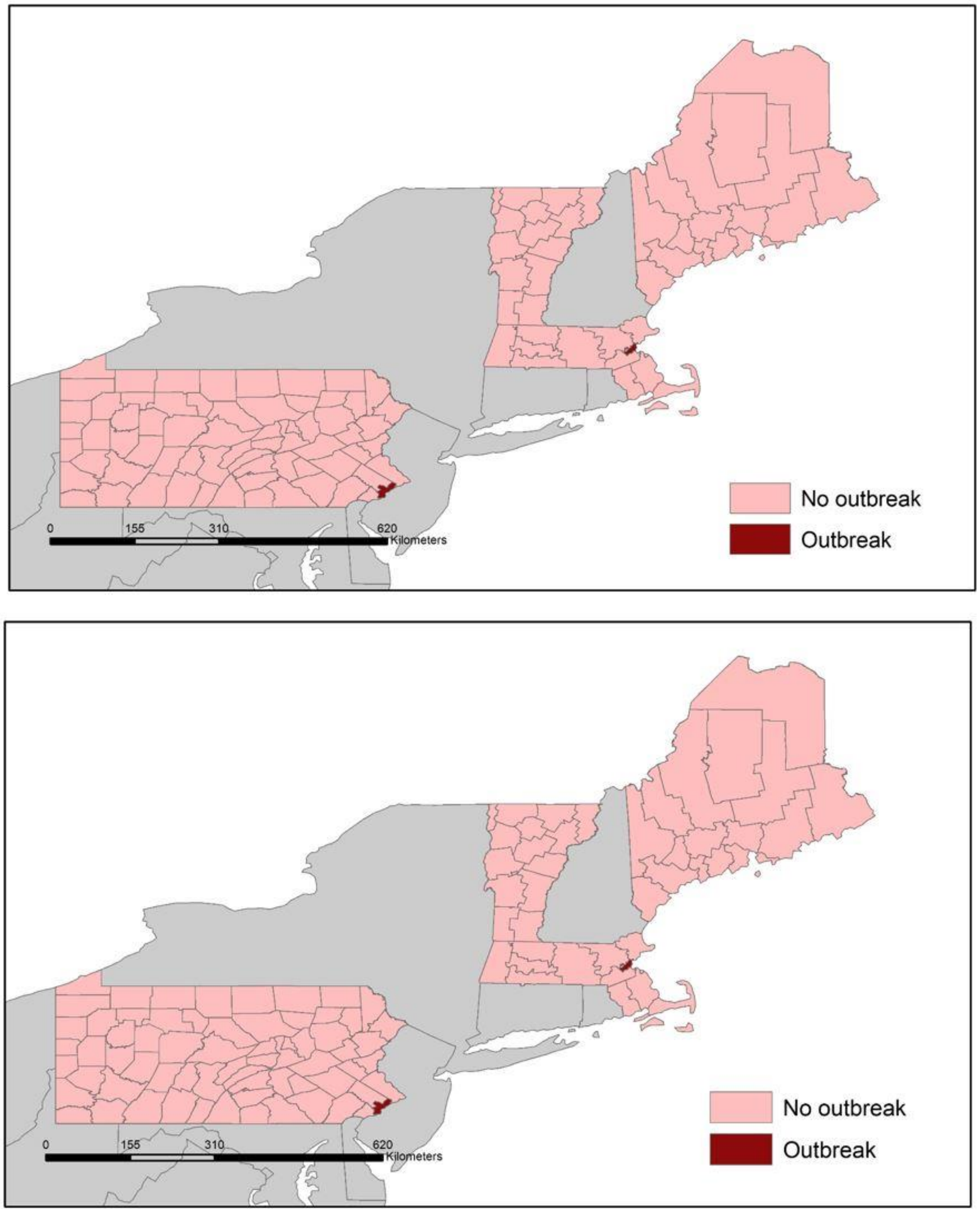

Figure 13: Predictions for New England and Mid-Altantic states

This figure shows the predicted outbreak counties for the compromise (top) and max PPV (bottom) models. Both models predict the same counties: Philadelphia, PA, and Suffolk, MA.

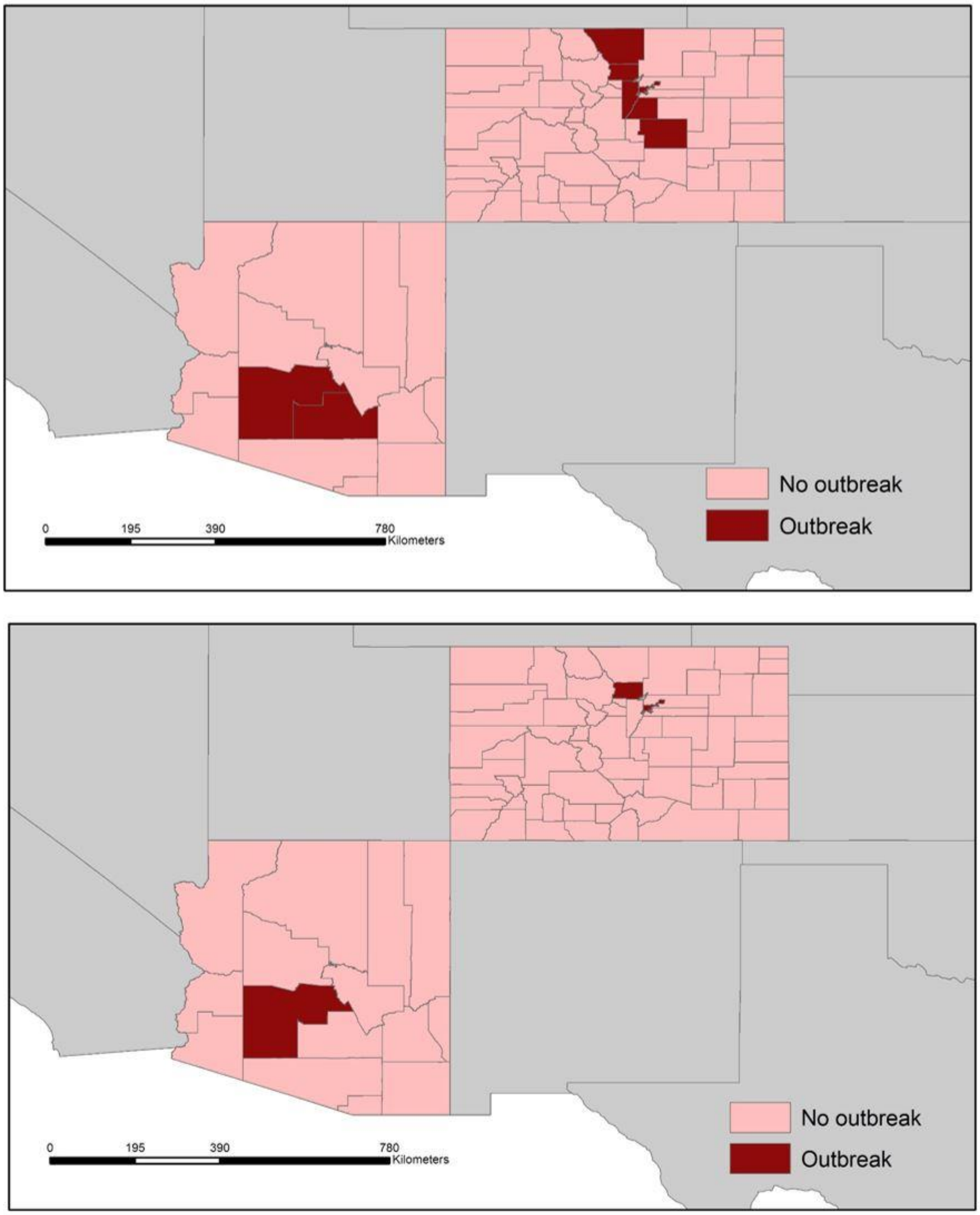

Figure 14: Predictions for the Southwest states

This figure shows the predicted outbreak counties for the compromise (top) and max PPV (bottom) models. The max PPV predicts three counties: Maricopa, AZ, and the neighboring counties of Boulder, CO, and Denver, CO. The compromise model predicts an additional five counties: Pinal, AZ, and four counties in Colorado: Douglas, El Paso, Jefferson, and Larimer.

Counties that are predicted at risk of outbreak in each model are detailed in Table 10:

Table 10: Results of prediction, compromise and max PPV models

State	Max PPV	Compromise
Arizona	Maricopa	Pinal, Maricopa
Colorado	Boulder, Denver	Boulder, Denver, Douglas, El Paso, Jefferson, Larimer
Maine		
Massachusetts	Suffolk	Suffolk
Minnesota		
Pennsylvania	Philadelphia	Philadelphia
Vermont		

There are no counties at risk of outbreak under either model in Maine, Minnesota, or Vermont. In Arizona, Maricopa is at risk under both the more conservative (max PPV) model and the compromise model, while Pinal County is at predicted risk only under the compromise model. The same pattern is shown with Boulder and Denver counties in Colorado, Philadelphia in Pennsylvania, and Suffolk in Massachusetts; all are at risk in both models while the remaining counties are only at risk of outbreak under the compromise model.

Within the same state, many of the counties predicted are adjacent. We expect that these may warrant additional consideration, as adjacent high-risk counties may compound risk of a larger outbreak as local travel between these counties may be greater than between more distant counties.

4.5 Discussion

This work took a systematic approach to improve on previous efforts by utilizing high-resolution local school-level data to predict areas at high-risk of measles outbreak. We have developed both a conservative model, maximized for highest PPV, and a compromise model, to allow public health decision-makers to employ the model they feel is best suited for their community. Additional models, tailored to level of risk, are also possible with this work, by changing the PPV – sensitivity tradeoff. This will allow local health departments to either pick up more possible outbreaks, with less certainty, or ensure that every outbreak pickup by the model is highly likely, at the risk of missing possible outbreaks.

Additional improvements to this work are possible in the very near future, as we suffered from limitations to data availability. In addition, we recognize that with the 12-month mark of the New York outbreak approaching in October 2019, the US is set to lose its measles non-endemic status, changing the landscape of measles transmission in the country.

4.5.1 Limitations

Because every state is responsible for its own data collection and dissemination, each state collects different variables, has different exclusion criteria, and publishes their data in different formats. This leads to several limitations.

4.5.1.1 Resolution

Every state collects, at minimum, some basic metric of coverage for the state for some time point in the CDC collection. Some states do not collect this data every year, even at the state level, and some collect this data by a non-census method, meaning it is unlikely that school-level data will be available at any point in the near future. Not all states that collect data through a census make this data available, though we have noticed an increasing push to make this data publicly available. Our current collection represents only publicly available data. More data will likely be available through partnerships, and given the public interest in this data, we expect more to be released publicly as well. For example, Oregon released its data publicly during the later stages of our analysis, but due to time constraints we were unable to include it in our analysis. We anticipate being able to add more states to the model as they are released. Since not all states perform a census, however (see Appendix, Table 11), we do not anticipate there being a time when a complete model can be created for the entire country.

4.5.1.2 Variables

Each state releases some metric of basic coverage data, but what this entails may vary. For our analysis, we have included both measles and MMR coverage. Some states collect MMR1, while some states collect MMR2. For the few states we have been able to compare MMR1 to measles to MMR2 data, we have noticed no significant difference in these numbers. Some states that publish county data publish only up-to-date statistics (with no definition of what vaccinations up-to-date includes). We are unable to include any states in our analysis without some measure of measles or MMR coverage. Most states that give data for MMR also publish data for DTP and polio, and many include varicella (with some states not defining which dose); these data points could lead to new models in the future.

Most states only publish coverage data. However, important research has also been done on the exemption rate. This was the basis for previous papers on which this work is built.[121,123] While it might seem reasonable to assume that the exemption rate can be inferred by the coverage rate (1-coverage = exemptions), in schools that publish exemptions, we have found that this is not that case. While either a valid vaccination certificate or exemption document is required to attend schools, many schools have large numbers of children who are non-compliant (lacking either document) or provisionally enrolled (enrollment while catching up on vaccinations). This is important data that is publicly reported by only a minority of states. This, in addition to the fact that it is a more widely reported metric, is one of the reasons we have chosen to use coverage data rather than exemption data in our model.

4.5.1.3 Exclusion Criteria

For states that publish their exclusion criteria, it seems to be common that schools with fewer than 10 students in a given grade are not included in the data set for privacy reasons. However, this exclusion criterion differs for each state, reaching as high as 30 in Massachusetts. Therefore, our analysis has some counties with no schools included in the analysis; every school in these areas either did not report data or was excluded from the report due to insufficient size. These schools are mostly in rural areas.

4.5.1.4 Data format

We have found data in one of three formats: parent-focused website, researcher-focused websites, and FOIA requests. Parent-focused websites often include web apps (usually maps) that help parents find their child's school. They may include additional educational materials on the importance of vaccination (the Massachusetts site has a link the FRED measles simulator), which also include a link to download the data.[128] Researcher-focused websites lack additional materials such as maps but have easy access to datasets. Data obtained through FOIA requests is usually available for one year only, on a local news site, and available in a format that is (so far) inaccessible.

In addition, because every state publishes its own data set, variable names even for data in accessible formats are not interoperable and must be standardized. Often, coverage and exemptions are not given as rates and must be converted.

We have also found mistakes in data reporting. Colorado, for example, reported several schools with greater than 100% vaccination coverage. Because these records are entered by hand by school nurses, mistakes are common, and if not cleaned by the health department (which involves communication back to the individual schools), they become common in the data. We lack the communication channels to source these mistakes back to their original locations. They appear to be rare (three schools in Colorado, for example).

There is also under-reporting in states, especially among small schools. Though it is mandatory to report vaccination coverage, there is no mechanism (other than reminders) to enforce this, and as a result, many schools simply do not turn in this information, resulting in up to 10% of school records missing due to under-reporting or shielded because of size / privacy laws.

4.5.2 Case for High Resolution Data

This work makes a strong case for high resolution data. This represents the culmination of a four-year effort to collect publicly available school-level measles vaccination data. Despite the limitations among this large dataset and additional work needed to synthesize this, we have used this data to demonstrate that high-resolution data performs better in the model than lower-resolution data.

Our Washington example of spatial resolution analysis showed that the higher-resolution data showed more clustering than the aggregated district and county-level data. Moreover, unlike the aggregated data, the school-level clusters localized to the locations of the current measles outbreak. This was not the case with even the district-level data.

Our prediction model uses this same school-level data to predict counties at risk of any outbreak. Though the previous work on which this model builds did not report metrics such as PPV or sensitivity for direct comparison, we believe that 80-90% PPV and 30-40% sensitivity is a strong model, useful for public health decision-making. It appears the local-level data improves this model. With additional metrics on the previous models, we could make a more direct comparison.

4.5.3 Improvements to the Model

There are several areas where we would hope to improve our model in the future. In this paper, we predicted only county-level outbreak risk. We were limited by reported cases, which are reported on the county-level. This same limitation also required us to remove NYC (which is responsible for more than half of the US's current measles cases) from the analysis. With higher-resolution cases data, we could create a future model that could predict risk at a more local level.

Measles outbreaks may be affected by other factors not considered in our model: age distribution, travel patterns, local laws, social tendencies, previous outbreaks. We have included and improved upon the variables of previous models, but additional variables, especially population age distribution, may improve sensitivity.

We do expect measles dynamics to change as the US loses its non-endemic status. However, our current model is based on two current, ongoing outbreaks (Washington and NY) as well as two previous outbreaks (Minnesota and California), which help stabilize it. Each of these outbreaks behaved differently. Minnesota, for example, was almost entirely in preschool children, and we found very little predictive ability of our school clusters. With a diverse base of previous outbreaks in our historical outbreaks dataset, this should give our model more longevity for the changing dynamics of measles in the United States.

4.6 Conclusion

This project highlights the importance of high-resolution data and its usefulness to public health decision-making. We were able to use this high-resolution data to create a model with a PPV of over 0.9, which represents an improvement over previous attempts which did not use school-level data.[121,123] Over the course of our four years of data collection, the rate of data release has increased dramatically, and we expect more states to release high-resolution school coverage data in the coming months and years. As more states release this data, we can use this to better train our model for increased accuracy. We can also add additional states to the model in order to predict possible outbreaks in new states. These predictions can be used by public health decisionmakers to more efficiently allocate resources, decreasing the impact of a possible outbreaks or preventing outbreak entirely.

5.0 Concluding Remarks

This dissertation has achieved several broad aims. Using DHS surveys, we have helped public health practitioners by creating a method to detect areas of high risk for measles outbreaks, allowing for more targeted utilization of resources. We have performed the most comprehensive longitudinal analysis on US vaccination laws to date, an analysis of vital importance as states begin to revisit old laws to reduce future outbreak risk. In the third paper of this dissertation, we have created a large (soon-to-be) publicly available database of US high-resolution school vaccination coverage data and will make this data available to researchers for future projects. We have used this data to build on our previous work, combining the data with more comprehensive methodology to create a model predicting areas at high-risk for measles outbreaks.

Most importantly, we have demonstrated the importance of high-resolution data collection and dissemination, particularly for modeling vaccine-preventable diseases. Our approach has allowed us to, with greater confidence, find communities at risk of outbreaks.

The landscape of the US and abroad both suffer from understudied heterogeneity: heterogeneity of methods used to calculate vaccination coverage and heterogeneity of vaccination coverage. This heterogeneity reveals under-vaccinating communities. Even as the US reaches its Healthy People 2020 goal (the CVF of measles vaccination of 95%) and Africa approaches the goals of the Measles and Rubella Initiative, we have witnessed multiple large outbreaks just within the last year. Studying this heterogeneity will help inform vaccine policy going forward. This project improves access and usability to vaccination coverage data, previously only available in scattered websites, to a community of researchers. As such, we enable additional analysis – beyond those performed in this work – to be performed. The methods developed in this project may be proposed as a mechanism for vaccination coverage collection of all diseases going forward.

Appendix A Law Change Data Visualizations

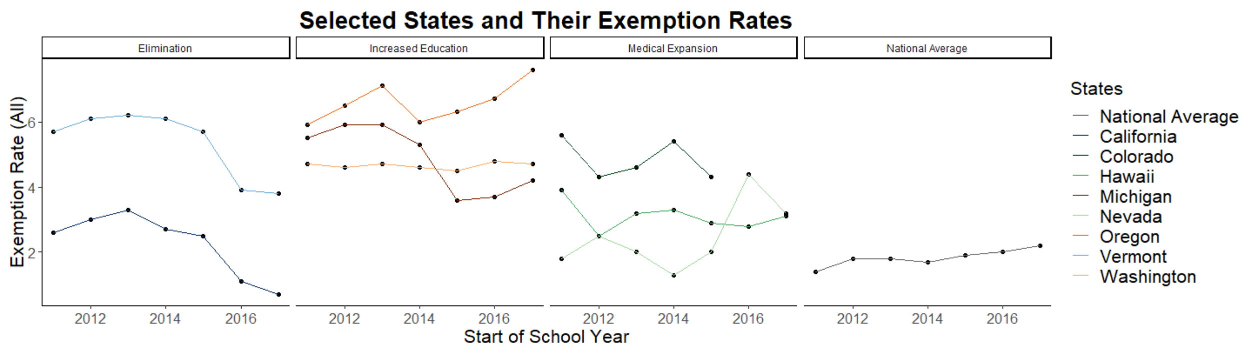

Figure 15: Selected states and their exemption rates

States are group by law changes type (elimination of exemptions, increased education requirements, and expansion of privileges to non-MD medical providers). While the national average steadily increased over our study period (far right panel), we saw more variability in our states, which had much higher exemption rates overall. The largest decrease is seen in states which eliminated exemption types.

Appendix B Types of Available US Data

There are many different datasets available in the US, but what is collected by health departments and the CDC for disease prevention is not often available to researchers. Because there is no one method for calculating vaccination coverage, and data availability may differ across the US, differences are hard to study. While the CDC collects state-wide data on vaccination coverage (Figure 1), data is not available for all states and states collect the data differently. The data reported by the CDC publicly is collected by the states. In most cases, states collect the data from schools, but only state-level data is reported nationally; this high-resolution (school- or county-level data) is unused, inaccessible data that needs to be collected by an independent source to be utilized.

The CDC also collects data via phone through the National Immunization Survey (NIS).[122] Because there is some level of inherent bias with phone surveys, it may not serve as an exact correlate for school-reported state-level data. The NIS has only been compared to local school-level data (as opposed to aggregate state-level data) once, where it was found to be a good proxy.[129] This study, however, was very small, both geographically (Chicago school district only) and sample size, and is over 10 years old. Without further study, it cannot be known if the NIS is a reliable measure for local school-level data, though it has been tested as a low-resolution measurement.

VaxView is the CDC's web interface for school vaccination surveys. Each year, the CDC disseminates surveys to each state, which in turn collect vaccination coverage data from schools. While this data is collected from schools (i.e., it exists usually at the school level), it is only available from the CDC at VaxView at the state level. VaxView has coverage data for major childhood vaccines and exemption data for most states from 2009-2010 and 2011 to present.

Most states perform a census, collecting data from every school. Some states perform a sample (including convenience samples), meaning data is not collected from every school. Most states collect this data through school records, but differences in state laws will result in differences in data collection.

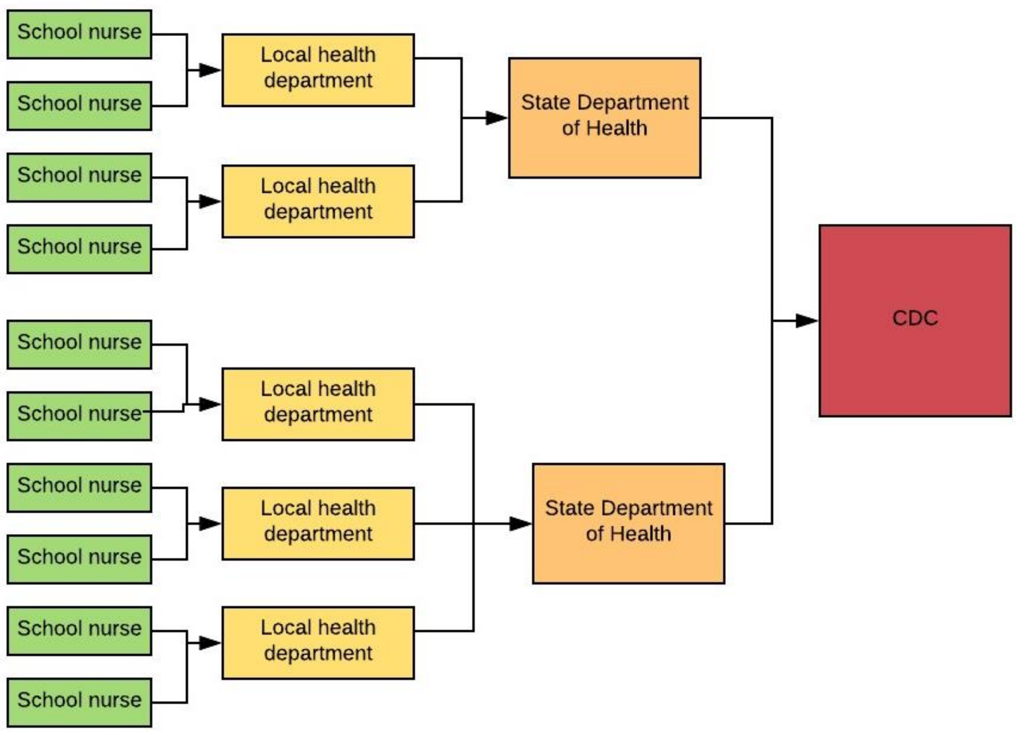

Figure 16: School vaccination data collection diagram

Some collect it through a different survey or at a different time than they do their higher resolution data. For example, in Pennsylvania, the state health department oversees the data sent to the CDC whereas Allegheny County Health Department performs a different, more comprehensive survey. In some years, some states do not collect or report this data at all.[9]

The CDC also collects exemption data from states. Like with vaccination coverage, this is subject to data availability and may be collected differently depending on state laws. Currently, exemption data is not collected for six states.[9] This data, depending on the state, may be collected for medical vs. nonmedical exemption, or all exemptions, or divided into the three exemption categories (medical, religious, philosophical).[9] As with coverage data, dependent on state laws, homeschooled children may or may not be included in this data; likewise, private school children. If there are large numbers of private school children in an area, it is possible this may bias the calculation of this data.

Appendix C Data Availability as of August 15, 2019

Table 11: Collected data as of August 2019

State	Resolution	Years	Access	Notes(most recently conducted survey, for CDC data)
Alabama	State	2009-10, 2011-2018	CDC VaxView[10]	Census (CDC)
Alaska	State	2013-2018	CDC VaxView	Stratified two-stage cluster sample (CDC
Arizona	School	2016-2018	State website[130]	
	State	2009-10, 2011-2018	CDC VaxView	Census
Arkansas	State	2009-10, 2011-2018	CDC VaxView	Census (public), voluntary response (private)
California	School	2000-2018	State website[52]; *Cleaned, geocoded (multiple years)*	Exclusion greater for earlier years
	State	2009-10, 2011-2018	CDC VaxView	Census
Colorado	School	2016-2017	State website[131]	
	State	2011-2018	CDC VaxView	Census
Connecticut	School	2017-2018	State website[132]	
	County	2013-2017	State website	
	State	2009-10, 2011-2018	CDC VaxView	Census
Delaware	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
District of Columbia	State	2014-2018	CDC VaxView	Census
Florida	County	2002-2019	State website[133]	Includes exemptions, temporary

Table 11 Continued

				Data IS available, collected at school level
	State		CDC VaxView	2009-10, 2011-2018
Georgia	Health district	2012-2018	State website[134]	Larger resolution than county
	State	2009-10, 2011-2018	CDC VaxView	Census
Hawaii	State	2015-2018	CDC VaxView	Stratified 2-stage cluster sample
Idaho	School	2015-2018	State website[135]; not accessible	Web app
	State	2009-10, 2011-2018	CDC VaxView	Census
Illinois	School	2003-2004	FOIA request[136]; Not accessible	One year only
	State	2009-10, 2011-2018	CDC VaxView	Census
Indiana	County	2014-5, 2017-8	State website[137]	
	State	2009-10, 2011-2018	CDC VaxView	Voluntary response
Iowa	School	2016-2017	FOIA request[138]; Not accessible	Schools >100 students; web app
	County	2011-2019	State website[139]	
	State	2009-10, 2011-2018	CDC VaxView	Census
Kansas	County	2009-2018	State website[140]	
	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
Kentucky	School	2016-8	State website[141]	Includes exemption data and provisional enrollment; websites says it is district data but clearly lists individual schools
	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
Louisiana	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample

Table 11 Continued

Maine	School	2014-2019	State website[142]; *Cleaned*	
	State	2009-10, 2011-2018	CDC VaxView	Census
Maryland		2009-10, 2011-2018	CDC VaxView	Census
Massachusetts	School	2013-2018	State website[128]; *Cleaned*	Additional resolutions / years available Childcare, college available Kindergartens < 30 excluded
	State	1975-2018	State website	
	State	2009-10, 2011-2018	CDC VaxView	Census
Michigan	School	2016-2018	State website[143]; *Cleaned*	
	State	2009-10, 2011-2018	CDC VaxView	Census
Minnesota	School	2012-2018	State website[144]; *Cleaned, geocoded*	Includes noncompliance
	State	2009-10, 2011-2018	CDC VaxView	Census
Mississippi	State	2009-10, 2011-2018	CDC VaxView	Census
Missouri	State	2009-10, 2011-2018	CDC VaxView	Census
Montana	State	2009-10, 2011-2018	CDC VaxView	Census
Nebraska	State	2009-10, 2011-2018	CDC VaxView	Census
Nevada	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
New Hampshire	State	2007-2018	State website[145]	
	State	2013-2018	CDC VaxView	Census
New Jersey	State	2012-2018	CDC VaxView	Census
New Mexico	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample

Table 11 Continued

New York	School	2012-2018	State website[146]; *Cleaned, geocoded*	Possible some public schools in NYC missing
	State	2009-10, 2011-2018	CDC VaxView	Census
North Carolina	State	2014-2018	CDC VaxView	Census
North Dakota	County	2013-2014	State data[147]	Relies on registry, not school entry data
	State	2009-10, 2011-2018	CDC VaxView	Census
Ohio	State	2009-10, 2011-2018	CDC VaxView	Census
Oklahoma	State	2009-10, 2011-2016, 2017-2018	CDC VaxView	Census (public), voluntary response (private)
Oregon	School	2018-2019	State website[148]	Not accessible
	County	2014-2015	State data	
	State	2009-10, 2011-2018	CDC VaxView	Census
Pennsylvania	School	2017-2018	State data release	
	County	2007-2018	State website[149]	
	State	2009-10, 2011-2018	CDC VaxView	Voluntary response
Rhode Island	State	2009-10, 2011-2018	CDC VaxView	Census
South Carolina	State	2009-10, 2011-2018	CDC VaxView	Stratified one-stage cluster sample
South Dakota	State	2009-10, 2011-2018	CDC VaxView	Census
Tennessee	State	2009-10, 2011-2018	CDC VaxView	Census
Texas	School / district	2015-2019		Private schools, public districts
	State	2009-10, 2011-2018	CDC VaxView	Census
Utah	Health district	2016-2018		Larger resolution than county
	State	2009-10, 2011-2018	CDC VaxView	Census

Table 11 Continued

Vermont	School	2015-2019	State website[150]; *Cleaned*	Also have childcare, university
	State	1990-2018	State website	
	State	2009-10, 2011-2018	CDC VaxView	Census
Virginia	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
Washington	School	2014-2017	State website[124]; *Cleaned, geocoded*	
	Districts	2012-2014	State website	
	State	2009-10, 2011-2018	CDC VaxView	Census
West Virginia	State	2009-10, 2011-2018	CDC VaxView	Voluntary response
Wisconsin	Schools	2014-2018	FOIA request[151]; Not accessible	Not accessible (web app) Exemption data for 2017-8
	State	2009-10, 2011-2018	CDC VaxView	Stratified 2-stage cluster sample
Wyoming	State	2012-13, 2014-6	CDC VaxView	

We see wide variability in this data, particularly with the states that release their data to the public (Figure 17).

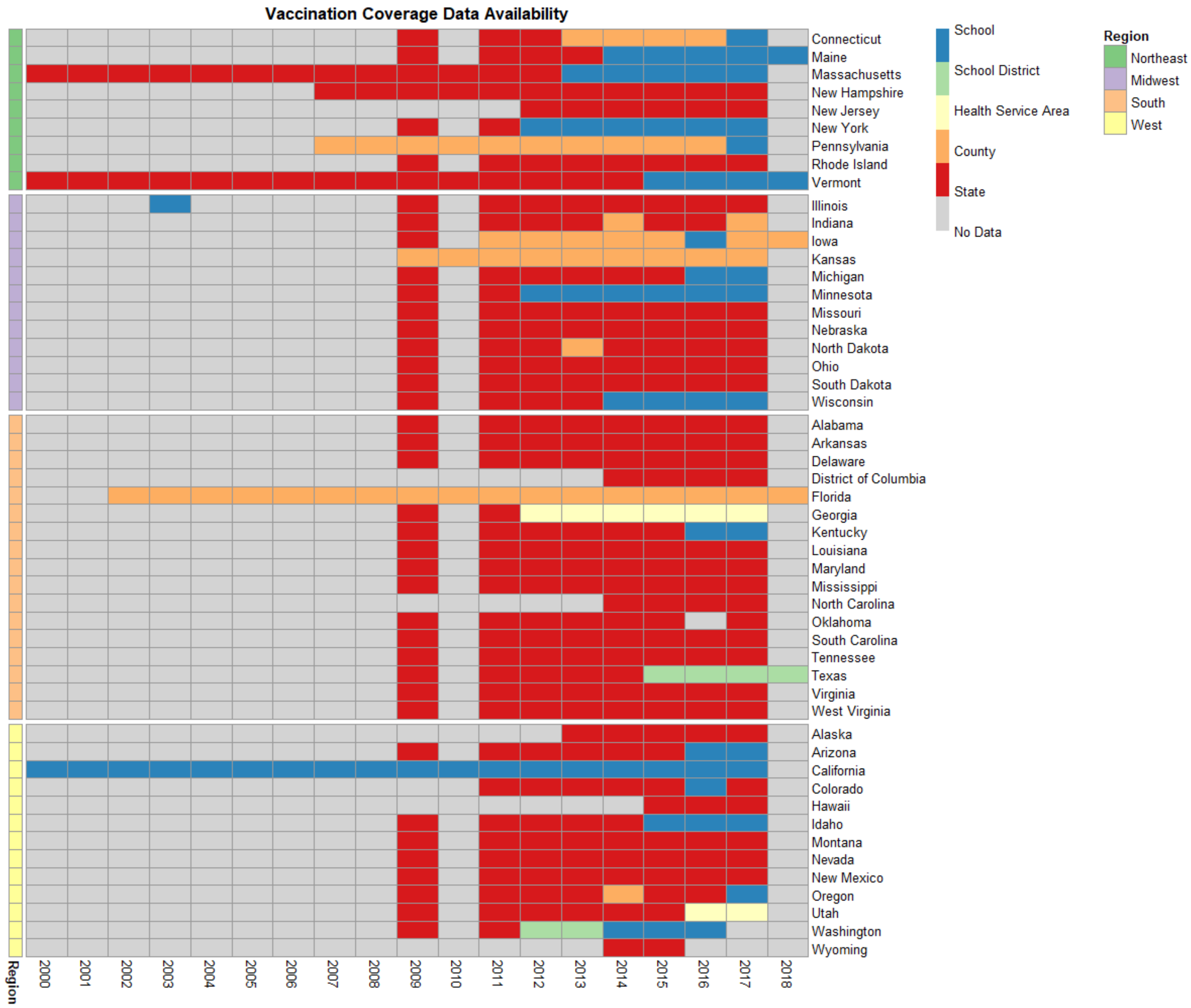

Figure 17: Heatmap of state vaccination data availability

In states that release their data, some (such as Colorado), may release only one year of data. Others (California and Massachusetts), may release as many years as they have available data. This is wide variety in both length of records release and resolution.

Appendix D Methods Visualizations

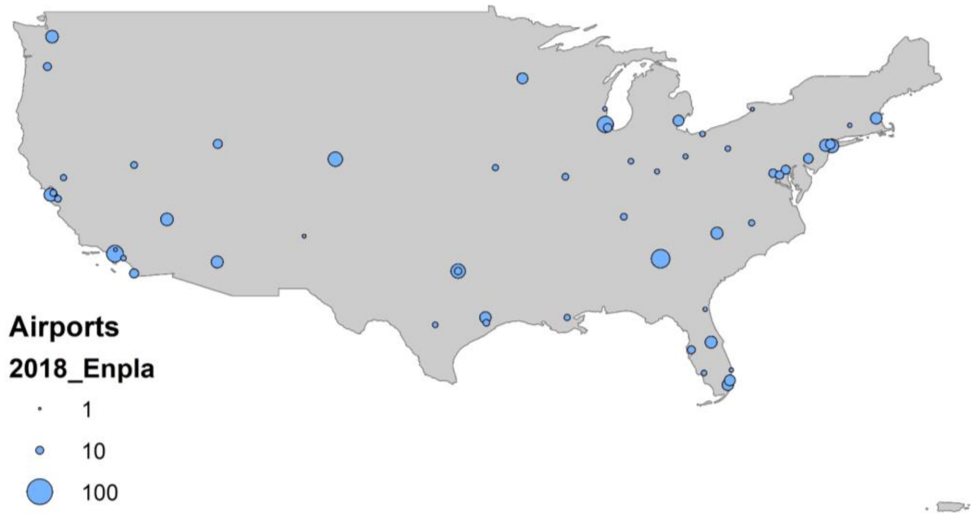

Figure 18: Airport Location and Size (in millions)

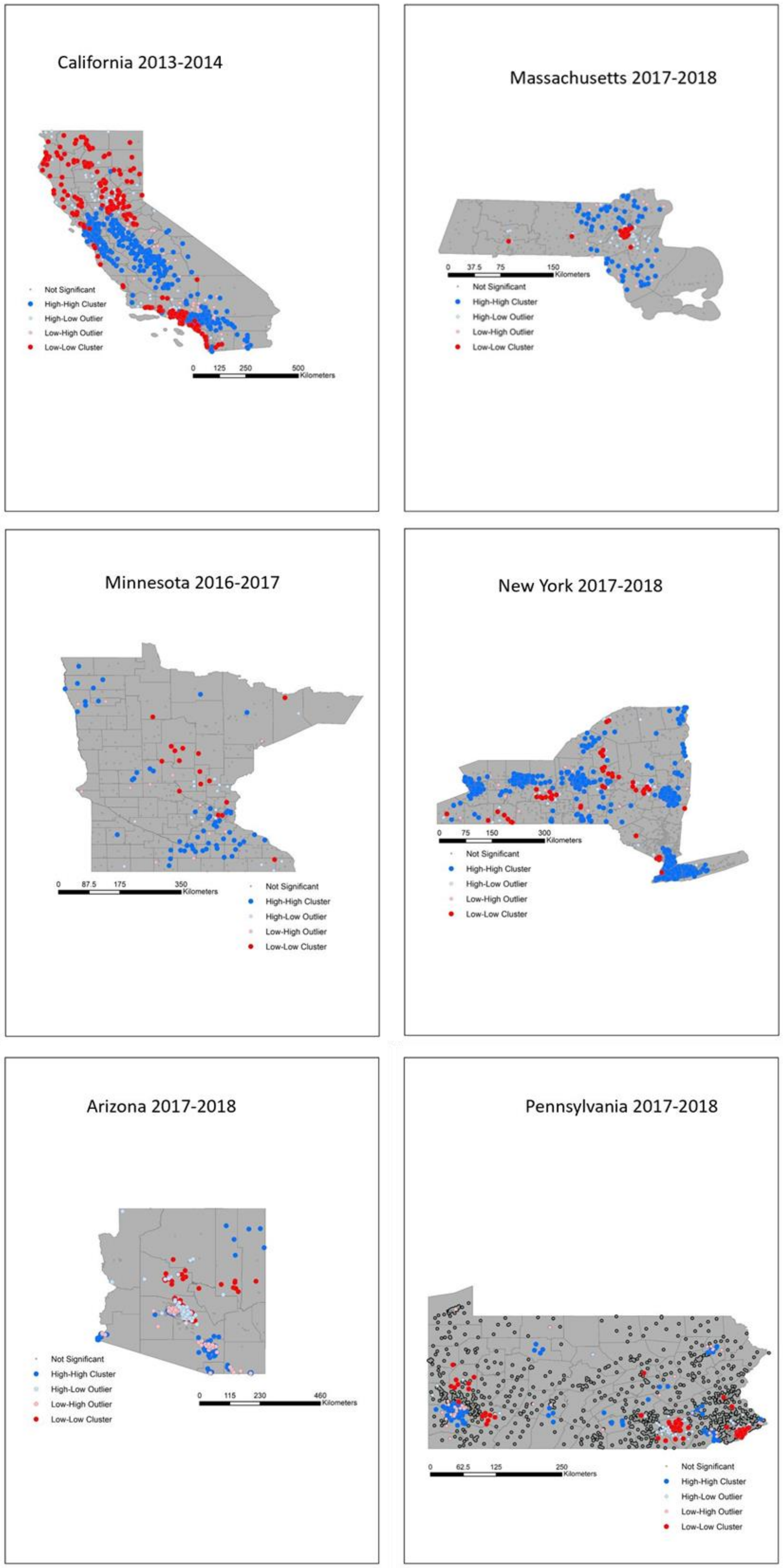

Figure 19: Cluster locations in model data

Low-low clusters are shown by red dots. We used number of LL clusters per county in our models.

Table 12: Model cutoff example

Cases Prediction	Outbreak Prediction	Cases Cutoff	Outbreak Cutoff	Prediction
2	0.6	1	0.5	Outbreak
2	0.6	3	0.5	No outbreak
2	0.6	1	0.7	No outbreak

In this example, the cases model (linear regression) predicted County X to have two cases of measles, and the outbreak model (logistic regression) predicted that County X had a 60% chance of a measles outbreak. If our model cutoffs are 1 for the cases model and 0.5 for the outbreak model, then the model will predict County X will experience a measles outbreak, since the cases prediction and the outbreak prediction were both higher than the cutoff values. However, if the we changed the cases cutoff to 3, and the outbreak cutoff remained at 0.5, then our model would predict no outbreak for County X, since now the cases prediction is below the cases cutoff. Similarly, if we adjust the outbreak cutoff to 0.7 while maintaining the cases cutoff at 1, our model would predict no outbreak for County X, since now the outbreak cutoff is above 0.6.

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