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The Associations between Mandatory Vaccination and Incidence of Measles and Pertussis and Vaccination Rates in Europe

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An abstract of
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Abstract

The Associations between Mandatory Vaccination and Incidence of Measles and Pertussis and Vaccination Rates in Europe

By Olivia Vaz

Background:

Vaccination legislation has played a major role in drastically decreasing the incidence of infectious diseases, including pertussis and measles, around the world. All countries in Europe recommend vaccination for their citizens but a subset of countries have mandatory vaccination requirements. These requirements may be important to the maintenance of high vaccination rates necessary to prevent disease outbreaks.

Objective: To determine if (1) the vaccination rates for pertussis-antigen vaccines and measles, mumps and rubella (MMR) vaccines are associated with mandatory vaccination and the availability of non-medical exemptions; (2) the incidence of pertussis and measles is associated with mandatory vaccination and the availability of non-medical exemptions; and (3) if the magnitude of the financial penalties faced by non-compliant parents is associated with the vaccination rates against pertussis and measles.

Methods:

We analyzed country-level vaccination rates and incidence rates from 2006 through 2015 for measles and 2006 through 2016 for pertussis, as well as the regulations for vaccination, non-medical exemptions, and penalties faced by parents who fail to comply with regulations, for 29 European countries.

Results:

Of the 29 countries studied, seven had mandatory vaccination, and of those seven, two allowed non-medical exemptions. There was no significant association between mandatory vaccination or non-medical exemption availability and vaccination rates or incidence or measles and pertussis. For every 100 € increase in the maximum possible penalty faced by non-compliant parents, rates for pertussis vaccinations were 0.15% higher (95% CI: 0.06, 0.23; p-value = 0.0007) and rates for measles vaccination were also 0.15% higher (95% CI: 0.06, 0.25; p-value = 0.0009).

Conclusions:

Neither mandatory vaccination nor non-medical exemption availability was statistically significantly associated with increased vaccination rates or decreased incidence rates, though the magnitude of the penalty face by parents was associated with an increase in vaccination coverage.

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Background

Measles

Characteristics of Measles

Measles is one of the most contagious diseases and for many years was considered a common childhood disease. Prior to the introduction of an effective vaccination, more than 90% of individuals were infected with measles before the age of 20, with an estimated 100 million cases globally each year. (1, 2)

The disease has a latent period of 10 to 14 days and goes through multiple stages of infection. Measles symptoms start as a nondescript fever, cough, runny nose, and conjunctivitis. The most identifiable feature of measles, the skin irritation, appears about three days after the initial mild illness and spreads from the arms and torso to the lower extremities over the subsequent days. This rash is accompanied by a sharp increase in the severity of fever, often reaching as high as 104 degrees F. (2, 3)

One of the qualities that makes measles so easily spread is that an individual can be contagious before the appearance of the characteristic rash. An infected individual can spread the disease for days before the appearance of the rash and a measles diagnosis. Additionally, they can then continue to infect others up to four days after the disappearance of the rash, when many would assume they have fully recovered from the illness. (4) Transmission can occur by droplet spread, direct contact with respiratory secretions of infected individuals, and is some cases contaminated fomites. (2)

Measles Vaccination

Vaccination against measles is commonly combined with mumps and rubella in the Measles, Mumps and Rubella (MMR) vaccine. The vaccination is extremely

effective against measles and is 93% effective after just a single dose. Most recommendations include two doses of MMR. The first dose is frequently recommended later than many childhood vaccines because of antibodies passed from mother to infant that can provide protection against the diseases during the early stages of life and cause the vaccine to be less effective if given at too young an age. (5, 6)

It is generally recommended that children receive two doses of the MMR vaccination, starting with an initial dose around 12 to 15 months of age and a second dose around 4 to 6 years of age, though the timing of vaccination can vary by region depending on whether or not there is ongoing transmission. (5, 7) 5-15% of nonimmune individuals will develop malaise and a fever about a week after vaccination. A rash, inflammation of the nasal cavity, and a mild cough may also occur. Infrequently, individuals will experience febrile seizures, but this is most common in children with a history of febrile seizures or a family history of seizures.

Vaccination should be continuous throughout the year because the likelihood of an outbreak of measles is directly related to the proportion of the population that is susceptible. As the number of individuals who are susceptible to measles increases, the more transmission can occur. Follow-up campaigns can be used to prevent the number of susceptible children from reaching the threshold where outbreaks will increase in intensity and frequency due to a lack of herd immunity. (2)

Measles in Europe

The availability of vaccines has had a drastic impact on rates of vaccine preventable diseases across the world. In the World Health Organization's (WHO) European region, the number of measles cases has decreased from over 250 million cases

in 1980 to a record low of 5,273 cases in 2016. However, that incidence has recently rebounded with 21,315 cases and 35 deaths in 2017. (8, 9) Many sporadic outbreaks continue to occur, primarily in children, teenagers, and young adults who are not fully vaccinated. (10) The American Centers for Disease Control and Prevention currently have Level 1 travel watches in effect for Americans considering visiting countries such as Romania, Italy, England and Greece because of these outbreaks. (11)

Pertussis

Characteristics of Pertussis

Pertussis is a highly contagious bacterial disease caused by *Bordetella Pertussis* or *Bordetella Parapertussis*, which is found in the mouth, nose, and throat of infected individuals. A disease of the respiratory tract, pertussis causes symptoms approximately 7 to 10 days after infection. Initially, these symptoms include sneezing, a runny nose, a mild cough, and mild fever. The cough then increases in severity and intensity, resulting in episodes of rapid coughs followed by a high-pitched whoop, hence the name "whooping cough". (12)

For infants and the immunocompromised pertussis can be a very severe, if not deadly, disease. About 50% of infants who contract pertussis require hospitalization and about 1 in 100 of infants under the age of one who contract the disease die because of their illness and resulting complications. (13) These complications can include pulmonary hypertension, pneumonia, seizures, encephalopathy, hernias, and atelectasis (collapse of the lung). (2)

Respiratory isolation is recommended for patients diagnosed with pertussis, especially from young children and immunocompromised individuals, until they have

received antibiotics for at least five days. If the individual does not receive antibiotics, they should be isolated for three weeks after the start of the cough or until the end of the coughing stage, whichever comes first. Treatment can include erythromycin or clarithromycin to shorten the period of communicability and is most effective if prescribed before the onset of the characteristic whooping cough. (2)

Pertussis Vaccination

In Europe, the vaccine for pertussis is most commonly given in combination as the diphtheria, tetanus, and pertussis (DTaP or DTwP) vaccination for young children, as well as in a pentavalent vaccine, which protects against pertussis, diphtheria, tetanus, polio, and Hib disease. Some countries, such as the United Kingdom, have started to vaccinate using a 6-in-1 vaccine that also includes protection against hepatitis B. (14)

Between two and twelve months of age, infants receive a primary course of three doses of a pertussis-antigen containing vaccine, commonly DTap or DTwP, which stand for acellular pertussis and whole-cell pertussis, respectively. Subsequent doses are recommended between 11–24 months of age and between three and six years of age.(12)

The vaccinations used have proven to be very effective at preventing the incidence of whooping cough. For example, about 98% of children who receive the 5 recommended doses of DTaP on schedule are fully protected against pertussis within a year of the last vaccination. About 70% of children who are fully protected against whooping cough will still be protected 5 years later.(15) Common reactions to the DTaP vaccination are redness and swelling of the location of the injection, fever, fatigue, loss of appetite, or vomiting. (13)

The only contraindication to vaccination is an anaphylactic reaction to a previous dose or a component of the vaccine. Vaccination may be delayed to allow for diagnosis of young infants with suspected developing and progressive neurological diseases in order to prevent confusion about the cause of the disease. (2)

Pertussis in Europe

Unfortunately, the incidence of pertussis has been on the rise since the end of a sharp decrease in incidence that occurred for a brief period after the introduction of pertussis vaccinations into national vaccination schedules 50 years ago. While this trend has occurred all over the world, in Europe this trend has been ongoing despite continued high vaccination coverage. One important factor, which has likely contributed to this observed increase in cases, is improved surveillance of pertussis. Additionally, more effective diagnosis guidelines for the disease in adults and adolescents have led to cases that would have previously not been diagnosed as pertussis are now accurately reported. (16)

Evolution of Vaccination Mandates in Europe

The Vaccination Act of 1853 in the UK was one of the first pieces of vaccination legislation, requiring all children born after August 1, 1853 to be vaccinated against smallpox within three months of birth. In less than two decades, two-thirds of infants were vaccinated and rates of the disease dropped. (17) For many other countries in Europe Later, including Poland, introduction of mandatory vaccination began under the former Soviet Union. (1) Coercive immunization campaigns were undertaken by Soviet leadership as a demonstration of the success of their administration and a display the benefits of extreme state control in the public sector. (18)

Poland, like many European countries, is experiencing an increase in vaccination refusals and vaccine hesitancy. In 2016, Poland saw 23,147 vaccination refusals, a more than four-fold increase from the 4,893 refusals recorded in 2007. (19) Many countries in Europe provide free vaccination as a part of nationalized healthcare. (20-22) However, according to the WHO, between 2000 and 2010, almost 5 million individuals in the European Union between the ages of 2 and 12 years of age had not received the MMR vaccination. (23) Paradoxically, individuals who have never seen or experienced the diseases these vaccinations are less likely to know and accept the severity of the disease and thus see vaccination safety as the primary risk when considering vaccination for their children. (23) Though the success of vaccinations may increase the difficulty in convincing parents to vaccinate their children, it should also encourage them to do so.

As countries see decreases in vaccination, the ministries of health of multiple European nations are considering changing their vaccination requirements to make certain vaccinations mandatory. France and Italy recently changed their vaccination laws to make previously recommended childhood vaccinations mandatory, pertussis and measles among them. (24, 25)

Impact of Mandatory Vaccination in the United States

Lessons learned from policies in place elsewhere can inform these policy changes and how to best implement and enforce them. In the United States, mandatory vaccination has been successfully implemented at daycare or school entry, requiring children to either be vaccinated or have the proper exemptions that are available in their home state. These laws establishing vaccination requirements are on the state-level and can differ between states. States also set the guidelines for exemption requirements and

establish the methods of enforcement for requirements and exemptions. (26) Following an increase in measles outbreaks, including an infamous outbreak that originated in Disneyland in Anaheim, CA, several states have changed their legislation or are debating doing so. In 2015, California removed all non-medical vaccination exemptions and Vermont added restrictions to religious and philosophical exemptions that parents could obtain. (27) While the results of these legislative changes has yet to be fully observed, changes in California are significant because of the size of the state, both geographically and population-wise, and will guide implementation of similar laws in other states. Regardless of whether or not these policy changes are successfully implemented in California, the results can provide guidance to other countries as they change their policies.

Future Control and Elimination

One of the goals of control of infectious diseases is complete control of the disease, resulting in elimination of transmission of that disease. Eliminating measles, as per the Europe Vaccine Action Plan (EVAP) of the World Health Organization (WHO), is a goal of most signing members, but this declaration has not translated into decreased incidence of measles. This is in part due to inconsistent regional and local implementation of vaccination. Political, financial, and operational infrastructures differ from country to country and these differences shape the response of the region, not the goals of the nation as a whole.(28)

Another major obstacle that is also dealt with as a part of EVAP is a lack of guidance in monitoring implementation of vaccination campaigns. While this issue is being dealt with by EVAP, the European Centers for Disease Prevention and Control, and

the WHO, lack of cohesive monitoring and methods can prevent accurate comparisons to be drawn between countries and stop true results from guiding interventions moving forward. (28, 29)

In the face of rising measles incidence the WHO and its Member States continue to pledge resources and efforts toward the elimination of the disease.(10) The European Regional Verification Commission for Measles and Rubella Elimination (RVC) was established in 2011 in order to evaluate the progress toward measles elimination in Europe and to study why efforts may or may not be successful. In 2014, the evaluation process that countries had to submit to was modified to better study efforts on a country-level instead of by region. This is to address the possible inconsistencies in law, implementation, and politics that can arise across borders and hinder public health efforts. Upon review in 2015, it was discovered that 24 countries had eliminated measles and a further 13 had interrupted endemic measles transmission. (10)

The control of pertussis incidence, unlike that of measles, will rely on continued research for an improved vaccine. While the pertussis vaccine is relatively effective immunity does wane after a period of time. Reinfection of previously infected or vaccinated individuals has been observed, and underscored major pertussis outbreaks in 2005, 2010, and 2012. (30, 31). Without a vaccine that conveys immunity for a greater period of time, elimination of pertussis would require decennial vaccination in the entire adult population, which is unlikely as current global adult vaccination rates are very low. (30, 32) In order to effectively control pertussis in the future, other methods of research and subsequent outreach may be necessary to increase vaccination rates in unprotected populations. EVAP include an objective to improve peoples' understanding of the value

of vaccinations through communications plans. These plans need to include social, cultural, and behavioral determinants and therefore research must be performed in order to best inform public health officials on how to tailor their interventions for their target populations. (28)

Introduction

Vaccination is one of the most useful tools of the public health community in preventing infectious disease. The availability of vaccines has had a drastic impact on rates of vaccine preventable diseases across the world. In the World Health Organization's (WHO) European region, the number of measles cases has decreased from over 250,000,000 cases in 1980 to a record low of 5273 cases in 2016. However, it recently rebounded with 21,315 cases and 35 deaths in 2017. (8, 9) Various immunization policies, including immunization requirements, have been an effective procedure in many parts of the world, drastically lowering the rate of vaccine-preventable disease incidence (33, 34). The recent resurgence of cases in Europe merits a reexamination of immunization requirements. All countries in Europe at least recommend a vaccination schedule, including vaccinations against measles and pertussis, but vaccination policies vary by country. (5) Many European countries, like the Netherlands, provide free vaccination services as a part of their National Immunization Program.(35) Others, like Bulgaria, have legislation in place that mandate vaccination (36).

In the United States, school vaccine mandates have been very effective in raising the rate of vaccination and lowering the incidence of vaccine-preventable diseases (33, 37). However, nearly all states in the US have policies in place that allow for religious or other non-medical exemptions to vaccine mandates. The ease of obtaining these exemptions has been linked to outbreaks of vaccine preventable diseases like measles.(38) Similarly in Europe, even among those countries that have legislation in place mandating vaccinations there is a spectrum of ease of attainment of exemptions for

non-medical purposes, as well as of the severity of penalties associated with refusing to vaccinate a child. For example, in Bulgaria, parents can refuse to vaccinate their children but the responsibility of declaring their refusal to both their general practitioner as well as the Regional Health Inspection belongs to the parents. On the other hand, Poland does not offer any alternative to vaccination and the only exemption that can be obtained by parents is a medical exemption. (39)

As has been shown at the state level in the United States, it is possible for outbreaks to still occur when a vaccine mandate is in place. (40, 41) Countries that mandate vaccination but also allow non-medical exemptions, such as Bulgaria, may experience lower rates of vaccination compared to countries that do not allow these exemptions. This in turn could result in higher incidence rates as herd immunity thresholds are not met and more individuals are susceptible to the disease. Mandatory vaccination may be important for pertussis and measles, both diseases that are highly transmissible and extremely dangerous for infants who are not old enough to receive the vaccine. (42) Although the associations among vaccine mandates, immunization rates and disease incidence has not been shown in the European context, countries are recognizing the need for policy change. In July 2017, France passed legislation to require children be vaccinated against eight additional diseases, among them measles and pertussis, also known as 'whooping cough'. Prior to this law, France had only required vaccination against diphtheria, polio, and tetanus. (43) As countries begin to change their laws to increasingly stricter regulations, it becomes increasingly necessary to study the actual effects of these laws.

The primary objectives of this study were to determine if: (1) the vaccination rates for pertussis-antigen vaccines and measles, mumps and rubella (MMR) vaccines are associated with mandatory vaccination and the availability of non-medical exemptions; (2) the incidence of pertussis and measles is associated with mandatory vaccination and the availability of non-medical exemptions; and (3) if the magnitude of the financial penalties faced by non-compliant parents is associated with the vaccination rates against pertussis and measles.

Methods

Data Collection Methods

Analyses were conducted using publicly available data on vaccine mandate policies and vaccine rates. The countries studied were 29 countries analyzed in the Vaccine European New Integrated Collaboration Effort (VENICE), which included the 27 Member States of the European Union (at the time of the study), as well as Iceland and Norway. (44) Vaccination rates were collected for the years 2006 to 2015 for measles and 2006 through 2016 for pertussis for these countries from the Global Health Observatory (GHO), a World Health Organization collection of health-related statistics for its 194 member states. (45) This country-specific information was compiled from reports by the health ministries or departments of WHO Member States and was reported by the WHO on a global level. Information on whether vaccination was mandatory was obtained from the VENICE 2010 survey, which indicated the 2010 status of vaccination requirements. (44) This early information was collected via survey, which was sent to national VENICE gatekeepers from the 29 participating countries. These gatekeepers were asked the requirements for their country, and were given a definition of "mandatory" and "recommended" in order to avoid misinterpretation. (44) Any changes in country-level vaccine mandate policies between 2010 and 2015 were confirmed using the Vaccine Scheduler, a tool maintained by the European Centre for Disease Prevention and Control which presented the vaccine schedules of all countries of the European Union.(5) A review of health ministry websites was conducted to collect data on the availability of non-medical vaccination exemptions.

The amount of the financial penalty faced by parents who fail to comply with their home country's vaccination regulations was also collected from health ministry websites and legislation. These financial penalties were transformed for accurate comparison among countries using Purchasing Power Parities (PPPs) on the actual individual consumption scale, calculated and provided by Eurostat. (46) PPPs are a measure of how the units of national currency of a country compare in value to a standardized unit of currency and market, which Eurostat set as one euro in the EU. These PPPs were calculated and aggregated using a set of annual prices for certain products and the breakdown of expenditure on Gross Domestic Product (GDP) provided by participating countries. (46)

Vaccination Rates and Associations with Vaccine Legislation

A linear regression model was fit to estimate the association between the vaccination rates and mandatory vaccination policies of our countries of interest. We used an autoregressive correlation structure to account for within-country correlation over time. We adjusted for demographic variables that have previously been shown to be associated with vaccine uptake or pertussis incidence including the percentage of the population living in urban areas, the proportion of adults aged 24-65 in three education categories and the GINI coefficient of the country, which is a statistical dispersion which is a commonly used measure of inequality as it represents the wealth distribution of the citizens of a nation. (47) Also adjusted for was the Universal Health Care service index, which combines 16 health service coverage indicators for reproductive, maternal and child health, infectious diseases, non-communicable diseases, and service capacity and access into a single metric.(48) Finally, we controlled for the age distribution of each

country using the percentage of the population that is under the age of 14 as well as the median age of the country's residents. The resulting regression coefficients comparing the presence of a mandatory vaccination policy, the presence of a non-medical vaccination exemption, and the presence of a financial penalty were interpreted as the percentage difference associated with each of these binary conditions.

Disease Incidence and Associations with Policy

We analyzed disease incidence for both measles and pertussis and the association between disease incidence and vaccine mandate legislations for the years 2006-2015 (for measles) and 2006-2016 (for pertussis) for the countries of interest. Both measles and pertussis case counts were acquired from the WHO's Centralized Information System for Infectious Diseases. This system used advanced technology to collect, analyze and present data on infectious diseases in the WHO European Region. (49) The population estimates used were from Eurostat, the statistical office of the European Union.(50) These population statistics are provided by member states from the country's statistical authorities, and were consolidated by Eurostat, which also ensured that methodology was harmonized across countries to ensure comparable data. (51) We used an autoregressive correlation structure to account for within-country correlation of the incidence of the disease over time.

To estimate the rates of pertussis and measles and associations with country mandates, a negative binomial model was fit with the assumption that the number of cases for each year was distributed as a Poisson random variable with mean μ. The offset termed used was the population of the country. We adjusted for demographic variables that have been previously shown to be associated with vaccine uptake. In examining the

measles incidence associations, the models did not converge while fully controlling for all covariates due to collinearity, so the models were run controlling for the variables that were not problematic (Table 2). In a sensitivity analysis, the pertussis models were run with the same combination of covariates in order to see the possible effects these missing variables might have on the associations between vaccine regulations and incidence of the disease. Incidence Rate Ratios (IRRs) were derived from the models as a measure of association between incidence and the vaccination requirements of the country. The IRR is interpreted as a multiplicative difference in the incidence of the disease associated with the presence of vaccine mandates in a country. Associations were considered not statistically significant with a p-value ≥ 0.05 or a 95% confidence interval (95% CI) containing 0 or 1 for linear regressions and incidence rate ratios, respectively. Analysis was conducted using SAS 9.4, RStudio Version 1.0.153, and R Version 3.3.3.

Results

Of the 29 European countries reviewed, seven countries mandated vaccination (Figure 1). (19, 22, 39, 52-55) Among these countries, only the Czech Republic and Latvia offered processes to acquire a nonmedical vaccination exemption. (52, 53) These processes required parents to either receive information about vaccination or provide a written refusal of the vaccination as well as discuss the decision with their child's healthcare provider.(52, 53) If parents failed to meet the requirements of their country's regulations and requirements, they faced a financial penalty. Of the seven countries that had mandatory vaccination legislation in place, Latvia was the only country that did not have a financial penalty for failing to vaccinate and not going through the proper routes to obtain a nonmedical exemption. (53)

When adjusted to the euro in the European Union, the country with the highest possible financial penalty was Hungary, where in 2016 parents could face a financial penalty up to 2258€ if they fail to follow vaccination requirements. (54) The country with the lowest financial penalty was Bulgaria, where parents could be fined a maximum of 236€ in 2016 if they failed to comply with vaccination requirements (Figure 1). (54)

Vaccination Rates and Associations with Vaccine Legislation

Countries with mandatory vaccination had a 2.2% higher vaccination rate for pertussis and 3.73% higher rate for measles vaccination when compared to countries that did not have mandatory vaccination, but these associations crossed the null (pertussis: percent difference = 2.2 (95% CI: -1.6, 6.1); measles: 3.73 (95% CI: -0.2, 7.6)). Countries that that offered non-medical vaccine exemptions also experienced insignificantly elevated rates of vaccination, with 0.3% (95% CI: -2.7, 3.2) higher rates of

pertussis-antigen vaccination and 2.1% (95% CI: -1.3, 5.6) higher rates of MMR vaccination.

The presence of a financial penalty for non-compliance with vaccination regulations was insignificantly associated with a 2.6% (95% CI: -1.2, 6.4) higher rate of pertussis-antigen vaccinations and a 3.3% (95% CI: -0.6, 7.2) higher rate of the MMR vaccination. It was found that for every 100 € increase in the maximum possible penalty faced by non-compliant parents, rates for pertussis-antigen vaccinations were 0.15% higher (95% CI: 0.06, 0.23; p-value = 0.0007) and rates for measles vaccination were also 0.15% higher (95% CI: 0.06, 0.25; p-value = 0.0009).

Disease Incidence and Associations with Policy

The mean annual incidence of pertussis and measles by country is presented in Figures 1a and 1b. Norway had the highest incidence of pertussis at 73.6 cases per 100,000 individuals per year. For measles, Bulgaria had the highest incidence at 32.9 cases per 100,000 individuals per year. Pertussis incidence in countries that had mandatory vaccination was 38% higher than in countries that did not have mandatory vaccination, though this result crossed the null (aIRR = 1.38; 95% CI: 0.32, 5.83). Countries with mandatory vaccination policies and non-medical exemptions experienced incidence rates of about three quarters of that of countries without mandatory vaccination (aIRR = 0.76, 95% CI, 0.0.11, 5.19) while countries that offered no non-medical exemptions to their mandatory vaccinations had statistically insignificant incidence rates of less than half that of countries without mandatory vaccination policies (aIRR = 1.70; 95% CI, 0.41, 7.11).

Countries with mandatory vaccination experienced insignificantly lower incidence rates of measles compared to countries without mandatory vaccination (aIRR = 1.78; 95% CI: 0.19, 16.64). The presence of a financial penalty was insignificantly associated with lower incidence rates of measles (aIRR = 1.07; 95% CI: 0.30, 3.74). The option of a nonmedical vaccine exemption in countries with mandatory vaccination was associated with lower incidence of the disease (aIRR= 0.13; 95% CI: 0.04, 0.35). Although there was a significant association between non-medical exemptions and incidence rates in this model, not all necessary covariates were controlled for due to collinearity issues. Finally, countries with mandatory vaccination and no non-medical vaccine exemptions had an insignificantly higher incidence of measles when compared to countries with no mandatory vaccination (aIRR = 2.61; 95% CI, 0.35, 19.22).

Because of the complications due to collinearity within the measles incidence models, the associations between the incidence rates and variables of interest were not adjusted for all covariates. A sensitivity analysis was run with the pertussis models with the same covariates adjusted in order to assess the possible effects these covariates could have on the associations between disease incidence and mandatory vaccination laws, non-medical exemptions, and the presence of financial penalties for non-compliance (Table 2). This analysis proved that neglecting to control for these variables could result in crossover bias or bias toward the null. Therefore, the associations of measles incidence might not be accurate in magnitude or direction.

Discussion

Although the presence of a financial penalty was not significantly associated with vaccination rates, the amount of the financial penalty faced by non-compliant parents was associated with higher vaccination rates. Every 100€ increase in the maximum penalty parents could face for failing to comply with their country's vaccination regulations was associated with a 0.15% higher vaccination rate for both measles and pertussis. Mandatory vaccination was not shown to be associated with higher vaccination rates for either pertussis or measles in countries studied. It was also not shown to be associated with lower incidence of the diseases. Higher vaccination rates were not associated with the presence of financial penalties for parents to who to comply with vaccination regulations. Although there was a significant association between mandatory vaccination policies for measles and incidence of the disease, these results are unreliable due to not being able to control for all necessary covariates. These results reflect the preliminary analysis and merit future examination.

Some European countries are considering making vaccinations mandatory, including implementing financial penalties for noncompliance, even if they do not have a history of such legislation. Italy and France have both made childhood vaccinations mandatory since the beginning of 2017. (43, 56) Yet, as demonstrated by this research, for diseases as contagious as measles or pertussis, compulsory vaccination might not be enough to prevent the outbreak of disease. The WHO recently released a *Guide to tailoring immunization programs (TIP)*, offering a process through which to identify obstacles and motivators to immunization in areas of low vaccination rates and how to design interventions tailored to meet those factors. (57) Financial penalties could be an

effective measure in a comprehensive vaccination program, though they will need to accompany other measures to reach those who refuse to vaccinate. Financial penalties also might not target the largest contributors to under-vaccination, who would need to be targeted in order to reach the necessary vaccination coverage to prevent the spread of these diseases. In places like Australia, individuals who objected to vaccination were about twice as likely to reside in areas of higher socioeconomic resources. (58)

An obstacle faced by vaccination efforts that may not be fully addressed by vaccine mandates is vaccine hesitancy. In the United States, where vaccine mandates have been in place since the 1960s as a result of measles outbreaks, vaccine hesitancy plays a large role in rates of vaccine acceptance even for mandated vaccines.(59) In European populations, vaccine safety has been shown to be the primary area of concern when examining the attitudes about vaccines, followed by the perception of the risk of contracting a vaccine-preventable disease, the perceived severity of these diseases, and beliefs that vaccines did not work. (60) Mandatory vaccination does not confront the root of vaccine hesitancy, but instead simply deals with the results of it.

There were several limitations to this study that should be considered. First, there was reliance on reporting by physicians and officials in each country. The collection of case numbers relied on individuals seeking medical care in case of disease, on their physician reporting the case to the local health authority, on these local health authorities properly reporting these cases to the national health ministry or other entity who would eventually report to the WHO or ECDC. Fortunately, organizations like the WHO and CDC offer structure and methodologies for individual countries to use to best collect a comparable data set. (29, 61)

Additionally, the effectiveness of mandatory vaccination relies on multiple factors, including the fulfillment of roles physicians play in educating parents and ensuring proper health procedure is followed (62, 63). The availability of non-medical vaccination exemptions as well as the magnitude of the financial penalties faced by those who fail to comply were measured using information that might not have reflected the entire time period studied. We were not able to find any indications that any countries changed their mandatory vaccinations from 2006-2016, using resources from 2006 and 2018. Italy and France changed their mandatory vaccination policies, effective in 2017 and 2018, respectively.

As countries change their policies, examining the changes in the vaccination landscape could be crucial in understanding how these mandates work within today's society and how to best implement them to achieve high vaccination rates. As this research demonstrates, it is not enough to merely require vaccination, but to also meet the multiple obstacles that prevent full vaccination coverage.

Conclusions

In enacting mandatory vaccinations, sanctioning financial penalties for failing to vaccinate, and limiting non-medical exemptions, European nations must also be willing to accompany those mandates with additional measures to negate the obstacles necessary to eliminate measles and pertussis. Our findings support the need for a multi-tiered system of interventions to ensure the maintenance of the necessary high vaccination rates, as have been shown to be effective in the United States. (64)

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Tables

Table 1. **Association of Compulsory Vaccination, the Availability of Non-Medical Exemption Option and the Penalty of Non-compliance With Vaccination Rates Against Measles (2006-2015) and against Pertussis (2006-2016)***

	No. of Country-Years	Difference in Vaccination Rate in Percentage (95% Confidence Interval)	p-value
Measles			
Mandatory Vaccination	287	3.73 (-0.2, 7.6)	0.06
Non-medical Exemption	287	2.1 (-1.3, 5.6)	0.23
Financial Penalty for Non-compliance (per 100€)	287	0.15 (0.06, 0.25)	0.0009
Pertussis			
Mandatory Vaccination	316	2.21(-1.6, 6.1)	0.27
Non-medical Exemption	316	0.3 (-2.7, 3.2)	0.85
Financial Penalty for Non-compliance (per 100€)	316	0.15 (0.06, 0.23)	0.0006

* All models are adjusted for GDP per Capita, GINI, Urban Population, Universal Healthcare Coverage, Median Age, Percent of the population under 14 years of age, and education levels (3 categories)

Table 2. **Association of Compulsory Vaccination, the Availability of Non-Medical Exemption Option and the Penalty of Non-compliance With the Incidence of Measles From 2006 Through 2015 and of Pertussis From 2006-2016**

	No. of Countries	Pertussis Incidence Rate Ratio (95% Confidence Interval)	Sensitivity Analysis	
			Pertussis Incidence Rate Ratio (95% Confidence Interval)	Measles Incidence Rate Ratio (95% Confidence Interval)
Mandatory Vaccination				
No Mandatory Vaccination	22	Reference	Reference	Reference
Mandatory Vaccination	7	1.38 (0.32, 5.83)‡	1.16 (0.28, 4.77)†	1.78 (0.19, 16.64)†
Nonmedical Vaccination Exemptions				
No Mandatory Vaccination	22	Reference	Reference	Reference
Mandatory Vaccination with Exemptions	2	0.76 (0.11, 5.19)	1.27 (0.36, 4.41)*	0.13 (0.05, 0.35)*
Mandatory Vaccination with No Exemptions	5	1.70 (0.41, 7.11)	1.23 (0.29, 5.25) ‖	2.61 (0.35, 19.22) ‖
Monetary Fine				
No Mandatory Vaccination	23	Reference	Reference	Reference
Mandatory Vaccination and Monetary Penalty for Noncompliance	6	1.84 (0.47, 7.19)	1.07 (0.30, 3.74) ‖	2.59 (0.30, 22.64) ‖

‡ Incidence Rate Ratio: countries that have mandatory vaccination had 38% higher incidence of pertussis compared to countries that do not have mandatory vaccination.

† Model terms: GDP per Capita, GINI, Urban Population

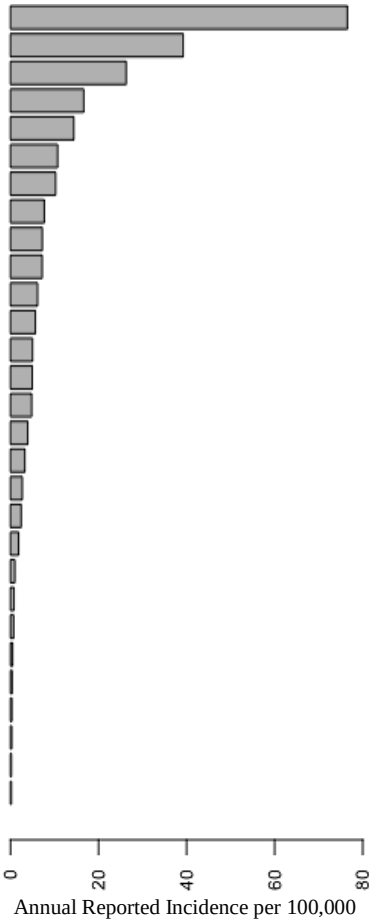
* Model terms: GDP per Capita, GINI, Urban Population, Universal Healthcare Coverage

‖ Model terms: GDP per Capita, GINI

Figures

Figure 1a: **Annual Reported Incidence Per 100,000**
Pertussis

Country	Mandatory Vaccination	Non-Medical Exemption	Financial Penalty	Financial Penalty
Norway	N	N	N	
Netherland	N	N	N	
Estonia	N	N	N	
Slovenia	Y	N	Y	741-1117€
Germany	N	N	N	
Slovakia	Y	N	Y	331€*
Denmark	N	N	N	
Czech Republic	Y	N	Y	10,000 Kč
Finland	N	N	N	
Belgium	N	N	N	
Poland	Y	N	Y	100-5,000 zł
UK	N	N	N	
Sweden	N	N	N	
Latvia	Y	Y	N	
Austria	N	N	N	
Spain	N	N	N	
Ireland	N	N	N	
Iceland	N	N	N	
Lithuania	N	N	N	
Bulgaria	Y	Y	Y	50-300 Лв
Luxembourg	N	N	N	
Portugal	N	N	N	
Cyprus	N	N	N	
Italy	N	N	N	
Malta	N	N	N	
Greece	N	N	N	
Romania	N	N	N	
France	N	N	N	
Hungary	Y	N	Y	5,000-500,000Ft

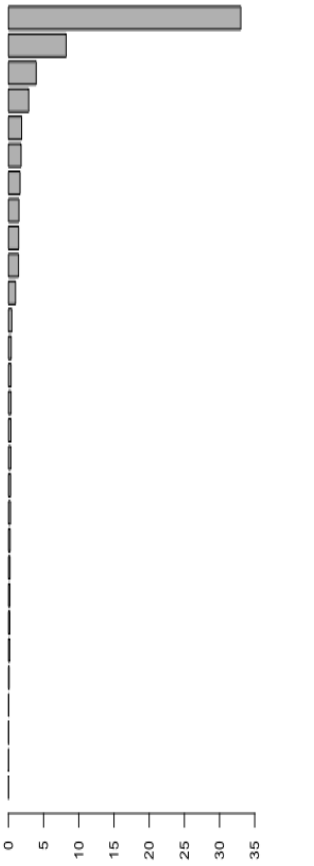


Mean annual reported pertussis incidence by country (2006-2016) among the entire population.

* Slovakia penalizes per parent so if it is a two-parent household, the total financial penalty would be 662€

Figure 1b: **Annual Reported Incidence Per 100,000**
Measles

Country	Mandatory Vaccination	Non-Medical Exemption	Financial Penalty	Financial Penalty
Bulgaria	Y	Y	Y	50-300 Лв
Romania	N	N	N	
France	N	N	N	
Ireland	N	N	N	
Italy	N	N	N	
Netherlands	N	N	N	
UK	N	N	N	
Austria	N	N	N	
Spain	N	N	N	
Germany	N	N	N	
Belgium	N	N	N	
Slovenia	Y	N	Y	741-1117€
Luxembourg	N	N	N	
Lithuania	N	N	N	
Cyprus	N	N	N	
Denmark	N	N	N	
Estonia	N	N	N	
Malta	N	N	N	
Czech Republic	Y	N	Y	10,000 Kč
Latvia	Y	Y	N	
Sweden	N	N	N	
Greece	N	N	N	
Poland	Y	N	Y	100-5,000 zł
Norway	N	N	N	
Finland	N	N	N	
Portugal	N	N	N	
Hungary	Y	N	Y	5,000-500,000Ft
Slovakia	Y	N	Y	331€*
Iceland	N	N	N	

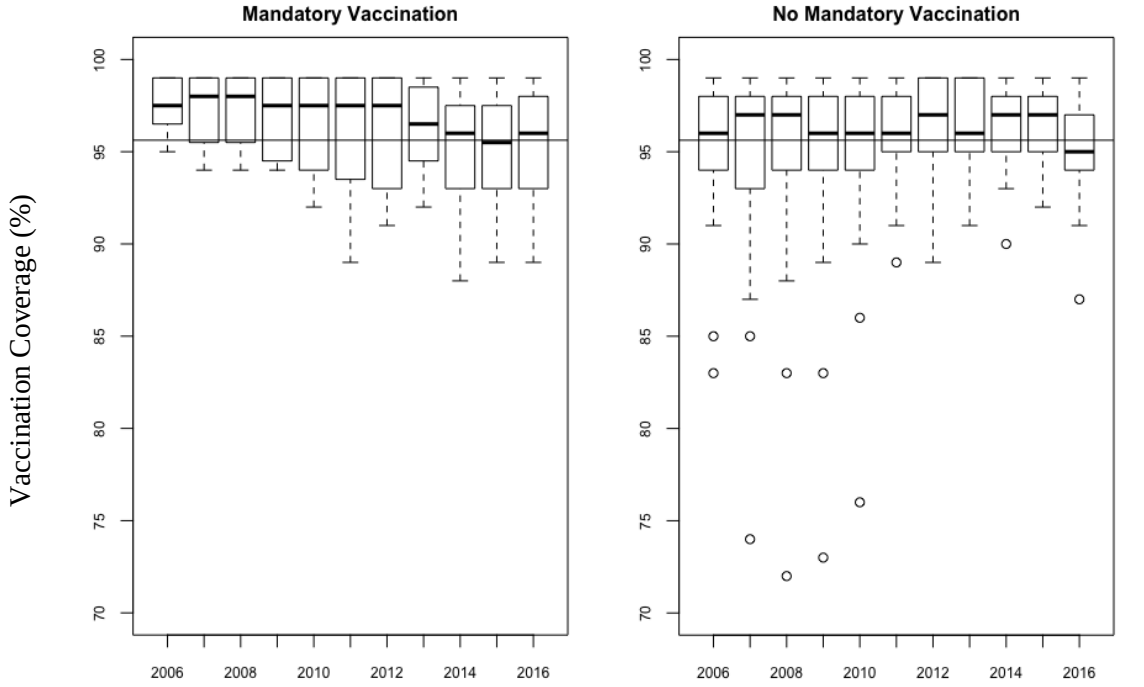


Mean annual reported pertussis incidence by country (2006-2016) among the entire population.

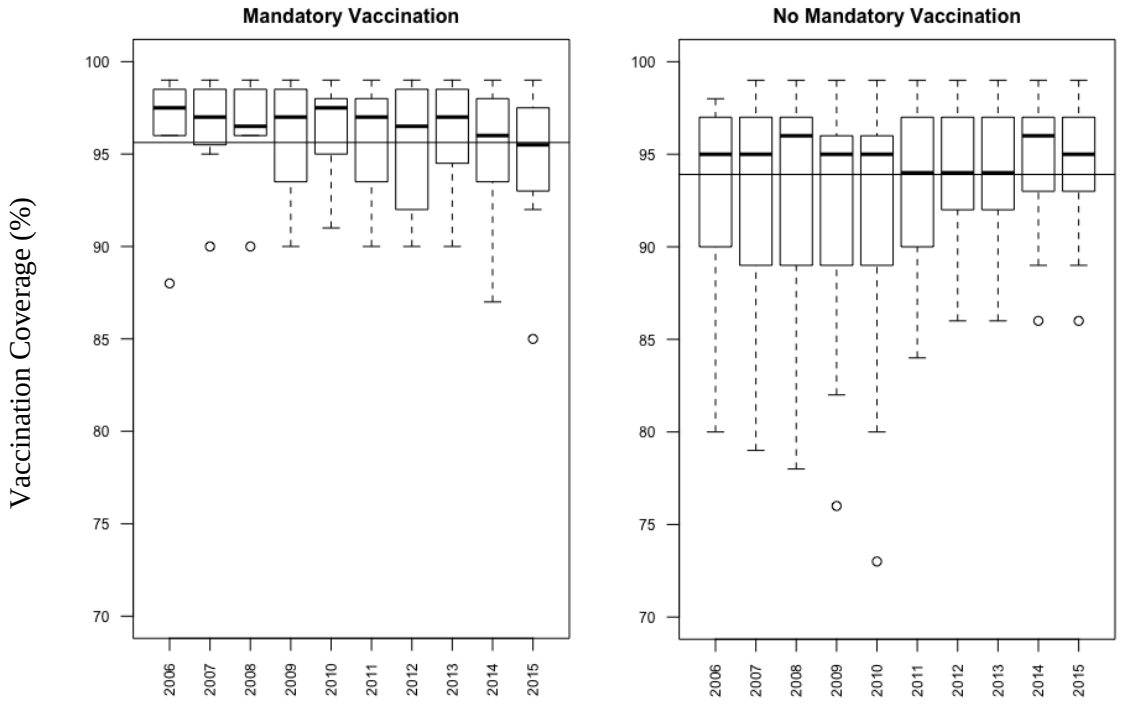
* Slovakia penalizes per parent so if it is a two-parent household, the total financial penalty would be 662€

Figure 2**. Mean Percentage and Interquartile Ranges of Vaccination Rates for Countries with Mandatory Vaccination and Countries without Mandatory Vaccination**

Pertussis: 2006-2016*



Measles: 2006-2015*



* The horizontal line indicates the average vaccination rate across all countries and years included in the study.

Public Health Implications

It is important to constantly monitor and evaluate the impact that different policies and interventions can have on vaccination rates and incidence rates of measles and pertussis. With this knowledge, officials can implement effective and efficient interventions instead of ineffectively using time and resources on interventions that will not yield the desired results. As additional countries in Europe are debating whether to implement mandatory vaccination as a part of their public health efforts, it is important to know whether these mandates have been effective in similar settings. If these actions are not going to be effective, it will important for public health officials to utilize other interventions to prompt change instead of relying on mandatory vaccination alone.

Measles and pertussis are both diseases that cause great harm to the entire population, but most specifically young infants who are too young to be vaccinated and individuals with compromised immune systems. Higher vaccination rates can protect these vulnerable populations by disrupting transmission paths. If the herd-immunity threshold can be reached, the majority of cases could be prevented. These results could inform decisions that help reach the herd-immunity threshold.

Additional work is needed to fully understand the relationship between vaccine mandates and disease incidence in Europe. A continuation of this study would be to analyze vaccination rates and responses as countries change their vaccination policies, just as Italy and France have in the past two years. The countries examined in this study did not change their vaccination policy over the time period studied, but continuing to follow the associations and responses of French and Italian populations as their regulations transition could advise other countries as they consider making the same

changes. Studies such as this one serve as a baseline canvassing of the landscape but continued research could see how that landscape changes over time.

In addition, it would be useful to do a further examination of the associations examined here by expanding the analysis to other areas of Europe or expanding the study to other areas of the world. Unfortunately, missing data could be an extremely limiting factor in this research. Surveillance of both incidence of disease as well as vaccination rates would need to be dependable and consistent. As surveillance efforts of incidence and vaccination rates are enhanced by organizations such as the World Health Organization or the Centers for Disease Control and Prevention (both American and European), these studies will become more precise and their results more informative for public health officials. High level surveillance on a global level will also lead to the possible detection of new diseases that may need control and intervention. (65) Some countries that were affected by Zika Virus, such as Colombia, had surveillance measures in place to track Chikungunya and other vector borne diseases and used those measures to begin tracking Zika at an early stage in its emergence. Increasing the surveillance capabilities both in Europe and worldwide for vaccine-preventable diseases and vaccination rates would make an expansion of this research possible.

Continuing studies about the effectiveness of other public health interventions aimed at increasing vaccination rates will be necessary to meet the obstacles that prevent full vaccination coverage. Though these studies have been performed in the past, continuing to examine the effectiveness of policies and interventions is necessary because of the fast-changing information landscape affected by the increased globalization of health issues.