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A Systematic Review on the Risk Factors Associated with the Resurgence of Pertussis in Highly Immunized Countries within the Last Ten Years (2004-2014)

By Lindsey Philip

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
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MASTER OF PUBLIC HEALTH

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Atlanta, Georgia

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APPROVAL PAGE

A Systematic Review on the Risk Factors Associated with the Resurgence of Pertussis in Highly Immunized Countries within the Last Ten Years

(2004-2014)

By Lindsey Philip

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ABSTRACT

BACKGROUND: Bordetella pertussis, otherwise known as whooping cough, is a highly contagious respiratory disease that was once a significant source of childhood morbidity and mortality. The availability and distribution of the pertussis vaccine beginning in the 1940s and onwards has helped to decrease transmission of infection, resulting in a major decline in pertussis incidence among highly immunized countries over time. However, there has been a reemergence of pertussis within highly immunized communities, with rates progressively increasing over the last 30 years and an observed epidemiological shift of higher incidence among adolescent and adult populations. Negative health outcomes in pertussis infected children less than one year of age continue to remain a major public health concern as intensity of symptoms and delay of recovery in this population often leads to hospitalization and even death.

OBJECTIVES: This systematic review examines published literature in the last ten years to provide an up-to-date analysis of the risk factors associated with the resurgence of pertussis among highly immunized populations.

METHODS: A literature search was conducted using PUBMED and EBSCO databases using combination searches with the key words pertussis, whooping cough, resurgence, reemergence, recurrence, and comeback. Retrieved articles were refined based on the date of publication and on the country in which the study was conducted. Only primary studies with data collected between 2004-2014 from highly immunized countries with equal to or greater than 90% of three doses of infant pertussis immunization coverage were included in this review.

RESULTS: Three main groups of risk factors contributing to pertussis reemergence were identified among fourteen primary studies. The first category included four studies assessing the risk factor of waning immunity. The second category comprised of six studies focused on the risk factor of bacterial mutations. A third grouping of articles based on immunization status and diagnosis recognition included one article associated with each of the following risk factors: non-medical exemptions, inadequate childhood immunizations, household transmission, and inadequate provider awareness.

CONCLUSION: Pertussis resurgence is a complex public health issue involving various components and interrelated risk factors. Research into the associated waning immunity through use of acellular vaccines and increased understanding of bacterial mutations contributing to vaccine ineffectiveness will be important to improving current available vaccines and should be a focus of continued efforts through collaboration among multiple disciplines. Emphasis on the importance of up to date immunizations among the general population and educational interventions directed toward health care providers and patients will be key to reducing pertussis transmission in highly immunized countries until new vaccines become available.

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BACKGROUND

1.1 Introduction

One of the top ten public health accomplishments in the twentieth century includes the development of vaccines protecting populations against dangerous infectious diseases (Centers for Disease Control and Prevention [CDC], 2013). The availability and administration of vaccines has helped to control the transmission and incidence of specific infectious diseases, which had once been significant sources of morbidity and mortality in communities of all ages. Areas of high vaccination coverage, in which large percentages of individuals were immunized, allowed for herd immunity to occur. Herd immunity is the concept that unimmunized individuals within a population with high immunization rates would be less likely to come into contact with individuals with the disease, thus decreasing transmission rates. However, recently, there has been a recurrence of vaccine preventable illnesses in areas where disease was once controlled due to high immunization coverage. The reemergence of diseases, once well-controlled among highly immunized communities, is becoming a significant public health issue. One example of this is the recurrence of Bordetalla pertussis, otherwise known as whooping cough. Pertussis is a highly contagious respiratory infectious disease that has made a comeback and is negatively affecting the health of infants, children, and adults in highly immunized communities (Cherry, J.D., 2012; Chiappini, E., Stival, A., Galli, L., Martino, M., 2013). The purpose of this systematic review is to examine recent literature published in the last ten years regarding risk factors associated with pertussis resurgence among highly immunized populations.

1.2 Pertussis Pathophysiology/ Symptoms

Pertussis is a respiratory disease caused by the gram–negative bacteria Bordetella pertussis in which humans are the only reservoir (World Health Organization [WHO], 2014). Transmission occurs through the spread of respiratory droplets among individuals (Dworkin, M.S., 2005). When a person breathes in the pertussis bacteria, the method of infection involves attachment of the bacteria to the cilia in the upper respiratory tract causing inflammation and swelling (CDC, 2013). Symptoms of pertussis can start off like the common cold but can progress into more serious coughing fits that last anywhere from 2-10 weeks. Pertussis progression may also lead to death in some individuals, often due to decreased oxygen due to prolonged and frequent coughing.

The clinical course of pertussis disease is divided into three stages: catarrhal, paroxysmal, and convalescent stages. During the catarrhal stage, possible symptoms include mild intermittent cough and low-grade fever. This stage can last anywhere from 4-21 days though 7-10 days is the average period. Individuals and health care providers may associate these symptoms with the common cold during this time, leaving many patients misdiagnosed (Dworkin, M.S., 2005). As the cough becomes more severe, the paroxysmal stage occurs and is defined by the paroxysmal type coughs. These coughs occur simultaneously and rapidly in efforts for the body to rid the lungs of thick mucous which has developed. Another symptom in this stage is the "whoop" sounds, which may occur at the end of each paroxysmal cough. Paroxysmal attacks occur at an average of 15 attacks per 24 hours, often causing vomiting and extreme fatigue. The usual time period for the paroxysmal stage is 1-6 weeks but may last anywhere up to 10 weeks. (CDC, 2013)

The last stage of pertussis disease is the convalescent stage and is characterized by a recovery time period with decreased frequency of paroxysmal coughs. The usual time period for this stage is 7-10 days, with a range of 4-21 days (CDC, 2013).

1.3 Complications of Disease

Infants below the age of one year old are at highest risk for developing the complications of pertussis. Approximately 50% of infants diagnosed with pertussis are hospitalized (CDC, 2013). Additional statistics from the CDC state that among infants who are hospitalized:

- 1 in 4 (23%) get pneumonia (lung infection)
- 1 or 2 in 100 (1.6%) will have convulsions (violent, uncontrolled shaking)
- Two-thirds (67%) will have apnea (slowed or stopped breathing)
- 1 in 300 (0.4%) will have encephalopathy (disease of the brain)
- 1 or 2 in 100 (1.6%) will die

Though milder symptoms are often seen in adolescents and adults who contract pertussis, complications from the cough can cause weight loss (33%), loss of bladder control (28%), passing out (6%), and rib fractures from severe coughing (4%). Less than 5% of teens and adults with pertussis are hospitalized (2013).

1.4 Diagnosis of Pertussis

Pertussis can be diagnosed through several laboratory tests including culture, polymerase chain reaction (PCR), and serology. The CDC (2013) defines culture as the gold standard to diagnosing pertussis due to its high specificity and its ability to identify specific strains and antimicrobial resistance. As a result, it is the preferred diagnosis method during outbreaks. Culture is obtained through nasopharyngeal aspirates or swabs.

Polymerase chain reaction (PCR) is another lab test used for pertussis diagnosis in patients, though it is often difficult to obtain from infants (Sintchenko, 2008). PCR tests allow for rapid results; however the high sensitivity of the assay may also produce more false-positive test results (CDC, 2013). Guiso (2014) addresses this topic of high sensitivity versus high specificity of lab tests in the adolescent and adult population arguing that the higher false-positive rates with PCR may lead to misdiagnosis, though providing the benefit of attaining quicker results for this age group (p. S121).

Serological blood test is another diagnostic test available and often beneficial in examining pertussis. Sintchencko (2008) states, "the greatest specificity for the serological diagnosis of B. pertussis infection is achieved by the measurement of IgG and IgA antibodies against pertussis toxin"(p.143). According to Bamberger, E.S. & Srugo, I. (2008), this test is often ineffective for infants with limited "measurable antibodies" though useful in older adults who have negative PCR and culture results after a prolonged course of whooping cough (p. 136).

The varying methods of diagnosis at different stages of symptom presentation can make acquisition of consistent measures of disease occurrence difficult. Guiso (2014) discusses the importance of formulating a standardized method for biological diagnosis of

pertussis in order to gain a more accurate perspective of pertussis incidence and prevalence rates. This is especially important in addressing the actual burden of disease occurring in immunized populations and in determining future expectation of outbreak occurrence.

1.5 Treatment

Different types of antibiotics for treatment of pertussis are available and are most effective if initiated earlier during the course of infection. Schaffner (2006) describes the challenges of how delayed diagnosis of pertussis may lead to suboptimal disease outcome, where antibiotic use may help symptoms yet do not "alter the course of the disease" (p. 29). This is because the exposure to the bacteria has already caused damage to the lining of the respiratory tract, and "treatment after three weeks of illness is unlikely to help because the bacteria are gone from your body though symptoms are still there" (CDC, 2013). However, the identification of infected persons would allow prophylactic treatment to be distributed to those who are in close contact with the infected individuals, thus helping to decrease the spread of the disease and severity of symptoms in those diagnosed in early stages of the disease (Schaffner, 2006). According to Bamberger & Scrugo (2008), the prophylactic recommendations in the Academy of Pediatrics Red Book instruct "Chemoprophylaxis to be administered to all household contacts and other close contacts, regardless of age and immunization status" (p. 136).

1.6 Whole Cell Pertussis Vaccine (wP)

Until the pertussis vaccine was introduced and dispersed among populations through public health efforts, pertussis was one of the main causes of childhood mortality in developed countries (Boven, M., Ferfuson, N.M. &Rie, A., 2004). In the 1940s the whole cell pertussis vaccine consisted of inactivated suspensions of the whole Bordetella pertussis bacteria (WHO, 2013). The pertussis vaccine was approved for routine use by the American Academy of Pediatrics in 1943, and in 1944 the American Medical Association recommended its use. (CDC, 2013; Shapiro–Shapin, 2010). Halperin, S.A. (2007) describes the benefits of the whole cell pertussis vaccine provision to communities in the 1940s and its effectiveness in reducing pertussis rates to its lowest in the U.S. until the 1980's (p.111). Statistics from the Centers of Disease Control describe the effect of vaccines on disease incidence by stating: "In 1934 the whooping cough incidence in the U.S. was 209 cases/100,000 residents, and the death rate was 5.9/100,000, yet by 1948, routine use of the vaccine reduced the incidence to 51 cases/100,ppp and death rate to <1/100,000. After 1960 incidence was 10 cases/100,000" (2013).

In regards to the use of whole cell pertussis vaccine outside the U.S., the World Health Organizations (WHO) indicates, "whole cell pertussis vaccine were first formulated in 1963 and revised and incorporated into recommendations for DTP in 1978. In 1989 the recommendations for the combined vaccine were revised and most recent revised recommendations for whole cell pertussis vaccines were adopted by the ECBS in 2005" (WHO, 2013).

1.7 Acellular Pertussis Vaccine (aP)

In efforts to limit negative vaccine side effects of the whole cell pertussis vaccine, acellular pertussis vaccines were introduced in 1991 as booster shots and as immunizations for primary vaccination in 1997 (Zhang, 2008). Acelluar vaccines were made up of components of purified, detoxified B. pertussis antigens (WHO, 2014). Use of these acellular vaccines versus whole cell vaccines helped to protect individuals from disease while decreasing side effects of redness and swelling that were often associated with whole cell pertussis vaccine administration (Zhang, 2008). Pertussis vaccinations were administered in a series of shots to maintain immunity. The number of doses recommended varied by country though most schedules included at least 3 doses of pertussis vaccine to be given before six months of age in infants (Tan, Trindade & Skowronski, 2005). In the U.S., a complete pertussis immunization schedule for children included a series of five immunizations, with the final dose given between 4-5 years old (CDC, 2013). However, with the reemergence of pertussis in highly immunized populations, an adolescent booster dose of the acellular pertussis vaccine became available and also recommended. In May 2005, the FDA approved Tdap, a tetanus and diphtheria booster immunization that also included an acellular pertussis booster component. The Tdap immunization was first approved as a booster dose for ages 10-18 years in May 2005 and then as the first pertussis booster vaccine in adults ages 11-64 years in June 2005 (Dworkin, M.S., 2005). Whole cell vaccines were completely stopped from use in the U.S. in 2001 (Witt, M.A., Arias,L., Katz, P.H., Truong, E.T., & Witt, D.J., 2013), although it is still commonly used in developing countries due to the decreased cost of vaccine (WHO, 2014).

1.8 Burden of Disease

The burden of pertussis disease has shown significant impact on both developing and developed nations. Estimates by the World Health Organization (WHO) state that in 2008, "16 million cases of pertussis occurred worldwide, 95% of which were in developing countries, and that about 195, 000 children died from the disease" (2011). Another source's findings describe global pertussis rates as attributing to 50 million cases and 300,000 deaths every year (He, 2008). Many of these developing nations are under-immunized for pertussis due to low socioeconomic conditions such as poverty and lack of quality healthcare structures. The Global Vaccine Action Plan (GVAP) started by the World Health Organization aims to increase vaccination rates in countries with low immunization coverage. According to the World Health Organization, the GVAP was developed to provide a framework of goals for prevention of vaccine preventable diseases globally (2014). The GVAP 2011-2020 defines a vaccine goal that "by 2020, coverage of target populations should reach at least 90% national vaccination coverage and at least 80% vaccination coverage in every district or equivalent administrative unit for all vaccines in national immunization programmes" (WHO, 2014). A study by Jackson and Rohani (2012), which assessed the global burden of pertussis disease in the last twenty years, concluded that developing countries continue to have high mortality and morbidity rates due to pertussis while specific developed countries with high immunization rates continue to experience resurgence in whooping cough (p. 2). Though Jackson and Rohani's results showed that a "mix of increasing, stationary, and decreasing trends in high-coverage countries" (p. 2) and a "lack of consistent geographical pattern in the trends" (p.3), increased incidence rates were reported in the 1980s for high vaccine coverage countries such as the U.S., Israel,

Australia, and Poland (p. 2). Challenges in regards to comparing rates of pertussis among highly immunized nations involve differences in vaccine schedules and variations in vaccine and disease tracking. Clark, T. A., Messonnier, N.E., & Hadler, S.C. (2012) states, "Differences in vaccination programs and surveillance systems limit the direct comparison of pertussis burden among countries" (p. 211). Researchers also attribute challenges due to variations in immunization coverage which impacts how the epidemiology of pertussis in the nation is interpreted (Wood, N & McIntyre, (2008), p.202). In the U.S., the CDC reported 48,277 cases in 2011, with increased disease incidence seen among 7- 10 year olds in 2010 and among 13-14 year olds in 2012 (2014). Many more pertussis cases in highly immunized populations may be undiagnosed. Infants continue to remain the most vulnerable population being affected by pertussis reemergence, as hospitalization and death often occur in this age group due to challenges in recovery (CDC, 2014).

1.9 Epidemiological Shift

A resurgence of pertussis disease began to emerge in highly immunized countries, such as in the U.S. in 1982 with peaks in 2005, 2010, and 2012 (Cherry, 2012). Halperin (2007) discusses the epidemiological shift seen in many highly immunized countries from increased cases seen in infants and children to adolescents and adults (p. 111). Leung, A.K.C. & Robson, W.L.M. (2007) describes this shift stating, "in recent years, almost 50% of reported cases occurred in individuals older than 10 y of age; the greatest increase has been noted in individuals 10 to 19 y of age" (Leung, A.K.C. & Robson, W. L.M., (2007), p. 355). Though pertussis in many adolescents and adults may present as mild illnesses and

even go unnoticed, the exposure of infants to these infected individuals may result in pertussis transmission in which severe illness and death can occur (Leung, A.K.C. et al. (2007) p. 354). Abuhammour (2008) further relates the increased infection rates of infants to possible exposure through contact with adolescents and adults. Dworkin, M.S. (2005) stresses the importance of identifying cases of pertussis in adolescents and adults to help stop the cycle of transmission to infants (p. 44).

METHODS

2.1 Literature Search Strategy

A literature search on January 17, 2014, was conducted using PUBMED AND EBSCO databases with key word phrase searches including the terms “pertussis and reemergence”, pertussis and recurrence”, “pertussis and comeback”, “pertussis and resurgence, “whooping cough and re-emergence”, “whooping cough and recurrence”, “whopping cough and comeback” and “whooping cough and resurgence”. Restrictions were placed on journal articles published within the last ten years and to research written in English. A second search was conducted on March 11, 2014 using the same key word phrases to verify inclusion of all pertaining articles. All primary articles that included data on risk factors associated with the resurgence of pertussis from 2004-2014 were included in this review.

2.2 Primary Outcome

All primary studies that assessed risk factors in association with pertussis infection as the primary outcome between 2004-2014 were included in this systematic review.

2.3 Inclusion Criteria

- Studies from countries with greater than or equal to 90% infant vaccine coverage for the third dose of pertussis vaccine specific to the year(s) in which the study was conducted
- Primary articles looking specifically at risk factor association and using data from human studies

- Studies published within the years 2004-2014 in which all data or part of the data was collected between 2004-2014

2.4 Exclusion Criteria (see Figure 1 and Table 1)

- Studies in which pertussis was not the main focus of the article
- Research printed in a language other than English
- Studies that were not primary studies identifying risk factor association to pertussis infection (includes review articles, descriptive articles, surveillance articles, case reports, intervention studies)
- Research conducted in countries exhibiting low immunization coverage, less than 90% of infant vaccine coverage for three doses or pertussis vaccine between 2004-2014
- Studies involving animal models or mathematical models
- Research containing data retrieved before 2004

2.5 Data Collection

Articles were organized into tables (see Tables 2-4), defining highly immunized countries where each study took place, study design, the researchers' end point being pursued from the article, risk factor identified, and results of the article. After identifying a list of articles from the initial search with use of various keywords, abstracts were reviewed and exclusion of articles that were non-English and articles in which pertussis was not the main focus were excluded from the review. Data analysis continued as full articles were reviewed and exclusion of non-primary study articles regarding pertussis was

initiated. Animal models, mathematical models, and studies with data from countries of low immunization coverage or with data collected prior to 2004 were also excluded from the review. A final list of fourteen primary studies were reviewed and then grouped together based on category of risk factor identified by the authors. The two largest categories of risk factors in which common article themes were found included the risk factor of waning immunity and bacterial changes. Four articles were grouped in the waning immunity list, while six articles were grouped in the bacterial changes list. A third category of articles was created based on one unifying article that included each of the following risk factors: non-medical exemptions, inadequate childhood immunization, inadequate provider awareness, and household transmission.

Figure 1: Flow Diagram of Literature Search

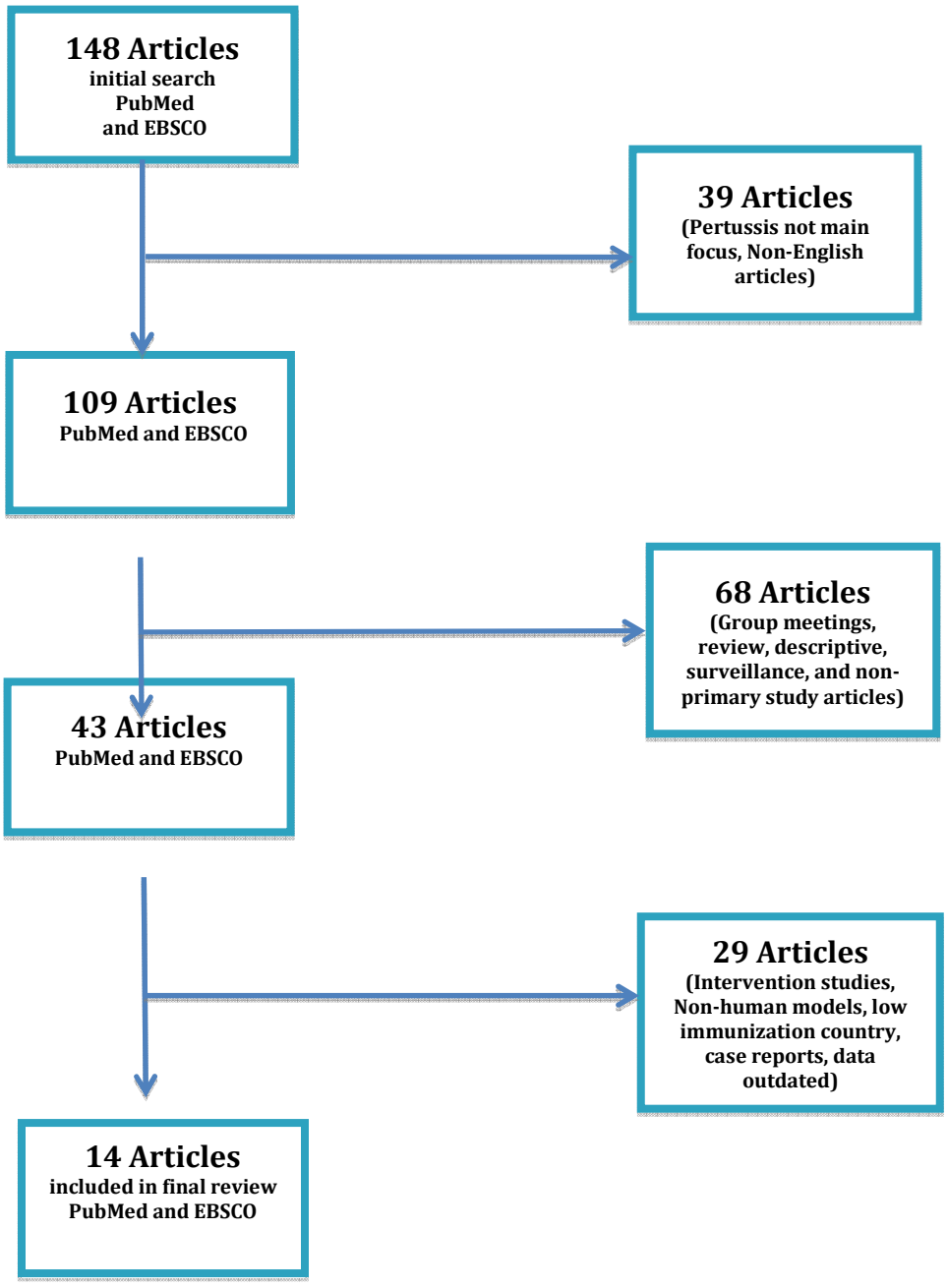

Table 1: Excluded Articles

Reason for Exclusion	Number of Articles
Non-primary study articles (review articles and descriptive articles defining pertussis, diagnosis, lab reporting, symptoms)	**43**
Topic (articles where pertussis is not main topic)	**22**
Non-English	**17**
Vaccine (history, description, developments, side effects)	**15**
Intervention articles	**12**
Surveillance	**8**
Countries with low immunization coverage	**7**
Immunity (not primary studies)	**7**
Animal models	**6**
Mathematical models	**3**
Case reports	**3**
Group meetings regarding pertussis	**3**
Data outdated (collected prior to 2004)	**2**

Table 2: Waning Immunity

Author/ Year	Country	Type of Study	Endpoint	Risk Factor Identified	Results
Witt, M.A., Arias, L., Katz, P.H., Truong, E.T. & Witt, D.J. (2013)	U.S.	Observational Study	Immunity	Use of acellular vaccines	Use of a complete acellular vaccine series is less effective than one or more doses of whole cell pertussis vaccine (RR= 8.57)
Smits et al. (2014)	Belgium	Observational Study	Immunity	Use of acellular vaccines	Use of wP induces longer lasting immunity than aP
Trollfors, B., Dotevall, L., Sundh, V &Welinder-Olsson, C. (2011)	Sweden	Observational Study	Immunity	Use of infant vaccine series only without more booster doses	Booster pertussis doses needed, number of booster doses and timing of doses for effective immunity still unknown
Han, W.G.H. et al. (2013)	Netherlands	Observational Study	Immunity	Limited immunological memory	Long-term immunity after infection is often lost in older age groups

Table 3: Bacterial Changes

Author/ Year	Country	Type of Study	Endpoint	Risk Factor Identified	Results
Pawloski, L.C. et al. (2014)	U.S.	Observational Study (Screening of 13000 isolates from outbreak and surveillance studies)	Bacterial mutations	Pertactin-deficient B. Pertussis Strains	Recent dramatic increase in pertactin-deficient B. pertussis isolates throughout the U.S.
Gent, M.V., Bart,,M.J, Han, G.J., Hedie, V.D., Heuvelman, K.J., & Mooi FR.R., (2012)	Netherlands	Observational Study	Bacterial mutations	Pathogen Mutations/Adaptation	Small mutations can drive large changes of bacterial pathogen and may cause resistance to vaccination
Kallonen,T. et al. (2011)	Finland Poland Serbia UK	Observational Study	Bacterial mutations	Bacterial mutations	Possible vaccine-driven differences in genomic content between old and recent vaccine strains among 4 different countries
King, A.J. et al. (2008)	Netherlands	Observational Study	Bacterial mutations	Bacterial mutations	Emergence of ptxP3 strains through bacterial adaptation causing divergence between vaccine and circulating strains.
Shuel, M. et al. (2013)	Canada	Observational Study	Bacterial strain domininace	Dominance of pertussis strain	One predominant B. pertussis clone in Ontario, Canada identical to strains involved in epidemics in Europe and Australia
Abu Raya B et al. (2012)	Israel	Observational Study (2 years)	Bacterial strain dominance	Predominance of strains	Circulating strains in Israel during high incidence rate years are similar to strains found in Europe

Table 4: Inadequate Immunization Coverage/ Provider Awareness

Author/Year	Country	Type of Study	Endpoint	Risk Factor Identified	Results
Atwell, J.E.(2013)	U.S.	Observational Study	Infection Route	Non-Medical Exemptions (NMEs)	NMEs: source of pertussis outbreak in California 2010
CDC, MMWR (2013)	U.S.	Survey	Immunization coverage	Inadequate Childhood immunization	Low SES and poverty may be contributing factors to inadequate childhood immunization dispersed across the U.S.
Kwon, H.J., Yum, S.K., Choi, U.Y., Lee, S.Y., Kim,J.H, &Kang,J.H.(2012)	South Korea	Observational Study	Infection Route/ Immunization Coverage	Household Transmission	Household transmission/ inadequate infant immunization
Abuhammour, W. (2007)	U.S.	Survey	Diagnosis	Inadequate provider knowledge	Misdiagnosis of pertussis patients leads to ineffective infection detection and control

RESULTS

3.1 Waning Immunity

In this review, four studies were identified that focused on waning immunity as a risk factor associated with pertussis re-emergence. Witt, M.A., Arias, L., Katz, P.H., Truong, E.T. & Witt, D.J.(2013) looked at the association of pertussis incidence with the type of pertussis vaccination received, assessing whether receiving whole cell pertussis (wP) vaccine at any point showed a lower risk of pertussis infection versus those who had received only acellular pertussis (aP) vaccines. Access to Kaiser Permanente's (KP) electronic medical records allowed researchers to examine lab confirmed pertussis results and vaccine histories for 263,496 patients ages 8-20 years old born between 1990-2001. 904 cases of pertussis were found among these patients. Results showed an increased risk of pertussis cases being highest in those who received 5 doses only of aP vaccine for both groups (RR= 8.75, P<.0001) when compared to patient histories who received at least one dose of wP. Members who received all 6 doses of aP had a 3.55 relative risk of pertussis (P< .0001) when compared to those with at least one dose of wP. Though a decreased risk of pertussis was seen in patients who received 6 doses versus five doses of only aP vaccine, this group still exhibited a high relative risk for pertussis infection when compared to those who had one or more doses of wP vaccine. The authors concluded that use of only acellular vaccines in a vaccination series of 5 doses provides a shorter immunity span than when one or more immunizations of whole cell vaccines are included in an immunization series. The authors also concluded that patients who received a sixth booster dose of acellular vaccine in a series of aP vaccine exhibited a longer lasting immunity against pertussis.

Smits et al (2014) assessed a cohort of 24 Belgian preadolescents with a median age of 10.1 years old. Through collected blood samples, indications of residual T cell memory were evaluated. Participants included those who received a pertussis vaccine from infancy through the last pertussis booster shot. The last booster shot was given at a median interval of 4.8 years for wP vaccinated children and at a median interval of 2.7 years for aP vaccinated children (p=0.004) from the last pertussis vaccine. Eleven adolescents had received wP in infancy and 13 adolescents had received aP in infancy. All 24 participants received aP as their last pertussis booster dose. Results showed that individuals who received the wP pertussis immunization in infancy had longer lasting immunity than those individuals who were vaccinated with aP as infants.

The study by Trollfors, B., Dotevall, L., Sundh, V &Welinder-Olsson, C. (2011) involved outcome assessment of a mass vaccination project in Gothenburg, Sweden held between 1995-1999 from infants to 10 years of age. Pertussis incidence was assessed between 1999-2009 through PCR and culture verified lab cases and hospitalizations. Among 1,973 cases identified, 450 cases were from patients who had received 3 doses of a monocomponent pertussis vaccine with highest incidence seen in infants below the age of 12 months of age. A recurrence of pertussis infection was seen in 1999 with a peak in 2004, marking an outbreak of the disease. However, disease incidence decreased again after 2004 when booster doses began to be recommended for children 10 years of age from 2005-2006 and for children 5-6 years of age from 2007 onwards. Study outcomes revealed a shorter span of immunity in pertussis vaccinations with improvement in immunity occurring when booster doses were given.

Finally, a study by Han et al (2013) conducted in the Netherlands analyzed blood samples for 62 pertussis patients at various time periods after infection. The age range was between 9.4-78.9 years with a median age of 37.5 years. Samples were placed in groups of < 30 years old, > or equal to 30 years old, < 3 months after diagnosis, and > or equal to 3 months after diagnosis. The blood sample analysis involved B. pertussis-specific (memory) CD4+ T cell activity at the epitope-level at different time periods after pertussis diagnosis. The authors state, " long-lived Th1 CD4+T cells are essential for protective immunity against pertussis." (p.1). Results showed a decrease in these memory cells among the older age group of this study who were previously infected. One conclusion by the researchers state, "Loss of multi-epitope specificity in memory pertussis CD4+ T cell responses could play a role in waning effectiveness of pertussis immunity in older age groups. These observations can have implications for vaccination strategies and vaccine development" (p. 5). The authors concluded a loss of long- term immunity occurs after infection in older age groups and recommended use of this knowledge of "limited immunological memory to B. pertussis" in future research towards novel vaccine development (p. 1, 5).

3.2 Pertussis Bacterial Strain Changes

Six studies in this systematic review involved analysis of pertussis bacteria strains to determine changes in the structure of the bacteria over time, while discussing the association of pertussis resurgence to mutation and adaptation of bacterial strains causing resistance against vaccines. An Australian study by King et al. (2008) identified pertussis bacterial strains with genetic changes in which the absence of 98 genes were found in "at least one of the b. pertussis strains tested" among 43 Dutch isolates between 1993-2004

(p.1). The authors discuss emergence of ptxP3 strains through bacterial adaptation causing "divergence between vaccine and circulating strains" and pertussis resurgence.

In another study by Kallonen et al. (2011), researchers examined old pertussis isolates (1941-1984) and more recent isolates (1996-2004) from Finland, Poland, Serbia, and the UK and identified genomic differences among the pertussis strains compared (p.2041, 2011). Since the reference bacterial strain Tohama I was used for production of both whole cell and acellular pertussis vaccines, strain resistance to pertussis vaccinations is highlighted due to changes in the bacterial genetic material over time (p. 2041).

In the study conducted by Pawloski et al. (2014), researchers looked at 1,300 pertussis isolates dated from 1935- 2009 in the U.S. and identified 306 isolates lacking pertactin (p. 119). These results show a link to the possible ineffectiveness of the acellular vaccine since pertactin is a significant antigen component in the acellular pertussis vaccine.

The study conducted by Gent, M.V., Bart, M.J, Han, G.J., Hedie, V.D., Heuvelman, K.J., & Mooi FR.R., (2012) assessed 704 Dutch pertussis strains between 1949-2010 also showed genetic mutations in pertussis bacteria. The authors concluded that even small genetic changes over time can produce unique pertussis bacterial strains. Increases in pertussis outbreaks could thus be attributed to unique pertussis bacterial strains emerging in resistance to vaccines.

In support of this notion, two studies identified similarity of strains found during outbreak seasons to that in other highly immunized countries. A Canadian study in 2013 examining 521 pertussis isolates from 1998-2006 showed similarities to pertussis isolates during epidemics in Europe and Australia, suggesting one predominant clone of pertussis bacteria having emerged and is related to the pertussis resurgence (Shuel et al. 2013).

Research conducted on pertussis strains in Israel between 2007-2008 identified a predominance of specific pertussis strains correlating to the most common European pertussis strain between 1999-2004 (Abu Raya B et al. 2012). These similarities in outbreak strains may signify an emergence of dominant pertussis strains correlating with pertussis mutations which differ from vaccine strains, thus leading to "increased pertussis activity" (p.762).

3.3 Non-Medical Exemptions

Lower rates of childhood immunization, either through higher frequency of non-medical exemptions or lower socioeconomic levels, were also identified as a risk factor for the resurgence of pertussis. A California study initiated after a major pertussis outbreak in 2010 identified unimmunized children through non-medical exemptions (NME's) as being a primary route of transmission of pertussis in highly immunized communities (Atwell, 2010). Researchers concluded pertussis re-emergence stemmed from clusters of non-medically exempted children experiencing pertussis infection and spreading it to other individuals within the higher immunized communities.

3.4 Inadequate Child Pertussis Immunization Rates

The National Immunization Survey (NIS), initiated through the CDC, conducted a random–digit-dialed telephone survey among households in the U.S. for children aged 19-35 months (CDC, 2013). Results for children born during Jan 2009- May 2011 showed 82.3% pertussis immunization coverage for greater than or equal to 4 doses of Dtap

which was actually below the Healthy People 2020 target percentage of 90% (p.733). Other specific results from this study included inconsistencies of immunization rates across the U.S. states and decreased pertussis immunization rates in families under poverty level (CDC,2013). Researchers defined the significant risk of low immunization coverage as "clusters of unvaccinated children leave communities vulnerable to outbreaks of disease" (p. 739). This study revealed low immunization coverage in children across the U.S., often correlating with low socioeconomic status, while exposing a possible route of pertussis infection among children in the U.S.

3.5 Inadequate Provider Knowledge

One study identified inadequate provider knowledge of pertussis identification and recurrence as a risk factor to the re-emergence of pertussis. Results of a 2007 health care provider survey distributed to physicians in Michigan showed a "decreased awareness" of the current need in identifying and diagnosing pertussis in adolescent and adult populations (Abuhammour, 2008). The survey included a case study to be reviewed by physicians with pertaining questions that followed. Results indicated a decreased identification of pertussis as a "differential diagnosis of adults with respiratory tract illness" (p. 44). Inadequate provider awareness of the importance in considering pertussis as a differential diagnosis in patients could lead to misdiagnosis and decreased identification and treatment of patients with pertussis, leading to increased risk of exposure to individuals in close contact with these infected persons.

3.6 Household Transmission

A prospective multicenter study conducted in South Korea recognized household transmission of pertussis among family members as the main route of transmission for infants below the age of six months (Kwon, H.J., Yum, S.K., Choi, U.Y., Lee, S.Y., Kim, J.H. & Kang, J.H., (2012) p.2). The authors indicate 85.7% of infant transmission was associated with contact from an infected parent though they did not specify the immunization status of the parent. In this cohort, all but one of the twenty-one infants showed an incomplete pertussis vaccination history. As infants less than the age of one are at highest risk for experiencing symptoms of pertussis that may lead to morbidity and/or mortality, this study shows the significance of ensuring infants receive the complete pertussis vaccination series and that parents and caretakers are up to date on booster pertussis vaccinations as being essential to decreasing infant pertussis transmission.

DISCUSSION

Public health efforts towards reducing pertussis transmission in communities with high immunization rates lie not only in keeping vaccination rates high, but also in addressing risk factors that are unique to pertussis transmission in highly vaccinated populations. Waning immunity through decreased efficacy of acellular vaccines and vaccine ineffectiveness due to genetic changes in pertussis bacteria are two main points addressed in this review. The promotion of immunization and educational interventions along with future research toward new vaccine development is essential in addressing the resurgence of pertussis in highly immunized populations.

4.1 Waning Effectiveness of Immunizations

Two studies point towards the recent use of the acellular vaccines versus whole cell vaccines as a contributor to pertussis comeback due to decreased long-term effectiveness of immunization series that contain only acellular vaccines (Smits et al. 2014; Witt et al. 2013). A study in Belgium evaluated T cell responses in preadolescents who had been vaccinated and identified longer lasting immunity in those with whole cell vaccinations (Smits et al. 2014). After a thorough evaluation of electronic medical records, Witt et al. (2013) correlated an increase in pertussis cases among individuals with acellular vaccination versus those who received at least one dose of whole-cell pertussis vaccine in the U.S. state of California. Both studies discussed the long-term effectiveness seen in whole cell pertussis immunization series versus acellular pertussis immunization series. These studies point to the idea that the shift to acellular vaccines from whole cell vaccines may be a driving factor contributing to the pertussis reemergence. Since acellular vaccines began replacing whole cell vaccines as booster shots in 1991, as primary immunizations in 1997, and completely in 2001, one hypothesis posited through these studies is that the use of acellular vaccines may contribute to the waning immunity observed in countries such as the U.S. and underlie the pertussis outbreaks among highly immunized communities.

4.2 Bacterial Changes Leading to Vaccine Ineffectiveness

Bacterial mutations and specific genomic variations of new pertussis strains may affect vaccine effectiveness as current pertussis vaccines were once developed to target older pertussis bacterial strains. Of the six articles identifying changes in bacterial strains of pertussis as being associated with whooping cough re-emergence, four articles discussed

genetic mutations and differences in new pertussis bacteria strains (Gent, M.V., 2012; King et al., 2008; Pawloski, L.C. et al. 2014; King et al. 2008). Pawoloski's study identifying pertactin deficient pertussis bacteria provides insight into the ineffectiveness of long-term immunity with acellular vaccines due to bacterial mutation, as pertactin is an important component of the acellular pertussis vaccine (2014). A study by van Gent, M.V (2012) concluded that small genetic mutations within a time span of 6 to 19 years may cause resistance to vaccination, confirming the idea of bacterial mutations affecting efficacy of current vaccines. The study from Australia by King et al. (2008) also describes bacterial adaptation and pertussis emergence that can recur through divergence between changed circulating bacterial strains and vaccines. The study consisting of data from Finland, Poland, Serbia, and the UK describe these bacteria changes noting clear differences in the structure of old circulating pertussis bacteria versus newer strains (Kallonen et al. 2011). Two studies in Canada and Israel each point towards a dominant pertussis strain having emerged and showing identity to pertussis bacterial strains from outbreaks across Europe (Shuel, M. et al. (2013); Abu Raya B et al. 2012). These results tie into the theory of new pertussis strains with increased fitness emerging across the world, thus causing decreased vaccine effectiveness of currently available pertussis vaccines.

4.3 Immunization Interventions

Promotion of immunization programs to all age groups as a prevention intervention can greatly help control pertussis outbreaks. Until a novel vaccine is approved for distribution, pertussis vaccination among children, adolescents, and adults is an important aspect to pertussis prevention. The importance of initiating quality immunization

intervention strategies to children, adolescents, and adults is to help ensure completion of childhood pertussis immunization series while preventing the transmission of pertussis from adolescents and adults to infants. The National Immunization Survey (NIS), initiated through the CDC, concluded that vaccination rates vary across states in the U.S. and groups of unvaccinated children often live under poverty level (2011). These unvaccinated children could be the source of transmission of whooping cough. Continued promotion of immunization programs in underserved areas may help decrease rates of unvaccinated children while helping maintain comparable rates of immunization across the U.S. and other highly immunized countries.

As the current epidemiological shift of pertussis rates show a larger percentage of confirmed pertussis cases in adolescents and adults, vaccination efforts to confirm and promote booster pertussis immunizations in adolescents and adults can help decrease disease transmission to infants. A study by Trollfors, B., Dotevall, L., Sundh, V & Welinder-Olsson, C.(2011) stresses the need for booster doses in children and adolescents as the study revealed how pertussis incidence can reoccur in children who only received infant pertussis doses versus those who received a booster vaccine in adolescence. The study by Han et al. (2013) showed how booster doses for adults is a significant component of pertussis prevention due to decreased T cell memory responses in older age groups who had previously been infected with pertussis. Immunization programs, focusing on immunizing parents and household members can also help with pertussis prevention. The study by Kwon, H.J. et al. (2012) revealed a large percentage of infant pertussis transmission occurring through household contacts may benefit from cocooning immunization intervention strategies. Cocooning is a method of immunizing healthcare

providers and family members who come in constant contact with newborns. Cherry (2012) encourages cocooning, immunizing pregnant women and promoting earlier immunization series for infants as a way of helping to decrease pertussis transmission in infants (p. 787).

4.4 Patient Education

One article in this review discussed unvaccinated children being a risk factor associated with the resurgence of pertussis and recent outbreaks in the U.S. Researchers associated the clusters of non-medical exempted children from attaining pertussis vaccinations with the 2010 outbreak of pertussis in California (Atwell, 2010). This outbreak resulted in >9000 cases, 809 hospitalizations, and 10 infant deaths. (Winter et al. 2012). Educating parents on the need of initiating and completing the pertussis immunization series in children and the benefits versus risks/side effects of vaccination can help decrease transmission of the disease from those who are not fully immunized to the communities in which they reside.

4.5 Provider Education

Educating health care providers on the importance of recognizing pertussis as a diagnosis for respiratory symptoms in adolescents and adults will also help decrease transmission of the disease through early recognition and treatment of disease. The survey results from family physicians in one northern state in the U.S. emphasized the need to increase physician awareness of pertussis being a differential diagnosis in patients with cold symptoms and/or prolonged cough (Abuhammour, 2008). Increased accurate

identification of pertussis cases by health care providers can help decrease transmission of pertussis by treating patients and their contacts accordingly. Interventions that accentuate the role of health care providers in preventing the spread of pertussis through promotion of vaccination and patient education may significantly impact public health efforts toward pertussis prevention (Abuhammour, 2008).

4.6 Collaboration Across Multiple Disciplines

Ten of fourteen studies in this review including data from eleven countries and three continents, point towards either waning immunity and/or bacterial changes as risk factors associated with pertussis resurgence. The two risk factors of waning immunity and bacterial changes may therefore be related in that mutations and adaptations of pertussis bacteria over time may be linked to the inability of current vaccines to address the correct pertussis antigen, leading to ineffectiveness of vaccine induced long-term immunity.

Collaboration of multiple disciplines is an important step to addressing pertussis prevention efforts in highly immunized communities. Clark, T.A., Messonier, N.E, Hadler, S.C. (2012) states, "It is time for all disciplines of vaccinology- epidemiology, microbiology, and immunology- to take up challenge of understanding this problem and try to solve it" (p. 21). Continued research efforts into understanding the combined areas of epidemiology of pertussis reemergence, the biological make-up of current pertussis strains, effectiveness of vaccines and immunology, and its' relation to current outbreaks in countries with high immunization coverage should be encouraged and increased.

4.7 New Vaccine Development

In efforts to address both the waning immunity of acellular vaccines and emergence of mutated pertussis bacteria with increased fitness, development of a new pertussis vaccine should be a significant focus in public health. Clark, T. A., Messonnier, N. E., & Hadler, S. C. (2012) discuss the importance of pertussis control through development of a new vaccine and emphasize the focus of this development as "durable immunity and the ability to interrupt transmission, not just to protect against severe or symptomatic disease" (p.212).

4.8 Strengths

Strengths of this systematic review include the use of a variety of terms to retrieve the most expansive list of articles published regarding risk factors associated with pertussis resurgence. Evaluating published articles in the last ten years allowed for the most recent and updated studies to be reviewed. Research results and conclusions obtained between 2004-2014 allowed for a targeting of recent outbreaks, updated data, and current risk factors focusing on immediate public health interventions and efforts towards future research strategies. Articles included in this review included studies from several highly immunized countries in various continents, showing similarities of results in different regions of the world, especially in regards to bacterial mutations.

4.9 Limitations

There are various limitations in this systematic review including having only published articles from PUBMED and EBSCHO included in this review and not grey literature or other databases. Searches based only in English may have limited data and associations than those found in studies published in other languages. Limitations may have occurred in the time frame in which the reviewer conducted the search for this review. Differing immunization schedules and timing of when the aP vaccine was solely administered to children and as booster doses, may affect comparison between waning immunity studies between various highly immunized countries.

4.10 Bias

Bias may have occurred in results found in published articles versus research found in articles that were not published. Possibility of reviewer bias may have occurred in regards to the shortened time frame of the literature search and article retrieval and assessment.

4.11 Conclusion

- Waning immunity through replacement of whole cell vaccines with acellular vaccines may be a driving risk factor towards pertussis resurgence
- Bacterial mutations and increased dominance of specific pertussis strains with increased fitness may be associated with vaccine ineffectiveness leading to pertussis reemergence
- Inadequate immunization coverage through non-medical exemptions, inadequate completion of childhood immunization series, and inadequate adult booster dose immunization coverage may cause increases in pertussis recurrence
- Inadequate provider awareness leading to misdiagnosis and delayed treatment of infected patients and contacts may contribute to pertussis resurgence
- Promotion of immunization and educational interventions to infants, children, adolescents, and adults is an important aspect to pertussis transmission control
- Educating healthcare providers on the importance of recognizing pertussis as a differential diagnosis for patients with symptoms of prolonged cough is a key component to decreasing the spread of pertussis
- Future research involving collaboration across multiple disciplines is essential to understanding the risk factors associated with and addressing the resurgence of pertussis in highly immunized populations
- Future research into novel vaccine development is a significant aspect to protecting populations from newly emerging dominant pertussis strains

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