Factors Influencing Undervaccination Prior to Measles Outbreaks in the United Kingdom from 2010 - 2019

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Abstract

Measles is a serious public health issue that is resurging in countries where it was previously on the path to eradication. The United Kingdom has recently experienced a multitude of large measles outbreaks that may be associated with a cohort of children whose vaccinations were withheld due to an autism scare in the late 1990s. However, it is still unknown what specific reasons for undervaccination are leading to outbreaks as national vaccination rates continue to hold steadily near or above the threshold considered necessary for measles eradication. Identifying the factors influencing undervaccination in specific regions that lead to measles outbreaks could have a significant public health impact and lead to the creation of specially tailored public health interventions to increase vaccination. This study aims to identify specific reasons for undervaccination prior to measles outbreaks in the United Kingdom between 2010 and 2019.

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Preface

I'd first like to thank my committee members for all of their help in the process of developing this thesis. Dr. Van Panhuis is an expert in this research, and has nurtured my interest in the field, mentoring me in research on measles outbreaks for over two years. Dr. Krier has been a wonderful advisor and support system throughout my master's degree; her guidance and listening ear have been there for me every step of the way.

Secondly, I'd like to thank my peers, colleagues, and supervisors for their support over the years. I have completed my master's degree part-time while working full-time in the Department of Emergency Medicine. Not only has their unwavering support helped me through this degree, but my ability to apply and grow my skillset through my research in emergency medicine has made me a better researcher. I would especially like to thank Dr. David Salcido and Dr. Lenny Weiss for all of their support and mentorship throughout this process.

Finally, I would like to thank my friends and family for their continuous support as I continue my education and career. My parents have supported all of my decisions, with my mom proofreading many essays along the way; my in-laws constantly provide encouragement to me; my friends have reminded me to relax and take time for myself along the way; and my dogs, Daisy and Jasmine, provide nothing but comfort in my time of need. Most importantly, I'd like to thank my husband, Chris, for his constant support; the countless nights he has made dinner for me on a late night, listened to a poster presentation, or took care of the house while I left the country; and for always being on my side.

1.0 Introduction

Measles is a vaccine preventable childhood disease that continues to affect the lives of thousands of children in Europe. According to the World Health Organization (WHO), pockets of undervaccinated groups led to disease in 83,540 people and the deaths of 74 in the European Region in 2018 alone.[1] As a preventable disease, measles only occurs in areas where vaccine uptake is below the 95% threshold for herd immunity.[2] In order to increase vaccine use in these areas, it is first necessary to understand the factors influencing low vaccine uptake. While there is mandatory reporting for measles outbreaks, there is a lack of data explaining parental and community factors that may have influenced outbreaks.

A cursory search of "measles outbreaks" and "vaccine hesitancy" on Pubmed produced only nine results, one of which is a case study. Previous systematic reviews have noted a lack of data on the specific reasons parents forgo vaccination prior to measles outbreaks, which makes tailoring immunization outreach programs difficult. Of these articles, there is no standardized method that categorizes the reasons for undervaccination underlying any type of disease outbreaks other than US-specific legal reasons for vaccine exemptions, broadly: personal beliefs, religion, or medical exemption. Moving forward in vaccine hesitancy research, our goal is to have more granular characterization of these reasons to gain comprehensive views of the outbreaks.

Our main objective is to characterize spatiotemporal patterns of reasons for vaccine hesitancy. We will use the United Kingdom as a pilot location.

2.0 Research Questions

We will address the following research questions in our study:

- What were the main reasons for undervaccination prior to measles outbreaks in the United Kingdom from 2010 to 2019?
- How did these reasons differ across space and time?

3.0 Background

3.1 Overview of Measles

3.1.1 Symptoms and Complications

Measles is an infection by the *Morbillivirus* virus (MV) transmitted through respiratory droplets.[3] Infection with MV can begin with asymptomatic shedding of the virus for one to two days, followed by fever, cough, and conjunctivitis. It is best known for its characteristic full-body rash, which begins on the face and spreads down to the torso and out to the extremities, and typically lasts for three to seven days.[4] While it is now commonly thought of as a harmless childhood disease of the past, these symptoms are frequently accompanied by more severe sequelae, with a mortality rate of approximately 1 to 3 in 1,000 in children.[5]

The complications of measles are diverse and range from acute, life-threatening conditions to chronic maladies. Pneumonia is the most common complication of measles, affecting mainly children under 5 and adults. Pneumonia is also the leading cause of death of measles infection.[5] Following MV infection, sufferers can experience a temporary loss in lymphocyte immunity, which can leave them susceptible to a whole host of opportunistic infections.[3] Neurological complications are also a concern with measles, such as subacute sclerosing panencephalitis, which can lead to permanent brain damage and death.[6]

3.1.2 MMR and Herd Immunity

During the 1960s and 1970s, there was increased availability of safe and effective vaccines against childhood diseases, largely thanks to the discoveries of Maurice Hilleman who helped develop over forty vaccines.[7] Prior to implementation of the measles vaccine, MV was responsible for an average of 530,217 measles cases per year and 440 deaths.[8] This single vaccine was combined into the Measles, Mumps, and Rubella (MMR) vaccine, and became one of the vaccines for routine childhood immunizations. In the 1980s, one dose of MMR became a requirement in the United States for children entering kindergarten[9], and two doses were recommended before entering kindergarten to be implemented before 2001.[10] However, the United Kingdom does not currently have any laws requiring children to be vaccinated before entering school.[11]

Measles is one of the most contagious diseases in the world with a reproductive number (R_0) of between 12 and 18.[2] This means that for each person infected, the infected individual will, on average, spread the virus to 12 to 18 other people. In order to prevent the virus from spreading, people need to be vaccinated. Vaccinations prevent the virus from infecting the host, and therefore prevent further transmission of the virus. The more people that are vaccinated in a community, the fewer opportunities there are for the virus to spread to others, and eventually the virus will die off if it cannot survive in another host or reservoir. Therefore, vaccinations also protect individuals who cannot receive vaccines due to autoimmune conditions, cancer treatments, allergies, or other reasons; the healthy, vaccinated population prevents transmission of the virus to the immunocompromised population. This concept is called herd immunity, where, if a certain threshold of the population is vaccinated against a disease, the disease will die out.[12]

Since measles is so contagious, the herd immunity threshold is quite high, requiring around 95% of the population to have their MMR vaccine before measles can be eliminated from an area.[2] There is a clear link between undervaccination and measles outbreaks, as lack of vaccination leads to a larger pool of "susceptibles" (i.e., individuals who are able to contract the virus), and less protected individuals. Some studies suggest that lingering below the herd immunity threshold while not achieving it has made MV even more dangerous in recent years; while the virus used to infect younger children who were then protected against the virus for life, it is now infecting older children or young adults, which leads to a more severe infection.[13] Though elimination may seem like an impossible goal, there are some regions on their way to achieving it.

3.2 Measles Elimination Goals in the United Kingdom

In the year 2000, the WHO set a goal of elimination of endemic measles in the European Region in 2010, which was postponed to 2015, and continues to be postponed due to failure of elimination in much of the European region.[14] The United Kingdom declared measles eliminated in 2016. In order to declare elimination of the measles virus, endemic transmission must stop for a continuous period of 36 months. However, endemic transmission of measles was reestablished in 2018, halting the UK's measles elimination goals.[15]

3.3 Vaccine Hesitancy and Anti-Vaccination Sentiment

Vaccine hesitancy has existed in some form or another since the days of variolation, when doctors would take the scabs of smallpox victims and insert them into a punctured bit of skin in a healthy person. Parents were justly concerned about inserting infected material into the skin of their children, as the science was not well known and the organism for causing disease had not been discovered yet. Once a licensed vaccine became available for smallpox, there were still groups fighting against the vaccine, arguing that it was dangerous for the child.[16] This pattern could be seen with every introduction of a new vaccine, especially for the polio vaccine after manufacturing processes led to thousands of infections with wild-type polio in vaccinated children.[17]

The modern era of vaccine hesitancy against MMR was sparked by the publication of a paper by Andrew Wakefield in 1998 claiming a link between the MMR vaccine and autism. This study was found to be fraudulent, the paper was retracted from the original publishing journal, and Wakefield's medical license was revoked.[18] Unfortunately, fears of autism as a consequence of vaccination are repeated by respected politicians, celebrities, and internet bloggers, fueling what is now known as the "anti-vax" movement. These fears now include misinformation about ingredients of MMR, developmental disabilities associated with MMR, benefits of experiencing the measles infection naturally rather than receiving the vaccine, and many other dangerous myths that are easily spread through the internet.[19] While important research is being done on vaccine hesitancy and its dissemination through the internet, including at our own institution[20], there are still some gaps in knowledge regarding the geographic connection between specific vaccine hesitancy ideology and measles outbreaks.

3.4 Spatial Clustering of Undervaccination and Its Consequences

While herd immunity should, in general, prevent outbreaks of disease even if there are susceptibles in the community, an issue arises when there are large pockets of unvaccinated or undervaccinated people. It has been found that undervaccination in the developed world actually tends to cluster in areas with a wealthy, highly educated population.[21] This suggests that ideology, rather than access or medical contraindication (as is frequently the case for other medical conditions and treatments), plays a crucial role in undervaccination in these communities.

This is also where we tend to see measles outbreaks. Although a state or county may appear to have high levels of vaccination coverage, these clustered, undervaccinated communities leave pockets of susceptibles that allow outbreaks to occur.[22] Keeping this in mind, research on the specific factors influencing undervaccination in these areas is crucial to achieving elimination in any country; while they may reach a regional or national vaccination goal, these susceptible pockets will prevent them from reaching elimination status.

4.0 Methodology

An outline of our methodology and all data can be found on Github at: https://github.com/ProjectTycho/MeaslesOutbreaksReview.

4.1 Data Collection Methods

4.1.1 Eligibility Criteria

Inclusion criteria was a paper about a measles outbreak identified by HealthMap that mentions reasons for undervaccination related to the outbreak. Articles that were excluded include opinion pieces, lab reports, and other systematic reviews.

4.1.2 Information Sources and Search Strategy

We used HealthMap data to identify outbreaks in the United Kingdom. We received HealthMap data from our collaborators, Elaine Nsoesie and John Brownstein. HealthMap receives data through real-time global outbreak news surveillance, adding outbreaks to their maps based on reports that are published. These frequently overlap, so we spent time condensing these into unique outbreaks before the study was conducted. We conducted a detailed search of Pubmed, Google Scholar, and archives of health agencies from the jurisdiction where the outbreaks occurred, as well as national-level agency reports. Each search covered the year before

the specified outbreak, and all subsequent years following the outbreak. Searches for the outbreaks began in 2010 and continued until the present time.

The following search was used in Pubmed: (measles[MeSH Terms] OR measles[Title/Abstract]) AND (Disease Outbreaks[MeSH Terms] OR outbreak[Title/Abstract] OR epidemic[Title/Abstract]) AND (United Kingdom[MeSH Terms] OR England[MeSH] OR UK[Title/Abstract]) AND ("2010"[Date - Publication] : "2019"[Date - Publication]). These results were exported as a CSV to Github and put into a Title/Abstract Review folder. A similar query was performed in Google Scholar. We reviewed the first 200 listings, and it was determined that more listings did not need to be reviewed. Finally, the Public Health England's website was queried. After initial Title/Abstract review was finished, the full texts of the Included articles were downloaded and added to their respective article files.

4.1.3 Data Items and Categorization

The main outcome variable for this study is reasons for undervaccination in the outbreak area. Other variables that were collected include the following outbreak variables: country, administration divide 1 code, administration divide 2 code, city, date of start of outbreak, date of end of outbreak, the number of cases, number of deaths, population at risk, age distribution, and any relevant subpopulation information that may be pertinent to the outbreak (ethnicity group, immigrants, etc.).

Reasons for undervaccination were extracted and classified into different categories. We identified categories of undervaccination based on themes previously identified by the SAGE Working Group on Vaccine Hesitancy and Heidi Larson, Director of the Vaccine Confidence Project, and the classification scheme used by Beth Hoffman, MPH, PhD student at the

University of Pittsburgh, in her analysis of vaccine hesitancy. We used the five categories provided by the WHO to describe reasons for undervaccination more broadly as our main categories for analysis, along with medical contraindication and access for a total of seven main categories. The WHO categories included an additional five to the two previously mentioned: (1) threat of disease, (2) trust, (3) alternatives, (4) effectiveness, and (5) safety. In order to determine which categories to use for the analysis, we identified vaccine hesitancy subcategories that were identified by Larson and Hoffman. Each sub-category was assigned to one of the seven main reasons for undervaccination for analysis. These categories and subcategories are mapped out in Table 1.

Table 1. Categorization of Reasons for Undervaccination

Threat of Disease	Trust	Alternatives	Effectiveness	Safety	Medical Contra-indication	Access
Belief that measles is not a dangerous disease	Negative experience with past vaccination *	Homeopathic remedies**	Reliability of vaccine supply*	Vaccination schedule*		
Belief that measles has been eradicated and vaccine is not necessary	Media, censorship, and "cover-up"**	Anthroposophical medicine	Belief that naturally acquiring measles is more effective for immunity	Mode of administration*		
	Belief in vaccination as genocide**	Religious objections		Mode of delivery*		
	Moral transgressions**			Introduction of new vaccine*		
	Belief that vaccination			Belief that vaccines		

Table 1 Continued

	is violation of civil liberties**			cause idiopathic illness**		
	Lack of trust in authoritative figures			Belief that vaccines cause autoimmune disease or cancer**		
				Belief that vaccines cause autism**		
				Belief that vaccines cause death**		

*Sub-category identified by Heidi Larson and the SAGE working group.

**Sub-category identified by Beth Halloran et. al.

After a full review was done of each included article, a quality ranking score was assigned to determine the overall quality of articles included in the analysis. The articles could receive a score of 1 through 3, with 1 being the best quality and 3 being the worst. Articles with a score of 1 included peer-reviewed research that directly linked reasons for undervaccination to outbreaks; articles with a score of 2 were peer-reviewed articles that may not have had reasons for undervaccination, or detailed surveillance reports with information about vaccine hesitancy; and articles with a score of 3 were generally outbreak alerts or news items from Public Health England that were not as detailed or reliable as the other categories.

In order for an article to be considered high-quality, there needed to be specific interviews, focus groups, or geographically isolated populations with unique cultural practices against vaccination that led the researchers to their conclusions about undervaccination. They also needed to be geographically specific; while there were some articles with specific

identification of undervaccination, they only referred to the United Kingdom as a whole and not specific cities or neighborhoods. In order to properly analyze the data, the data needed to be at least at the city level.

4.2 Data Analysis

4.2.1 Data Synthesis

Data from the full text review of each article was first appended into a single file using STATA 15. Reasons for exclusion were grouped and accounted for in the inclusion/exclusion process. Once all reasons for exclusion were accounted for, a new file with only the included articles was created.

4.2.2 Outbreak Categorization

Individual outbreaks from HealthMap were identified by combining overlapping data items by location and time period, i.e., outbreaks identified from articles that occurred in the same city at the same time. Once outbreaks were identified, we used data from our literature review to categorize them as either single-factor or multifactor outbreaks. Single-factor outbreaks were outbreaks where only one reason for undervaccination was identified; multifactor outbreaks identified more than one reason for undervaccination within the same outbreak. Some outbreaks did not report a reason for undervaccination - these were excluded from the final

analysis. Single factor versus multi-factor outbreaks were identified based on the results of the literature review.

After categorizing outbreaks by either single-factor or multifactor outbreaks, the outbreaks were mapped using a Google Map. Single-factor and multifactor outbreaks were coded in different colors with increasing sizes of the outbreak represented by increasing sizes of points on the map. Then, a separate map was made identifying the seven main reasons for undervaccination identified per outbreak. Multifactor outbreaks were assigned multicolor points to distinguish them from the single-factor outbreaks.

5.0 Results

5.1 General Findings

5.1.1 Inclusion/Exclusion Process

The initial article search produced 306 results. After the initial Title/Abstract review, 74 articles were saved for a full text review. From the full text review, 30 were included in the initial undervaccination analysis, and 10 were included in the final analysis as the other 20 were country-level and did not provide sufficient granularity for analysis. Figure 1 displays the inclusion/exclusion process that led to the final articles included in the analysis. The “Other” category that was excluded in full text review included articles that were not in the United Kingdom, opinion pieces, and papers that modeled outbreaks but did not discuss reasons for undervaccination related to the outbreaks.

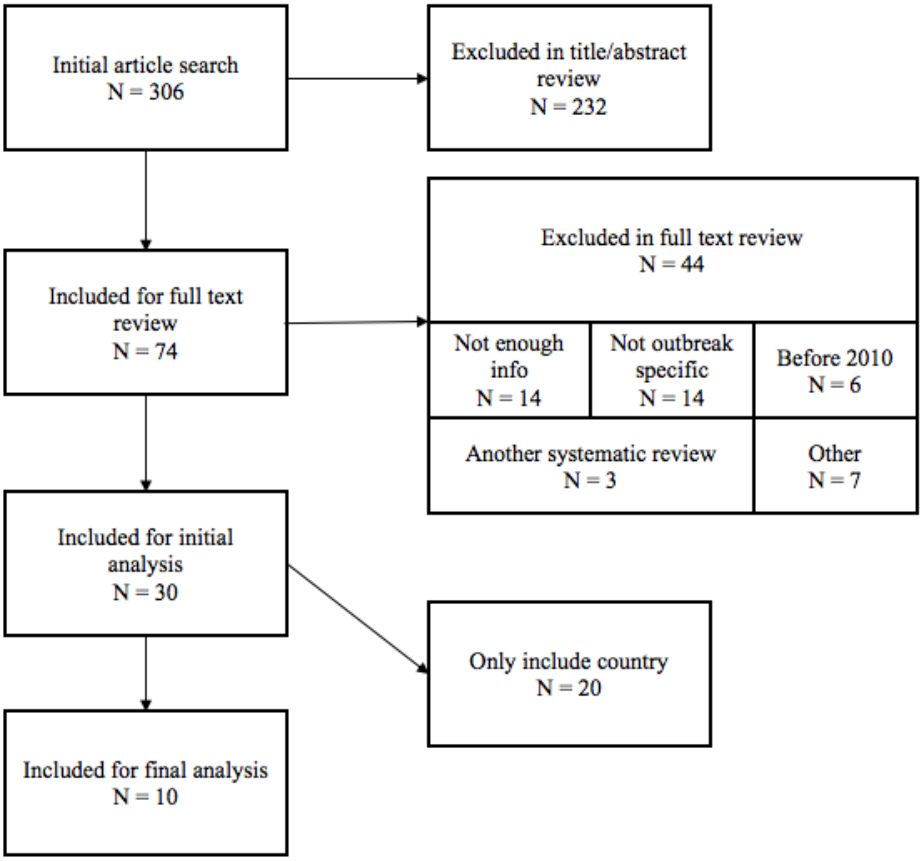

Figure 1. Inclusion/Exclusion Process

5.1.2 Article Quality and Outbreak Descriptions

The articles that made it through the exclusion process were overall very good to somewhat good quality; 4 (40%) had a rank of 1, 5 (50%) had a rank of 2, and 1 (10%), had a rank of 3, for an overall mean ranking of 1.7. Of the 10 articles, there were 9 unique outbreaks spread across 12 different cities: Bolton, Edinburgh, Liverpool, London, Manchester, Merseyside, Newport, Salford, Swansea, Torfaen, Wigan, and Yorkshire, shown in Table 2. Figure 2 shows each outbreak labeled by the year of the outbreak, with deepening shades of red

indicating more cases, while shades approaching the green part of the color scheme have less cases. Only outbreaks with both case information and start date were included in the map.

Figure 2. United Kingdom Measles Outbreaks

Table 2. Outlook Location, Date, and Case Count

Country	Location	Start Date	Cases Used in Analysis
England	Merseyside, Bolton, Wigan, Salford, Manchester	January 2012	647
England	London	July 2016	4
England	Liverpool	December 2012	2,534
Scotland	Edinburgh	September 2016	18
Wales	Newport, Torfaen	May 2017	17
England	London	December 2012	62
England	Yorkshire	December 2012	8
Wales	Swansea	November 2012	808

Of the 8 outbreaks with information on the start date of the outbreak, five of them occurred in 2012 (62.5%), two occurred in 2016 (25%), and one occurred in 2017 (12.5%). The smallest outbreak's article only investigated 4 cases (London 2016), while the largest outbreak included 2,534 cases (Liverpool 2012) with a median (IQR) of 210.5 (17-693) cases per outbreak investigation. Only two outbreaks were distinctly described as affecting more than one city, though it could be possible that the outbreaks in 2012 were related to one another. There were no deaths associated with the final outbreak investigations. Though one death did occur during the Swansea outbreak, the reason for undervaccination related to this death was not investigated.

5.2 Reasons for Undervaccination

Of the final 9 outbreaks identified, only 5 (55.6%) identified reasons for undervaccination prior to the outbreak. These reasons were Trust (1), Access (1), Alternatives (1), and Safety (2). Unfortunately, none of these outbreaks' articles provided enough information make any association between socioeconomic or demographic factors, and the sample size is so small that findings would likely not be significant. However, they did provide some qualitative data, which could be useful in developing future research in this area and identifying gaps in knowledge of hesitancy prior to outbreaks; each had its own challenging characteristics that will be described in the following sections. Figure 3 shows each article, their quality ranking score, and an associated line that indicated which category to put them into.

Table 3. Outbreak Articles and Characteristics

Location	Article Title	Article Quality	Quote from Article
London 2012	*Mass vaccination response to a measles outbreak is not always possible. Lessons from a London prison*	1	"...the majority of inmates in Yorkshire were vaccinated following the outbreak, while in London only a minority consented to vaccination. Language barriers, differing understanding or knowledge, lower immunisation rates in countries of origin as well as the high number of prisoners with mental health problems may have contributed to this."
Liverpool 2012	*Effect of socioeconomic deprivation on uptake*	1	"Our analysis supports the hypothesis that the MMR

Table 3 Continued

	of measles, mumps and rubella vaccination in Liverpool, UK over 16 years: a longitudinal ecological study		safety scare reduced population-level MMR uptake."
Newport and Torfaen 2017	*Measles outbreak linked to European B3 outbreaks, Wales, United Kingdom, 2017*	2	"…there were children in the schools who were completely unknown to the health system. They were recent migrants to the area from abroad and had not been registered with general practitioners (GPs), a factor known to be linked with poor vaccination uptake…"
London 2012	*Ongoing Measles Outbreak in Orthodox Jewish Community, London, UK*	2	"Health beliefs, family size (the average Charedi household size is 6.3 persons), and underutilization of immunization services contribute to low coverage"
Swansea 2012	*Largest group of children affected by measles outbreak in Wales is 10-18 year olds*	1	"A small investigative study funded by the Medical Research Council recently showed that there were many gaps in teenagers' understanding of vaccination. The Scottish study of 12 focus groups, involving 59 self selected teenagers, showed that they tended to underestimate the risks from diseases of which they had had little direct experience."

5.2.1 London, England 2012 - Trust

This outbreak was unique in that it affected an incarcerated population; the reason for undervaccination identified here was Trust. It occurred in a London men's prison where measles was introduced into the population through an infected, unvaccinated staff member. A large percentage of the incarcerated people were either not vaccinated or did not have vaccination records, which led to a mass vaccination catch-up campaign for both the staff and the incarcerated men. However, this proved to be difficult as the incarcerated men may not have trusted the authority figures to administer the vaccine, which was also identified as a reason for undervaccination prior to incarceration.[23]

5.2.2 Liverpool, England 2012 - Safety

An outbreak in Liverpool occurred in 2012-2013 that affected mainly mid-to-late teenagers who would have received their MMR vaccine around the time that Andrew Wakefield published his falsified study in the Lancet, putting this outbreak under the Safety category. The authors' findings supported their hypothesis that low immunization rates in the community that led to the large 2012-2013 outbreak were associated with the vaccine safety scare in the late 1990's-early 2000's, presenting statistically significant associations between the immunization gaps in the age group most affected by the outbreak. This immunity gap was primarily seen in affluent populations, but is now becoming more of an access issue than a safety issue. However, the current issues with access were not considered for this article because they do not directly relate to an outbreak at this time.[24]

5.2.3 Newport and Torfaen, Wales 2017 - Access

The outbreak that occurred in Newport and Torfaen began with an imported case which then spread throughout unvaccinated members of the community; this outbreak was part of the Access category, though other reasons that were not definitively found from the study may have contributed to the undervaccination in the area. While the authors speculated on reasons for undervaccination in some of the members of the community, they were certain that the migrants in the community had very poor access to health care. Some children were not in the public health system and did not have any established connection to a general practitioner - making it much less likely for them to have any access to vaccination.[25]

5.2.4 London, England 2012 - Alternatives

This outbreak was not included on the map or in the table because it did not have a specific case count within the article, but it is categorized as Alternatives. A community of Orthodox Jewish people, including a Charedi population, was affected by this measles outbreak. While not everyone in the denomination adhere as strictly to practices as others, it has been documented that measles outbreaks frequently occur in Orthodox Jewish communities due to religious practices. [26, 27, 28] This outbreak's undervaccination also seems to be stemmed from religious beliefs, and therefore is put under the Alternatives category.

5.2.5 Swansea, Wales 2012 - Safety

The main report from this outbreak outlined that the age cohort most affected by the outbreak was the same cohort that missed their vaccinations due to the Wakefield scare in 1998, putting this in the Safety category. We are able to see how, down the line, undervaccination can affect a large age cohort - in this case, mainly 10 to 18 year olds. They also note that those who missed both doses of the vaccine due to trust-related issues were concentrated within one area of the county, which led to a dramatic drop in herd immunity in that specific area.

6.0 Discussion

6.1 Common Themes Seen in Results

6.1.1 Outbreak Findings

It was apparent from the outbreaks that were identified by the search that each outbreak is unique and may not necessarily require the same type of public health interventions as the others. For example, the outbreak in the London prison would have required an approach that took into account the vulnerability of the population before administering a mass-vaccination campaign to its inmates. On the other hand, a mass-vaccination campaign for the minors in Swansea who may have missed their vaccines as a child would need to be more targeted towards quelling the concerns of the parents who may not have been confident in the decision to vaccinate in years prior.

We also do not see any cases in which an outbreak was precluded by a large amount of medical exemptions. Generally, medical contraindications are rare, and would not be clustered in a way that would lead to an outbreak in a specific area. However, this is still important to note because it shows that regardless of which reason for undervaccination precluded any given outbreak, it was not medically necessary and could have been prevented.

When we look at the final five outbreaks which contained information about reasons for undervaccination, they all identified a single cause as to why the population was undervaccinated prior to the outbreak. However, during the initial analysis of the 30 articles (which were not included due to the broad country-level reports), there were both single- and multi-cause

outbreaks, meaning that multiple reasons for undervaccination may have been identified in a single article. In fact, some of the articles in the final analysis contained speculation of other reasons, but did not have sufficient evidence for these reasons to be included in the analysis. Sufficient evidence would have data directly linking the outbreaks to parents' specific decisions to forgo vaccination, whereas the articles that were excluded only had outbreak information and speculated reasons with no data to validate the speculation. What we can learn from this is that addressing undervaccination cannot be addressed by a simple, one-size-fits-all public health intervention.

Each area had its own reason for undervaccination, suggesting that national or regional-level campaigns to increase vaccination would not be effective for reaching these clusters, as suggested in previous research. Even within these areas, there were differences on the specific reasons why parents chose not to vaccinate their children. A study done interviewing parents after an outbreak in Merseyside identified 16 unique reasons for forgoing vaccination prior to the outbreak just within that community, ranging from "belief in homeopathy" to "vaccine not offered".[29] Multi-factor outbreaks such as this highlight the need for individual attention to parents' concerns and development of new approaches to vaccine hesitant parents, as well as ensuring all parents both have access to and are aware of their access options for vaccination.

Another interesting trend that we can observe from the outbreaks in the final analysis is a tendency for rates of measles outbreaks to drop for a few years after a particularly large outbreak. In 2012, the United Kingdom experienced a large wave of outbreaks, which were also identified from the search. It has been suggested that vaccination is a victim of its own success; that, because parents are no longer seeing the consequences of vaccine-preventable diseases, their perceived risk of disease is lower and therefore makes them less likely to vaccinate.

However, it has also been suggested that if a large outbreak of a vaccine-preventable disease occurs, this may lead to a shift towards vaccination.[30]

We also must continue to take into consideration socioeconomic status and other demographic factors as we explore reasons why some children do not receive their vaccinations. Although most of this study focused on vaccine hesitancy, there was one outbreak where the reason for undervaccination was an access issue in a migrant population. Future work on this could look into why these populations were not properly connected to the health system and how migratory status is related both to socioeconomic status and vaccination coverage.

6.1.2 Data Availability

Through this systematic review, it became apparent that the availability of data addressing measles outbreaks in depth is vastly underwhelming, let alone undervaccination prior to the outbreaks. Many articles that were produced through the search were not specific to any region and just broadly mentioned "the United Kingdom" or only explored serological results that would not necessarily be helpful to an epidemiologist in contact tracing. The few studies that did include contact tracing did not include any interviews with the contacts as to why they were not vaccinated, only their vaccination status.

Although interviewing contacts to determine *why* they arrived at their vaccination status may not be the epidemiological standard, in light of the current situation in the United Kingdom, it seems that this is a necessary step towards understanding why so many clusters of susceptibles exist across the region. As stated previously in the discussion, it is necessary to understand the individual characteristics of the undervaccinated person and their parents to truly get a grasp on

closing the gaps in susceptibility and ultimately leading the way to measles elimination in the United Kingdom.

Moving forward, we can work with local health departments that we know investigated outbreaks but may not have published their reports.

6.2 Limitations

There are several limitations to this study that should be highlighted. First, systematic reviews may not capture all of the literature available. There are likely databases that could have been used in this search that were not explored that may have provided more results than the search conducted for this review. Also, there may have been search criteria that were important for detecting the information we were interested in that were not included in the search query. Secondly, the results gathered did not have nearly the amount of spatial granularity that we had hoped to gain from this study. As undervaccination occurs in spatial clusters, it is important to conduct analyses such as these in the most specific areas possible; however, as shown by the results, only 8 outbreaks were identified as having both city information and case count information. Even cities can be too broad of a spatial area to detect clusters of undervaccinated communities that can lead to outbreaks, so this data is very limited. For future expansions of this research, it would be important to look at vaccination rates, perhaps at the school level, paired with the information gained from the systematic review.

Finally, there was an overall lack of data produced from this systematic review. This is, in one sense, an important finding. This review demonstrated the lack of knowledge as to what factors are influencing communities to avoid vaccination prior to outbreaks. However, in order to

conduct any further analyses of the data collected, much more information would need to be gained from the search. It would be possible to expand the analysis back to the initial 30 articles, but this would lead to much broader areas of analysis that would not take into consideration the granular clustering of undervaccination leading to outbreaks.

7.0 Conclusions

Reasons for undervaccination prior to measles outbreaks is an area which requires further investigation to gain an understanding of why clusters of susceptible populations appear in regions and countries that are otherwise at an acceptably high vaccination threshold. Interventions to increase vaccination need to be improved and individualized to specific areas, and this will not happen unless further qualitative research is done, honing in on populations and cohorts who are most affected by measles outbreaks.

Appendix – Vaccine Category Definitions

1. Threat of disease: “arguing that vaccine-preventable diseases are eradicated or harmless”
    a. Belief that measles is not a dangerous disease
    b. Belief that measles has been eradicated and vaccine is not necessary
2. Trust: “Questioning the trustworthiness of health authorities”
    a. Negative experience with past vaccination
    b. Media, censorship, and “cover-up”: “...government cover-ups of vaccine effects, physicians motivated by profit...”
    c. Belief in vaccination as genocide: “vaccination is used to kill people….used in third world countries to depopulate”
    d. Moral transgressions: “vaccination is evil”
    e. Belief that vaccination is a violation of one’s civil liberties: “parents have the right to choose”
    f. Lack of trust in authoritative figures
3. Alternatives: “Arguing that there are safer and/or more effective prevention methods than vaccination”
    a. Homeopathic therapy: “homeopathy as an alternative to vaccines….food as medicine”
    b. Anthroposophic medicine: While the official statement on vaccines from the International Federation of Anthroposophic Medical Association condemns anti-vaccination, this reason is cited in enough sources that it needed to be included in the categorization scheme.
4. Effectiveness: “Questioning the effectiveness of vaccines as a prevention method”
    a. Reliability of vaccine supply
    b. Belief that naturally acquiring measles is better for immunity
5. Safety: “Questioning that vaccines entail more benefits than risks and raising general safety issues”
    a. Vaccination schedule

b. Mode of administration
c. Mode of delivery
d. Introduction of new vaccine
e. Belief that vaccines cause idiopathic illness
f. Belief that vaccines cause autoimmune disease or cancer
g. Belief that vaccines cause autism
h. Belief that vaccines cause death

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