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Review Article

Resurgence of Diphtheria: A Narrative Review

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Abstract

Background: Changes in the epidemiology of diphtheria are occurring worldwide. Waning immunity to diphtheria was observed over time after childhood vaccination. After immunization in childhood, appropriate re-vaccinations are omitted for various reasons. Fear of adverse reactions in the course of diphtheria booster vaccination bears much of the responsibility. A large proportion of adults in many industrialized and developing countries are now susceptible to diphtheria. Inadequate boosting of previously vaccinated individuals may result in increased risk of acquiring the disease from a carrier, even if adequately immunized previously. The continuous circulation of toxigenic C. diphtheriae emphasizes the need to be aware of epidemiological features, clinical signs, and symptoms of diphtheria; so that cases can be promptly diagnosed and treated, and further public health measures can be taken to contain this serious disease.

Key Words: Diphtheria; immunization; re-emergence; epidemiology

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Introduction:

Diphtheria is an ancient disease, known since the time of Hippocrates. Diphtheria is a highly-contagious life threatening disease caused by toxigenic strains of Corynebacterium diphtheriae an aerobic Gram-positive bacterium, which are transforme d by a bacteriophage carrying the toxin gene. Diphtheria causative agent and its major virulence factor diphtheria toxin are well studied, but outbreaks of disease still occur worldwide.[1] Diphtheria is generally an upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane (a pseudomembrane) on the tonsil, pharynx or nose. A milder form of diphtheria is limited to the skin.[2] Complications may include myocarditis, inflammation of nerves, kidney problems, and bleeding problems due to low blood platelets. Myocarditis may result in an abnormal heart rate and inflammation of the nerves may result in paralysis.[3] Most of the clinical manifestation of diphtheria results from the action of an exotoxin produced by the pathogen. Diphtheria toxin (DT) produced by toxigenic strains of C. diphtheriae is considered as the main pathogenic factor of infection. Toxigenicity of C. diphtheriae is controlled by bacteriophage conversion. Thus toxin production occurs only when the bacterium is infected by lysogenic Corynephage carrying the tox gene encoding DT.[1] Humans are the only natural host of C.diphtheriae. Both toxigenic and non-toxigenic organisms reside in the upper respiratory tract and are transmitted by airborne droplets. The sites of infection are fauces, nose, larynx, conjunctiva, vulva, vagina, wound and ear.[3] The organism can also infect the skin at the site of a pre-existing skin lesion. This occurs primarily in the tropics but can occur worldwide in indigent persons with poor skin hygiene.[4] Overcrowding, poor health, substandard living conditions, incomplete immunization and immunocompromised states facilitate susceptibility to diphtheria and are risk factors associated with transmission of this disease.[5] Although diphtheria is now reported infrequently in the world, in the pre-vaccine era, the disease was one of the most common causes of illness and death among children.[2] Outbreaks though very rare, still occur worldwide, even in developed

nations. After the breakup of the former Soviet Union in the late 1980s, vaccination rates in its constituent countries fell so low that there was an explosion of diphtheria cases.[3] Between 1990 and 1998, the countries of the former Soviet Union reported more than 1,50000 cases and 5000 deaths, which represented more than 80 percent of diphtheria cases reported globally.[5] It was the largest diphtheria epidemic since the 1950s, when widespread diphtheria immunization began.[6] Today diphtheria evolves from children's disease into disease affecting predominantly, adults, with severe respiratory forms of infection.[7] Despite the widespread use of immunization, diphtheria remains endemic in several regions including Africa, India, Bangladesh, Nepal, Indonesia, Vietnam, the tropics and areas of South America including Brazil.[1] However, the majority of the adult populations in Europe, Australia and the United States have no immune protection against this infection. Diphtheria remained endemic in some states of United States through the 1970s, with reported incidence rates of greater than 1.0 per million population in Alaska, Arizona, Montana, Mexico, South Dakota and Washington.[5] Most of these infections were attributed to incomplete vaccination. In the United States, diphtheria currently occurs sporadically, mostly among the Native American population, homeless people, lower socioeconomic groups, and alcoholics. Immigrants and travelers from regions with ongoing epidemics are also at risk.[5] This issue draws renewed attention to the immunology of this infection, because lowered immunity levels within population can cause outbreaks of diphtheria.[1]

The reasons for re-emergence of epidemic in countries where immunization programs had nearly eliminated are not fully understood but are thought to include-The introduction of toxigenic C.diphtheriae strains of a new biotype into the general population; The low coverage with diphtheria vaccine among children; crowding and poor personal hygiene have contributed to transmission and increase in diphtheria infections in adults.[8] Importation of the microorganism from regions where diphtheria remains endemic also poses a constant threat, particularly among subgroups of individuals with low vaccination levels. Between 1986 and 1994 the majority of toxigenic strains isolated in the United Kingdom was imported from the Indian subcontinent, Pakistan, Africa, Somalia and the Tropics.3 In Netherlands, the introduction of diphtheria into religious communities, refusing vaccination constituted a danger of spread of the bacterium, as more than 60% of orthodox reformed persons had no protective diphtheria antibody levels.[8] In the last 10 years, there have been a number of reports of either re-emergence or persistence of diphtheria from several Indian states including Andhra Pradesh, Delhi, Assam, West Bengal etc.[9] The data on vaccine-preventable diseases provided by the Government of India to the World Health Organization (WHO) during 1980-2008 indicated persistence of diphtheria without much decline over the last 25 years.[3] India accounted for 19-84% of the global burden of diphtheria from 1998 to 2008.[9] These data brought out important features about the epidemiology of diphtheria in India. For example, the disease, which was common among under five children in the past, is now affecting older children (5-19 years) and adults. Persistence or resurgence of diphtheria in the country was mainly due to low coverage of primary immunization as well as boosters.[10] India has accounted for 3,123 cases of the total of 4,053 cases (77.05%) reported in the world in 2010.[11] As India is our neighboring country, this data is of particular concern for us. In Bangladesh however there is continuous occurrence of few cases of diphtheria in every year. During the year from 2011 to 2015 in Bangladesh number of diphtheria cases were serially 11,16,02,13 and 06.[12] The reasons for the recrudescence of diphtheria are the decreasing immunity due to relaxation of endeavors for appropriate vaccination and the introduction of toxigenic pathogens, especially from developing countries and from the East. In the absence of antigen stimulation by circulating toxigenic diphtheria bacteria strains or without regular booster vaccinations, the protective antibody titres fall below the protective threshold. Unprotected persons then do not only have a high individual risk, but also once more enable spreading of diphtheria on an epidemic scale.[13]

Epidemiology

At the beginning of the 1980s, many countries in the world were progressing toward the elimination of diphtheria.[3] Diphtheria incidence rates reached their lowest levels, and there was optimism that elimination of indigenous respiratory diphtheria could be achieved in the European Region by 1990 by maintaining and strengthening immunization services.[13] However, a striking resurgence of epidemic diphtheria in the Newly Independent States (NIS) of the former Soviet Union has drawn attention to our lack of a full understanding of the epidemiology of the disease.[14] The epidemic began in the Russian Federation at the end of the 1980s and had affected all 15 NIS countries by the end of 1994.[15] Since 1992, some of the diphtheria cases reported

from other parts of Europe have been linked to transmission from the NIS epidemic: in Belgium, in England and Wales, in Finland, in Germany, and in Greece.[16] In Poland, 19 of 25 persons diagnosed with diphtheria in 1992–1995 had traveled to Russia, Ukraine, or Belarus or had contact with visitors from these countries.[17] Importation of diphtheria cases to European countries and Mongolia and diphtheria cases among US citizens traveling or residing in the NIS gave rise to the fear that the NIS epidemic might spread over a wider area.[14] As late as 1997, as the epidemic was waning, the NIS countries reported <40% of the diphtheria cases worldwide.[13,14]

The diphtheria epidemic in NIS provided important information. First, there was a high proportion of cases among adolescents and adults, especially in Belarus, Russia, Ukraine, and in Baltic States (Estonia, Latvia, and Lithuania), and a lower proportion of cases in these age groups in the southern republics of the Caucasus area and Central Asia.18 Second, the epidemic began as an urban epidemic, with a progressive transition to include rural areas over time. Third, the epidemic initially amplified in groups with high rates of close contacts (e.g., hospitals, military troops, kindergartens, schools), and later, it made a transition to a more generalized epidemic involving socioeconomically disadvantaged groups (e.g., alcoholics). The Soviet armed forces may have played a role in the introduction and spread of toxigenic Corynebacterium diphtheriae, and several diphtheria outbreaks were reported in Russia among military staff. Military recruits were not routinely vaccinated against diphtheria until 1990.[16,18] The first cases of diphtheria in Moscow in 1990 were among paramilitary construction workers. From May 1988 to February 1989, the demobilization of 100,000 Soviet troops who had served in Afghanistan, where endemic diphtheria was reported, may have contributed to the introduction and spread of toxigenic strains of C.diphtheriae.[19]

In developing countries, high levels of vaccination of infants with diphtheria-tetanus toxoids-pertussis vaccine (DTP) have been achieved following implementation of the Expanded Program on Immunization of the World Health Organization (WHO) in the 1970's (WHO 1984).[11] Despite the widespread use of immunization, diphtheria remains endemic in several regions including Africa, India, Bangladesh, Vietnam, the tropics and areas of South America, including Brazil. Several countries where coverage has been high for 5-10 years have reported diphtheria outbreaks.[20] High case fatality rates, a large proportion of patients with complications, and their occurrence in both young and older age groups characterized these outbreaks.[8] The diphtheria epidemic in NIS provided important information. First, there was a high proportion of cases among adolescents and adults, especially in Belarus, Russia, Ukraine, and in Baltic States (Estonia, Latvia, and Lithuania), and a lower proportion of cases in these age groups in the southern republics of the Caucasus area and Central Asia.[18] Second, the epidemic began as an urban epidemic, with a progressive transition to include rural areas over time. Third, the epidemic initially amplified in groups with high rates of close contacts (e.g., hospitals, military troops, kindergartens, schools), and later, it made a transition to a more generalized epidemic involving socioeconomically disadvantaged groups (e.g., alcoholics). The Soviet armed forces may have played a role in the introduction and spread of toxigenic Corynebacterium diphtheriae, and several diphtheria outbreaks were reported in Russia among military staff. Military recruits were not routinely vaccinated against diphtheria until 1990.[16,18] The first cases of diphtheria in Moscow in 1990 were among paramilitary construction workers. From May 1988 to February 1989, the demobilization of 100,000 Soviet troops who had served in Afghanistan, where endemic diphtheria was reported, may have contributed to the introduction and spread of toxigenic strains of C.diphtheriae.[19]

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In the last 10 years, there have been a number of reports of either reemergence or persistence of diphtheria from several Indian states, including Andhra Pradesh, Delhi, Maharashtra, Chandigarh, Gujarat, Assam, West Bengal, Madhya Pradesh, Uttar Pradesh, Rajasthan and Haryana.[9] The data on vaccine preventable diseases provided by the Government of India to the World Health Organization (WHO) during 1980-2008 indicate

persistence of diphtheria without much decline over the last 25 years.20 India accounted for 19-84% of the global burden from 1998 to 2008.[10]

These reports bring out certain important features about the epidemiology of diphtheria in India. First, the disease, which was common among under five children in the past, is now affecting older children (5 to 19 years) and adults. Second, in certain states, the disease is common among females and Muslims. Third, the majority of the cases are reported from children who were unimmunized/partially immunized against diphtheria. Persistence or resurgence of diphtheria in the country was mainly due to low coverage of primary immunization as well as boosters. According to the WHOUNICEF estimates, the DPT3 coverage was 66% in 2008, whereas as per the three National Family Health surveys, DPT3 coverage during 1992–2006 was only 52–55%.[11] Because the immunity acquired through primary immunization wanes in early childhood, adequate coverage of booster doses is equally important.[10]

Evolution of the disease

Incubation period: usually 2-4 days.[4] The toxigenic strains of C. diphtheriae after colonizing the tissue of susceptible individual remain localize at the site. Here they multiply and cause coagulative necrosis producing a typical grayish white false membrane. They liberate a powerful exotoxin.[4] The toxin by the help of its spreading factor is absorbed into the circulation and gets fixed to cells of various organs. For a time this union is dissociable but afterwards permanent fixation takes place. The toxin kills the cells by interfering with its protein synthesis.[3]

Pathogenesis

The principal human pathogen of the genus Corynebacterium is Corynebacterium diphtheriae, the causative agent of respiratory or cutaneous diphtheria. In nature, Corynebacterium diphtheriae occurs in the respiratory tract, in wounds or on the skin of infected persons or normal carriers. It is spread by droplets or by contact to susceptible individuals; the bacilli then grow on mucous membranes or in skin abrasions, and those that are toxigenic start producing toxin.[4] All toxigenic Corynebacterium diphtheriae are capable of elaborating the same disease-producing exotoxin. In vitro production of this toxin depends largely on the concentration of iron. Toxin production is optimal at 0.14 μg of iron per milliliter of medium but is virtually suppressed at 0.5 μg/mL.[21] Other factors influencing the yield of toxin in vitro are osmotic pressure, amino acid concentration, pH, and availability of suitable carbon and nitrogen sources. The factors that control toxin production in vivo are not well understood. Diphtheria toxin is a heat-labile polypeptide (molecular weight [MW], 62,000) that can be lethal in a dose of 0.1μ g/kg.[22] If disulfide bonds are broken, the molecule can be split into two fragments. Fragment B (MW, 38,000), which has no independent activity, is functionally divided into a receptor domain and a translocation domain. The binding of the receptor domain to host cell membrane proteins CD-9 and heparin-binding epidermal growth factor (HB-EGF), triggers the entry of the toxin into the cell through receptor-mediated endocytosis.[23] Acidification of the translocation domain within a developing endosome leads to creation of a protein channel that facilitates movement of Fragment A into the host cell cytoplasm. Fragment A inhibits polypeptide chain elongation—provided nicotinamide adenine dinucleotide (NAD) is present—by inactivating the elongation factor EF-2. This factor is required for translocation of polypeptidyl-transfer RNA from the acceptor to the donor site on the eukaryotic ribosome. Toxin fragment A inactivates EF-2 by catalyzing a reaction that yields free nicotinamide plus an inactive adenosine diphosphate-ribose-EF-2 complex (ADP-ribosylation). It is assumed that the abrupt arrest of protein synthesis is responsible for the necrotizing and neurotoxic effects of diphtheria toxin.[24]

Pathology

Diphtheria toxin is absorbed into the mucous membranes and causes destruction of epithelium and a superficial inflammatory response. The necrotic epithelium becomes embedded in exuding fibrin and red and white cells, so that a grayish “pseudomembrane” is formed—commonly over the tonsils, pharynx, or larynx.[4] Any attempt to remove the pseudomembrane exposes and tears the capillaries and thus results in bleeding. The regional lymph nodes in the neck enlarge, and there may be marked edema of the entire neck, with distortion of the airway. The diphtheria bacilli within the membrane continue to produce toxin actively. This is absorbed and results in distant toxic damage, particularly parenchymatous degeneration, fatty infiltration, and necrosis in heart muscle (myocarditis), liver, kidneys (tubular necrosis), and adrenal glands, sometimes accompanied by gross hemorrhage.[25] The toxin also produces nerve damage (demyelination), often resulting in paralysis of the soft palate, eye muscles, or extremities. Wound or skin diphtheria occurs chiefly in the tropics,

although cases have also been described in temperate climates among alcoholic, homeless individuals and other impoverished groups.[25] A membrane may form on an infected wound that fails to heal. However, absorption of toxin is usually slight and the systemic effects negligible. The small amount of toxin that is absorbed during skin infection promotes development of antitoxin antibodies. The "virulence" of diphtheria bacilli is attributable to their capacity for establishing infection, growing rapidly, and then quickly elaborating toxin that is effectively absorbed. Corynebacterium diphtheriae does not actively invade deep tissues and practically never enters the bloodstream.[26]

Changes in Immunity Patterns by Age Changes in the age-wise distribution of the immunity patterns usually have been explained by the argument that immunization led to a marked decrease in the incidence of the disease and to a subsequent reduction of the reservoir of toxigenic C. diphtheriae organisms. In the pre-vaccine era, exposure to toxigenic strains of diphtheria organisms was common, and this provided natural boosts to the development and maintenance of immunity against diphtheria.[27] Children were susceptible, and most adults remained immune to the disease. However, after immunization of children became widespread, diphtheria became rare, so exposure to these bacteria (and the concomitant natural boost of immunity) become uncommon. If adults do not have natural exposure to diphtheria-causing organisms or receive booster doses of diphtheria toxoid, their immunity induced by childhood immunization wanes, and they become susceptible to the disease.[28] A large body of evidence has documented changes in the immunity levels of various age groups in the pre and post-vaccine eras. In the pre-vaccine era, when the circulation of C. diphtheriae organisms was common and the prevalence of diphtheria cases was high, natural immunity was acquired by overt or subclinical infection.[29] Most newborn infants passively acquired antibodies from their mothers via the placenta. In 1914 in Vienna and in 1923 in New York City, 80% of newborns showed evidence of diphtheria immunity.[16,18] During the first several months of life, this passive immunity waned and was gradually replaced by active immunity, which was acquired through increasing exposure to natural infection. By 15 years of age, 80% of the children had acquired natural immunity against diphtheria. The rate of acquisition of natural immunity, however, differs from country to country, probably due to differences in the intensity of early contact with diphtheria organisms, overcrowding, sanitation, and hygiene. Available data suggest that the pattern of acquiring diphtheria immunity in developing countries in the 1960s and 1970s resembled the pattern observed in Europe and the United States before the introduction of childhood immunization programs.[15] Infections of skin lesions with C.diphtheriae organisms seem to play a role in the rapid development of natural immunity in developing countries. In areas where diphtheria has been controlled through immunization programs, the immune status of the population has changed considerably: Children have high levels of diphtheria immunity as a result of childhood immunization.[27] The level of immunity declines in late childhood and adolescence, depending on the schedule of immunization and the remaining reservoir of C. diphtheriae in the population. Without the periodic administration of booster doses of diphtheria toxoid or repeated exposure to toxigenic strains of C.diphtheriae, adults become susceptible to diphtheria.30 The likelihood of having protective antibody levels decreases with age, and in some industrialized countries, 50% of adults are susceptible to diphtheria. Although the design and laboratory methods used in different sero surveys conducted in different countries and at different times varied considerably, the results of the sero surveys suggested a clear shift in the immunity distribution in different age groups.[27] This gap of immunity among adults exists in many industrialized countries: France, Germany, Norway, and Italy. In Germany, newborns and persons 50 years of age constituted the least protected groups. In the early 1980s, the lowest levels of diphtheria antibodies in various areas of the Soviet Union were found in persons 20–40 years old, and at present, this least protected group has shifted to persons 30–40 years old.12 In other countries, low-level protection was found in persons 40–50 years old in Australia, England, Germany, and Poland and in persons 50 years old in Denmark, Finland, Sweden and the United States.[15] A lower percentage of adults, especially men, in the north western areas of Russia have protective levels of diphtheria antitoxin compared with adults in northern Norway.[18] Thus, a high proportion of the adult population in industrialized countries lacks immunity and remains susceptible to diphtheria. A large pool of susceptible adults constitutes the potential for an epidemic, especially if this pool is coupled with the presence of susceptible children.[13]

Changes in the Age Distribution of Diphtheria Cases

When diphtheria was a common disease, it most frequently affected children: At least 40% of diphtheria cases were among children< 5 years of age, and some 70% of the cases

were among children< 15 years of age.18 Shifts in the age distribution of diphtheria case has usually been explained by the impact of immunization. However, historical data show that a shift of the disease to older ages began before mass immunization was introduced. Many European countries experienced diphtheria outbreaks during World War II, and it was estimated that in 1943 alone, there were a million cases of diphtheria in Europe, with 50,000 deaths.[8] Changes in the age distribution have been observed in many countries. In Netherlands, Norway and Denmark a sharp shift toward infection in older persons was seen in the 1940s. In Netherlands, the proportion of diphtheria cases in persons 18 years of age rose from 6% in 1930 to 37% in 1944. In 1944, an epidemic of diphtheria started in Copenhagen of 2200 cases, 1500 (68%) were among adults.[12] This outbreak may have been the result of a documented fall in immunity to diphtheria in adults in Copenhagen during the late 1930s, which was thought to have been due to a period when the incidence of diphtheria was low. The most interesting changes occurred in Germany, where diphtheria was endemic before World War II and where an alarming rise in the incidence of diphtheria was seen beginning in 1941.[16] Frequent references were made to the spread of malignant diphtheria in Germany in the early 1940s, the course of which was so rapid that serum therapy, even at a very early stage of disease development, had no effect.[31] Unexpectedly, the proportion of adult patients rose concomitantly with the overall rise in diphtheria incidence. In 1943, more than half of the diphtheria cases reported were among adults. This was a clear change in the age distribution of diphtheria patients in Germany from the beginning of the twentieth century, when only 1%–2.5% of diphtheria cases were among adults. Furthermore, among all diphtheria deaths reported, those involving adults also increased (from 12% in 1939 to 48% in 1943). Diphtheria was also an important cause of death in the German army, particularly as a complication of chest wounds and typhus.[32] In addition, the extent of vaccination against diphtheria during World War II was probably too small to change the age distribution of cases. All these observations suggest that changes in the age distribution of diphtheria cases resulted from factors other than vaccination. Socioeconomic factors, such as a general increase in the standard of living, smaller families, and less overcrowding, created an environment in which children were not subjected to the same intensity of infection in their preschool years as they had been previously. On the other hand, increasing enrollment in schools, summer camps, and meetings of children, adolescents, and adults from different neighborhoods and social backgrounds probably contributed to wider circulation of C.diphtheriae within these age groups.[9] Likewise, migration and displacement of many people during World War II probably enhanced the circulation of diphtheria organisms and contributed to the shift toward more adult cases. In many areas of Germany late in World War II, conditions were far from normal. People were at work during the day and in overcrowded bomb shelters at night. They were under constant stress, which was reinforced by shortages of food, water, and electricity. Some of these conditions enhanced the transmission of infection. Recent outbreaks of diphtheria in Europe and the United States have occurred in poor, socio economically disadvantaged groups living in crowded conditions. Crowding and poor personal hygiene may contribute to transmission and an increase in diphtheria infections. An epidemic of diphtheria that occurred in the United States in the early 1970s mainly affected adults from low socioeconomic groups who were heavy alcohol users. The role of cutaneous diphtheria has been emphasized by several diphtheria outbreaks in the United States among homeless alcoholic men and impoverished groups.[8]

Changes in the Epidemiology of Diphtheria in Developing Countries

Changes in the epidemiology of diphtheria are also occurring in developing countries. In such countries, a high rate of skin infections caused by C.diphtheriae creates a primary reservoir of diphtheria organisms, and the circulation of C.diphtheriae organisms still appears to be an important factor in the early development of natural immunity against diphtheria. However, the epidemiologic patterns of diphtheria may be changed by (1) successful immunization programs among children. (2) Socioeconomic changes (including migration from rural to urban areas and sociocultural changes with improving hygiene) and (3) changing lifestyles. With these changes, diphtheria can emerge as an epidemic disease, with more serious forms of the disease attacking older children, adolescents, or adults. As an example, diphtheria outbreaks in developing countries in the last 2 decades document a shift in age distribution similar to the shift witnessed in industrialized countries 30–40 years ago. The shift to older age groups seems to occur in two stages: In the first stage, the disease mainly attacks school children (Jordan1977–1978, Algeria1993–1996), and in later stages, the age distribution shifts to adolescents and young adults

(Jordan 1982–1983, Lesotho 1989, China 1988–1989). These outbreaks have been characterized by high case fatality rates, a large proportion of patients with complications, and the occurrence of the disease in both young and older age groups.[6-8] A high-incidence outbreak (118/1000 population) reported in preschool children in Yemen and diphtheria outbreaks in Jordan and Sudan demonstrated these changing age patterns. Outbreaks in Lesotho and Algeria occurred after periods of high immunization coverage.[21] In a province of China, after a period of low incidence (3 years with no diphtheria cases), an outbreak occurred with 70% of cases in persons 20 years of age. In a diphtheria epidemic in Algeria and in Ecuador, most cases were reported among older children, adolescents, and young adults.[13]

Situation in Bangladesh

Diphtheria is an important public health problem in Bangladesh and at times it reaches epidemic proportions. In the vast majority of instances the disease strikes the pre-school children (< 5 years). All the three biotypes are encountered in Bangladesh, but the gravis type is most frequently isolated. Next in frequency is the mitis type, intermedius being the least common.[3]

In Bangladesh however there is continuous occurrence of few cases of diphtheria in every year.

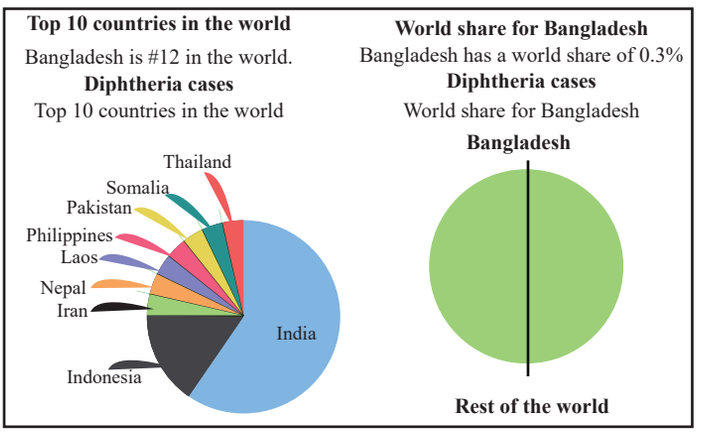

Figure: Diphtheria cases in the world 2016.[3]

The impact of routine childhood immunization on the epidemiology of many diseases is well known. A clear example is the dramatic decline in the incidence of diphtheria in industrialized countries. In parallel, many of these countries have realized that large segments of their adult populations are susceptible to diphtheria as a consequence of the decrease in the asymptomatic carrier status of toxigenic Corynebacterium diphtheriae and of the natural boosters that used to occur in the pre-vaccination era. When the circulation of toxigenic strains of C. diphtheriae is reduced, repeated doses of diphtheria toxoid are needed to maintain immunity in the adult population. However, acquisition of immunity against other diseases has not changed with time: protection against tetanus, for instance, can only be achieved through vaccination of each individual and subsequent boosters are needed in order to maintain protective antibody levels. Vaccination of the elderly population has now been recommended as a routine in some countries. Assessing immunity to vaccine-preventable diseases in the elderly is necessary in order to provide a correct immunization scheme. In Brazil, the First National Influenza, Pneumococcus, Tetanus and Diphtheria Vaccination Campaign for the Elderly took place in 1999.[15] Diphtheria is still a great public health concerns in many developing countries. During the past two decades, in spite of the low incidence of diphtheria in developed countries, limited outbreaks have been reported in the United States and parts of Europe.[8] So there is concern about outbreaks of these diseases especially in developing countries. After vaccination programs children are not threatened group by these diseases and recent cases are more common in the adult population. Vaccination against diphtheria has resulted in a fast decrease in morbidity and mortality due to this diseases . According to the current Iranian National Immunization program a primary series of 4 doses is recommended, with a booster dose at 4 to 6 years of age. A primary series of 3 doses is required if the vaccine is first administered after 7 years of age. Boosters of DT vaccine for adult are recommended every 10 years. When more than thirty percent of a population are non-immunized against diphtheria there is a chance of epidemic diphtheria occurring in that community. In order to achieve adequate levels of herd immunity and to prevent outbreaks, it is obligatory to analyze the immunity levels of the general population and to identify and vaccinate insufficiently protected groups.[33] Bangladesh has already achieved UN award in 2010 for fulfilling all the parameters of MDG goal including EPI coverage. So to achieve Sustainable Development Goal (SDG) it is important to focus on maintaining the immune status against communicable diseases like diphtheria.

Assessment of anti-diphtheria protection

Serologic methods of diphtheria diagnosis based on the detection of diphtheria toxin or on increased level of antitoxic antibodies.

Therefore, measurement of antitoxin level in diphtheria patients could provide important clinical information about course of infection. In addition, determination of anti-toxin antibodies is essential for characterization of the immune status of population, and evaluation of the immunogenicity of diphtheria vaccines in clinical trials, as well as for monitoring long-term immunity and thus provides recommendations for vaccination policy. Data obtained from serological studies serve as an important guide in choosing of local strategy of vaccination. Detecting the existence of a cohort of susceptible subjects can predict the risks for disease outbreaks. Therefore, it is of critical importance to have methods for assessment of anti-diphtheria immunity that are accurate, reproducible, specific, and sensitive. Most symptoms of diphtheria are resulted from the diphtheria toxin action; therefore, protection against disease depends on antibody level against the toxin (antitoxin). The assessment of the anti-diphtheria protection in healthy population is common for a surveillance system within any National Program of Immunization. Antitoxic antibodies probably play a main role in the immunity against diphtheria. Serum titers of antitoxin usually are expressed in International Units per milliliter (IU/ml) according to the diphtheria antitoxin standard. The cut-off of protective serum level of antitoxin is 0.01 IU per ml. (but it also depends on the method of titer determination). As believed, the powerful anti-toxin immunity (>1.0 IU/ml) can completely protects the body from infection caused by toxigenic strains. Although, the very little is known about protection associated with non-toxigenic strains. Classical serological tests tend to underestimate low concentrations of diphtheria antibody. That is why antitoxin level under 0.1 IU per ml could not be defined precisely in many laboratories where hemagglutination test is used for this purposes.[1] Numerous in vivo and in vitro tests for the measuring of diphtheria antitoxin levels in serum have been standardized and implemented for laboratory practice. Among the in vivo protocols are the Schick test in humans and the classical toxin neutralization (TN) assay in rabbits or guinea pigs. There is also the in vitro toxin neutralization test in microcell culture plates using highly sensitive Vero (green monkey renal epithelium) cell line. Several in vitro serologic techniques for diphtheria antitoxin determination are described.[1]

\Immunity to diphtheria

Diphtheria toxin produced by C. diphtheriae during the disease or the carrier state has ability to induce production of naturally acquired antibodies against the toxin (anti toxin). Artificial immunity to diphtheria can be stimulated with diphtheria toxoid immunization. Antitoxin can pass through the placenta providing passive immunity to the infant during the first few months of life. Patients can acquire passive immunity to diphtheria by injection of equine antitoxin in course of the disease therapy. As supposed, the primary role in the protection against diphtheria belongs to the antibodies of IgG class, but protection potential of IgA and IgM antibodies is remains underestimated. As mentioned earlier, antibodies to B fragment of DT are more protective than antibodies to A-fragment. Recovery from diphtheria is also associated with activity of phagocytes at site of infection. However, there is little known about cell mediated immune responses to toxin or toxoid and other antigenic substances of C. diphtheriae.[1]

Passive immunity to diphtheria

Passive immunity to diphtheria can occur naturally when maternal antibodies are transferred to the fetus through the placenta. Thus, most infants have protective antitoxin level acquired passively from their mothers. However, the half-life of passively acquired antitoxin by newborns is about 30 days, thus level of these antibodies significantly decreases between 6 and 12 months. Mothers and their infants have highest diphtheria antitoxin titers (above 0.1 IU/ml) in areas with normal circulation of toxigenic C. diphtheriae in population. High titers of maternal antibodies can interfere with serologic response of infants to diphtheria vaccination. The modifying effect of passively-acquired maternal antibodies in young infants is strongest under the age of 4 weeks. High titers of passively transferred antibodies may temporarily interfere with active immunization of infants. Maternal transferred antibodies may suppress responses to the first or second vaccination. Thus in the countries where circulation of toxigenic C. diphtheriae is common the early immunization of infant is not so effective due to the presence of high level of maternal antitoxin. At the other hand, early immunization of these infants can deplete their passive immunity due to the absorbance of maternal antibodies by injected toxoid.[1]

Resistance and Immunity

Because diphtheria is principally the result of the action of the toxin formed by the organism rather than invasion by the organism, resistance to the disease depends largely on

the availability of specific neutralizing antitoxin in the bloodstream and tissues. It is generally true that diphtheria occurs only in persons who possess no antitoxin (or less than 0.01IU/mL). Assessment of immunity to diphtheria toxin for individual patients can best be made by review of documented diphtheria toxoid immunizations and primary or booster immunization if needed.[14]

Conclusion

Long time diphtheria was considered as well-controlled vaccine-preventable disease but cases of diphtheria are still occur in Ukraine, Russia and Latvia and also it is endemic in India, Bangladesh, Indonesia, Nepal, Angola and Brazil, that primarily affects unvaccinated or inadequately vaccinated individuals. Diphtheria was a major cause of childhood mortality in the pre-vaccination era but now diphtheria evolves from children's disease into disease affecting predominantly, adults. It is well recommended that high immunization coverage, prompt diagnosis and rapid identification of close contacts are principal things in control of diphtheria outbreaks.

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