Pertussis

A reemerging and an underreported infectious disease

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ABSTRACT

يعد السعال الديكي أو الشاهوق من الأمراض المعدية التي يمكن الوقاية منها أو توقيها بالتطعيم. انخفض ظهور المرض بشدة منذ ظهور لقاح الخناق، والكزاز، والشاهوق DTP. لوحظ بكثرة إعادة ظهور المرض لدى العديد من الأشخاص المطعمين في الدول الغربية منذ 1990م. بعض الأسباب التي كانت مسؤولة بشكل رئيسي على حالات السعال الديكي كانت ضعف جودة اللقاح المقدم، وانخفاض المناعة الناتجة بعد التطعيم، وتلاؤم المرض، وتعزيز نظام المراقبة، وتطور التشخيص في المرافق الصحية. أن تشخيص السعال الديكي مهمل وقد لا يلاحظ نظراً للمظاهر الشاذة في الأشخاص المحصنين جزئياً أو الأشخاص ضعيفي المناعة. في هذا التقرير نستعرض مراجعات بخصوص عودة السعال الديكي من دول عديدة ومحاولة التحقق من الأسباب خلف إعادة ظهور المرض. كما تركز على الحقيقة أن السعال الديكي من الأمراض المعدية غير المبلغ عنها إلى الآن. كما أن الإحصائيات المقدمة من الدول النامية لا تعكس الصورة الحقيقية للمرض. لذلك، تحتاج هذه الدول إلى تطوير نظام المراقبة.

Pertussis or whooping cough is a highly infectious, vaccine preventable disease. The incidence of the disease has greatly been reduced since the introduction of the diphtheria, tetanus, pertussis vaccine. Pertussis resurgence has been observed in highly vaccinated populations of Western countries since 1990s. Poor vaccine quality, waning vaccine induced immunity, pathogen adaptation, and enhanced surveillance as well as advancements in diagnostic facilities are some of the reasons considered responsible for the increased reporting of pertussis cases. Pertussis may have been ignored and unnoticed due to its atypical manifestations in partially immunized population or people with waning immunity. We review the reports of pertussis resurgence from different countries and attempt to investigate reasons behind the reappearance of the disease. Pertussis is still an under reported disease and the available data from the developing countries is not a true picture of the story. Therefore, developing countries need to improve their surveillance systems.

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Pertussis or whooping cough is an acute respiratory tract diseases caused by a Gram negative bacterial species *Bordetella pertussis* (*B. pertussis*).[1] A milder form of the same disease is caused by another member of the same genus, *Bordetella parapertussis*.[2] There has been a global decline in the incidence of the disease in both developed as well developing countries of the world since the introduction of diphtheria, tetanus, pertussis (DTP) vaccine. in 1940s.[3,4] However, a resurgence of pertussis cases has been observed in a number of reports from highly immunized vaccinated countries.[5-9] An increase in the pertussis incidence in some highly immunized populations of industrialized countries raises questions on the efficacy of the DTP vaccine. Pathogen adaptation to vaccination, enhanced surveillance, advances in diagnostic facilities, waning immunity, and poor vaccine quality are the possible explanations for the rise in reported pertussis cases in the Western countries.[1,10] Pertussis, once thought of as a disease of infants and children is very common in adolescents and children. It has been observed that the immunity conferred by both the acellular diphtheria, tetanus, pertussis (DTaP) or whole cell diphtheria, tetanus, pertussis (DTwP) vaccine has waned in the last few years. Waning vaccine induced immunity against pertussis vaccine has been a major obstacle in beating pertussis, despite massive vaccination. Waning immunity is also thought to be responsible for a shift of the diseases to adolescents and adults. A high pertussis

incidence in a 7-10 year age group in a California outbreak in a 2010[5] also indicates a waning immunity despite practice of booster vaccination at age 5 in the USA.[11-13] Further, pertussis resurgence in western countries has been worrisome; however, the true picture of the situation is still unavailable from the developing world. A sudden rise in the pertussis incidence was reported in the Netherlands in 1996.[14] Similar reports have also been published from many other countries of the world. The World Health Organization estimated 16 Million pertussis cases and 195,000 deaths in the year 2008, mostly in developing countries (WHO, 2014).[13] However, reports of laboratory confirmed case outbreaks, and molecular epidemiological studies are scarce from this part of the globe.[15] In the last 2 decades, a number of reports have been published focusing mainly on the pertussis resurgence in the developed countries of the West. However, data is rare from developing countries with massive populations and are expected to be high risk areas. In the present review, we attempt to discuss various reasons for the pertussis reemergence in the last decades in different countries of the world. We also discuss the situation in developing countries, such as Pakistan.

Literature search strategy. An extensive literature searched in "PubMed" and "Google Scholar" was carried out using key words such as pertussis resurgence, pertussis reemergence, pertussis outbreak, adult pertussis, waning immunity and pertussis, pertussis in developing countries, pertussis in Pakistan, antigenic diversity in *Bordetella pertussis*, waning immunity to pertussis, pertussis outbreaks in USA, UK, Germany, Russia, Japan, China, Netherlands, and so forth. We collected the data from the original articles, review articles, and short communication from the internationals journals.

Pertussis outbreaks in developed countries. Pertussis is a worldwide endemic infectious disease following a cyclic pattern every 3-5 years. Pertussis outbreaks have been reported from European countries such as the Netherlands, Finland, and Germany,[14] Canada and the USA in children, adolescents, and adults, which indicates that pertussis is a diseases of all age groups.[1,16-19] Pertussis has been is on the rise in the USA for the last few years, and many outbreaks have been reported. The recent 2010 outbreaks involved 9,477 children, mostly under the age of 3 months.[20] Another outbreak in the American city of Washington reports 2,520 cases, mostly children aged <1 year old.[21] A similar situation has also been witnessed in Europe where pertussis is on the rise, and outbreaks are being reported in people of all age groups.[22-25] Surveillance data from Germany, Netherland, Finland, Russia, France, Switzerland, Italy, Norway, and other European countries reveal pertussis resurgence.[6,20,26-28] Furthermore, pertussis epidemics and outbreaks in vaccinated populations have also been reported from South American and Eastern European countries.[29-31] Data from the study conducted by Nitsch-Osuch[30] in Poland indicates a rise in the number of reported pertussis cases, with the highest incidence rate in the age group of >6 months to 10-14 years, which coincides with the surveillance data from the California outbreak in USA.[28] However, another paper[31] reports the highest incidence in the age groups 3 to 10-14 years. Pertussis has not been an uncommon disease in Australia, with an incidence rate of 40/100,000 per year.[32-34] However, a shift in the pertussis occurrence has been witnessed from infants to adolescents.

Adolescent and adult pertussis. Pertussis is characterized by its typical symptoms of severe coughing spells, inspiratory whoop, and post-tussive vomiting. However, these symptoms may be mild in adolescent or adult patients. Therefore, diagnosis of adolescent and adult pertussis may be complicated by the fact that pertussis in these age groups may show atypical manifestations. Adolescent and adult pertussis has been reported to be common in persistent cough patients who usually do not manifest typical pertussis symptoms. However, adult pertussis cases with typical symptoms have also been reported. Furthermore, pertussis in these age groups may have been largely ignored due to lack of awareness on adult pertussis as well diagnostic facilities.[35-37] Pertussis outbreaks have been reported from schools, colleges, oil refineries, hospitals, and surgical wards, and so worth.[37-39] A number of reports track adults as a source of infection in infants and small children, which testifies their possible role in pertussis outbreaks and transmission into the younger age group.[40]

A precise diagnosis of pertussis in adolescents and adults is often difficult due to the fact that patients often fail to produce typical symptoms. Patients usually fail to receive a proper explanation for their cough which last for months. Impartial immunity conferred by the childhood vaccination as well-developed anatomy are thought to attenuate the classic clinical signs of typical pertussis, making it difficult to properly diagnose it.[39] Although vaccine induced immunity to pertussis wanes in 4-10 years after vaccination, partial immunity

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against *B. pertussis* may hinder onset of typical pertussis symptoms. A major shift of pertussis from children to adults may be merely due to enhanced surveillance and awareness of pertussis in these age groups in the last decade. Absence of typical pertussis symptoms in adolescents and adults make the diagnosis complicated for the physicians and health care professionals. Despite reports of an association between prolonged cough in adults with the *B. pertussis* infections, adolescent and adult pertussis remains underestimated and a high number of physicians fail to diagnose cases.[41-43] It is still difficult to decide whether the increasing number of cases in this age group, is due to enhanced surveillance or there is a real change.

Pathogen adaptation and pertussis vaccines. One of the hypotheses behind the increasing incidence of pertussis in countries with high vaccine coverage is the difference in the protective antigens of the circulating, and the vaccine strains of *B. pertussis*.[44] This hypothesis of adaptation of *B. pertussis* to vaccine was proposed by Mooi et al[7] from the Netherlands. Just like antibiotics, vaccines may also impose selection pressure on bacterial strains circulating in the population. The first report from the same group from the Netherlands on the temporal trends of the *B. pertussis* population structure showed that the antigenic type of bacterial strains have greatly changed since the introduction of the DTP vaccine. Their report suggested diversity in the genes coding for pertactin (prn) and pertussis toxin subunit S1 (ptxS1), which has also been reported from other studies carried out in other countries thereafter.[45]

Bordetella pertussis produces a number of virulence factors including toxins, adhesins, and integrins. Pertactin and pertussis toxin are 2 major virulence factors as well as protective antigens of *B. pertussis*. Pertussis toxin is a secreted toxin whereas pertactin is an outermembrane protein. By performing DNA sequence analysis of the genes coding for pertactin (prn) and pertussis toxin (ptx)of *B. pertussis* strains isolated from an epidemic in a highly vaccinated population of the Netherlands, Mooi et al[7] showed that these strains were distinct from the vaccine strain used in the Netherlands.

It is also evident in reports from other countries that the sequences of these virulence factor genes are polymorphic.[44-46] Previous studies[47] carried out in countries such as the Netherlands, UK, and Poland, reported that there is a temporal trend in nucleotide sequence change in the prn and pertussis toxin S1 (ptxS1) gene sequences of the circulating *B. pertussis* strains.

As mentioned above, prn and ptx play a key role in the pathogenesis of *B. pertussis* infections. Polymorphism in the prn gene is confined to a region that contains tandem repeats proximal to the arginine-glycine-aspartic acid (RGD) motif, involved in the attachment to the host tissues. Reports from many countries indicate that the vaccine alleles are being replaced by the non-vaccine alleles after the introduction of whole cell vaccine. Strains carrying the variant prn and ptx alleles were uncommon in the pre-vaccine era. It is argued that this polymorphism is not random or due to genetic drift, as the strains isolated from the vaccinated cases are different when compared to the non-vaccinated cases. This variation is of utmost significance, since both prn and ptxS1 sub-unit have a role in protective immunity to *B. pertussis*. Pertussis toxin S1 binds directly with the T cell receptors. Therefore, these 2 virulence factors may have a crucial role in the efficacy of the vaccine. Furthermore, experiments on animals have shown that variation in pertactin amino acid sequence results in the variation in vaccine efficacy.[6,9,48,49] Dissemination of non-vaccine alleles of these genes in some outbreaks and individual pertussis cases reported has been reported by many groups in last.[50-53] More studies are needed.

Like many other countries of the world; there is a noticeable increase in the incidence of pertussis in Australia.[53] In a study carried out by Poynten et al,[53] prn3 allele of pertactin, which was not common prior to 1989, was found in 42% of the circulating *B. pertussis* strains. There was a decrease in the strains carrying the prn1 allele used in the DTwP vaccine in Australia.[53] Similarly, in a study on 129 *B. pertussis* isolates from Italy, they found 4 prn alleles (prn1, prn2, prn3 and prn5), and prn2 and prn3 consisted of 92% of all alleles. The antigenic allele used in the vaccine in Italy was prn1.[30] This is from Poland not Italy strains were analyzed for pertussis toxin S1 (ptxS1) gene polymorphism. All variants showed sequence of ptxS1A variant. The vaccines used in that area contained ptxS1B and ptxS1D.[54]

In a similar type of study conducted in Argentina[51] on 28 *B. pertussis* isolates, it was found that many strains were antigenically different from the vaccine strains. Of all 28 strains studied, 26 contained prn2 allele, whereas only 2 contained vaccine type prn1. Studies on ptxS1 showed that all of them were non-vaccine type allele.[48] Investigation of antigenic divergence between the clinical and the vaccine strains in Moscow, Russia showed a clear reduction in the pre-vaccine prn, ptxA, and fim alleles after the introduction of the DTP vaccine. The 3 strains used in the vaccine development harbored ptxA1, ptxA4, prn1, fim2-1, and fim3A. The 2 ptxA alleles, ptx2, and ptx4 were characteristic of the pre-vaccine era and predominated between 1960-1970.

These alleles were replaced by the ptxA1 allele in 1980 and still predominated. The vaccine allele prn1 was replaced by non-vaccine alleles prn2 and prn3. Strains with fim2-2 and fim3B were found prevalent in that study.[55] An interesting finding in this regard is the discovery of *B. pertussis* strains with increased pertussis toxin production from pertussis cases in a vaccinated population.[56] The available data by date from many countries clearly indicates pathogen evolution in response to vaccination by changing antigenic type; therefore, resistance to vaccination. Further, studies are needed to present a clear picture of the problem.

Pertussis surveillance and the developing world. Pertussis is eradicable as a vaccine preventable disease. Reports of pertussis resurgence and outbreaks are mostly arriving from the developed world with sophisticated diagnostic facilities and the surveillance systems of infectious diseases. It is highly probable that pertussis is being greatly under reported from countries such as China, India, Indonesia, Nigeria, Pakistan, and other countries with large population.[6] Although there is a lack of pertussis surveillance data in developing countries, WHO estimates that most of the pertussis cases (95%) occurred in developing countries.[57,58] A clear understanding of pertussis resurgence may be hampered by unavailability of data in developing countries, where pertussis is mostly diagnosed by clinical picture only. Atypical, adolescent, and adult, pertussis cases remain mostly undiagnosed and underreported.

Although pertussis is a reportable disease in many countries of the world, few research groups are engaged with pertussis in Asian and African continents. Furthermore, a clear picture of disease occurrence is needed to plan for booster and adult formulation of DTP vaccines as well as its eradication in this part of the world. Most of the studies carried out in developing countries are based on the sero surveillance of pertussis toxin antibodies.[59-61] High pertussis toxin antibodies in the adolescent and adult population are an indication of recent infection with *B. pertussis*.[4,62-65] Adequate surveillance of *B. pertussis* infections is equally important in both developing as well as developed countries for prevention and control of the diseases.

A shift from whole cell pertussis vaccine to acellular pertussis vaccine. The whole cell pertussis vaccine (PTwP), although reliable and effective suffers from safety concerns as happens with most of the whole cell vaccine. The DTwP has been replaced by the acellular pertussis vaccine (DTaP) in most countries from the 1990s. Interestingly, a rise in the pertussis cases starts at the same when there is a switch between the DTwP and DTaP vaccine. The DTaP was supposed to produce short lived immunity as compared with DTwP vaccine. This short lived immunity conferred by the DTaP vaccine is one of the reasons behind the pertussis shift to adolescents and adults.[65] A recent study carried out by Klein et al[66] on the 2010-2011 pertussis outbreak in the USA concluded that children who were immunized with DTwP vaccine were more protected in the outbreak than those with DTaP.[66]

Similar results have also been published by other groups inside and outside the USA. Since the motivation behind this switch was to avoid adverse effects of the DTwP vaccine, one needs to weigh the benefits and harms of immunizing with each type of vaccine. Some suggest continuing with the same DTaP vaccine and continuously trying to improve its efficacy[67] while others favor going back to whole cells vaccine.[68] In summary, a switch from the DTwP to DTaP vaccine may be one of the valid reasons behind pertussis resurgence in the immunized population.

Pertussis in Pakistan. Pertussis has been endemic in Pakistan in the pre-vaccination era. There has been a continuous decrease in the reported pertussis cases in Pakistan since the introduction of the DTP vaccine in 1979 in Pakistan (personal communication with EPI Pakistan). However, pertussis cases are still to be found in both vaccinated as well and non-vaccinated children.[69,70] Pertussis cases with typical symptoms frequently visit pediatricians (author`s personal observation and survey). Although a notifiable disease, exact data on the prevalence and incidence of *B. pertussis* infections remain unclear.

Laboratory confirmed cases of pertussis have been reported from Pakistan in recent studies.[69,70] Interestingly, most of the pertussis cases have been found to be caused by *B. parapertussis*. Pertussis has been found to be more prevalent in the Khyber Pakhtunkhwa province of Pakistan, since fractions of population in this area are not vaccinated due to cultural reasons.[70,71] Nonetheless, major focus of their investigation was infants and children with typical pertussis symptoms. A systematic study of atypical, adolescent, and adult pertussis remains unexplored. The only evidence of adult pertussis in Pakistan is the sero-epidemiological study conducted by Syet et al.[4]

In conclusion, pathogen adaptation and antigenic diversity among circulating *B. pertussis* strains have been witnessed in many reports since 1998.[49] However, this cannot be the single reason behind pertussis resurgence in the countries with high vaccine coverage. Since there has been switch from whole cell pertussis vaccine to acellular pertussis vaccine in 1990 in many countries,

the efficacy of the DTaP vaccine needs to be considered. Evidence does exist favoring the waning immunity as a reason behind pertussis in adolescents and adults. Available data suggests that the whole cell pertussis vaccine conferred longer lasting immunity as compared with acellular pertussis vaccines. Acellular DTP vaccine (DTaP), although safer than the whole cell pertussis vaccine, fails to protect for a longer period of time. Further research and data will produce a clear situation, and a road map on weather to continue with the same DTaP or go back to the DTwP vaccine. Nonetheless, efforts are on the way to improving the efficacy of the available DTaP vaccine.

Pertussis is estimated to kill approximately 2 million people around the globe, mostly in the developing countries. However, reports of laboratory confirmed pertussis are very rare. Unavailability of epidemiological data as well as diagnostic facilities from populations masses from developing countries may be a hurdle in managing the disease in this part of the world. Pertussis has been an under-reported disease. Advancement in diagnostic facilities and reporting systems in developed countries in last 2 decades may be one of the reasons behind its resurgence.

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