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PRACA POGLĄDOWA
REVIEW

Corynebacterium diphtheriae – An underrated threat? An analysis of the epidemiological risk of diphtheria in the 21st century

Corynebacterium diphtheriae – niedoceniane zagrożenie? Analiza ryzyka epidemiologicznego błonicy w XXI wieku

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ABSTRACT

Diphtheria is a potentially severe infectious disease caused by *Corynebacterium diphtheriae*, whose primary pathogenic factor is diphtheria toxin. Despite a significant reduction in incidence due to vaccination, recent years have seen a resurgence of cases, indicating a persistent epidemiological threat. The aim of this study is to present the current status of diphtheria as an epidemiological threat and to assess whether, in light of contemporary medical knowledge and current vaccination statistics, the threat remains significant both in Poland and globally. A narrative review of the literature from 2000 to 2024 was conducted using the PubMed, Scopus and Google Scholar databases, as well as WHO and CDC documents. Scientific, clinical, and epidemiological data were analyzed for their relevance and utility for public health. Diphtheria still poses a risk of serious cardiac and neurological complications, particularly in populations with reduced herd immunity. Effective prevention requires early diagnosis, rapid treatment (antitoxin and antibiotic therapy), and high vaccination coverage. Although diphtheria is now rare, it should not be underestimated. Educational, preventive, and epidemiological efforts are essential to prevent its resurgence. Vaccination remains the most effective form of protection.

KEYWORDS

Corynebacterium diphtheriae, diphtheria toxin, vaccination, epidemiology, prevention, antitoxin

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STRESZCZENIE

Błonica (dyfteryt) to potencjalnie ciężka choroba zakaźna wywoływana przez *Corynebacterium diphtheriae*, której głównym czynnikiem chorobotwórczym jest toksyna błonicza. W ostatnich latach, mimo znacznego ograniczenia liczby zachorowań dzięki szczepieniom ochronnym, obserwuje się ponowny wzrost liczby przypadków, co wskazuje na utrzymujące się zagrożenie epidemiologiczne. Celem pracy jest przedstawienie aktualnego stanu zagrożenia epidemiologicznego błonicą oraz ocena, czy w świetle współczesnej wiedzy medycznej i aktualnych statystyk dotyczących szczepień zagrożenie to pozostaje istotne zarówno w Polsce, jak i na świecie. Przeprowadzono przegląd narracyjny literatury z lat 2000–2024, korzystając z baz PubMed, Scopus i Google Scholar, a także dokumentów WHO i CDC. Analizie poddano dane naukowe, kliniczne i epidemiologiczne pod kątem ich znaczenia i przydatności dla zdrowia publicznego. Błonica nadal niesie ryzyko poważnych powikłań kardiologicznych i neurologicznych, zwłaszcza w populacjach z obniżoną odpornością zbiorowiskową. Skuteczna profilaktyka wymaga wczesnej diagnostyki, szybkiego leczenia (antytoksyna i antybiotykoterapia) oraz wysokiego poziomu wyszczepienia. Choć obecnie błonica występuje rzadziej, nie należy jej lekceważyć. Działania edukacyjne, profilaktyczne i epidemiologiczne są niezbędne, by zapobiec jej nawrotom. Szczepienia pozostają najskuteczniejszą formą ochrony.

SŁOWA KLUCZOWE

Corynebacterium diphtheriae, toksyna błonicza, szczepienia, epidemiologia, profilaktyka, antytoksyna

INTRODUCTION

Diphtheria (also known as diphtheritis or croup) is caused by an unencapsulated, non-motile, aerobic, Gram-positive bacillus *Corynebacterium diphtheriae* (*C. diphtheriae*; *diphtheria bacillus*) [1]. The disease may be asymptomatic, but often affects the respiratory and cutaneous systems, and can also lead to complications involving other organ systems [2]. The main risk factor for infection is remaining unvaccinated. Transmission occurs primarily via respiratory droplets. The pathogenicity of the bacterium depends on its ability to produce exotoxins that can spread through the bloodstream and cause damage to the myocardium and nervous system [1,2,3]. Patients infected with *C. diphtheriae* typically present with a characteristic thick, grey pseudomembrane adhering to the tonsils and pharynx. Immunization against diphtheria is part of the routine vaccination schedule, administered as a component of the combined diphtheria, tetanus, and pertussis (DTP) vaccine [3,4,5]. Due to widespread immunization, the global number of cases significantly decreased from approximately 98,000 in 1980 to around 4,200 in 2010. However, a recent increase in cases has been observed, suggesting that diphtheria remains an epidemiological challenge [1,2,3,4,5].
The aim of this study is to explore why *C. diphtheriae* still constitutes an epidemiological threat and to determine whether this threat remains relevant in Poland and worldwide, considering current scientific knowledge.

Methods

This study employed a narrative literature review to comprehensively discuss the epidemiological threat posed by *Corynebacterium diphtheriae* and to assess the current state of knowledge regarding diphtheria in Poland and globally. The objective was to collect, analyze, and synthesize data from various scientific, clinical, and epidemiological sources related to the etiology, pathophysiology, clinical symptoms, diagnostics, treatment, and prevention of diphtheria. Materials were collected by searching scientific databases including PubMed, Scopus, and Google Scholar. The review encompassed scientific publications, review articles, clinical guidelines, and official epidemiological reports published between 2000 and 2024, with particular emphasis on the most recent decade. The inclusion criteria called for publications in Polish or English addressing the clinical course of diphtheria, articles discussing its diagnosis, treatment, and prevention, clinical guidelines for the management of diphtheria cases, and peer-reviewed works or documents issued by recognized medical and public health institutions. The exclusion criteria applied to publications without clinical data, such as purely laboratory or molecular studies without clinical relevance, popular-science and non-peer-reviewed articles, local or historical papers without current relevance to healthcare, texts in languages other than Polish or English, and duplicates or conference abstracts without full data. Additionally, historical and classical medical sources were reviewed to present the development of knowledge about diphtheria over time. The information was subjected to qualitative analysis, with attention to data currency, consistency with current guidelines, and relevance in both epidemiological and clinical contexts.

Historical background

The first references to a disease resembling diphtheria can be traced back to Hippocrates (circa 300 BCE). A more comprehensive description was later provided by Aretaeus of Cappadocia (1st century CE), who described pseudomembranes on the tonsils and respiratory distress, among other features [6]. In 1821, Bretonneau was the first to use the term “diphtheria”, and in 1883–1884, Klebs and Löffler discovered and isolated its etiological agent, *Corynebacterium diphtheriae* (also known as the Klebs–Löffler bacillus). By the end of the 19th century, diphtheria posed a significant threat, including to medical personnel [6]. A major breakthrough in treatment occurred with the introduction of an equine antitoxin by von Behring in 1890. In 1924, an effective vaccine based on the diphtheria toxoid (PW8) was developed, leading to vaccination programs and a substantial reduction in the number of cases [7,8,9].

MICROBIOLOGICAL CHARACTERISTICS OF *C. diphtheriae*

C. diphtheriae is a Gram-positive, non-motile, non--encapsulated bacillus with a characteristic club--shaped morphology, often arranging in V- or L-shaped formations. The bacterium does not form spores. In addition to *C. diphtheriae*, cutaneous diphtheria can also be caused by *C. ulcerans* [1]. Four main biotypes of *C. diphtheriae* are distinguished – gravis, mitis, intermedius, and belfanti – all of which can produce diphtheria toxin [1,10,11,12,13,14]. The toxigenicity of the bacterium depends on the presence of a bacteriophage carrying the *tox* gene. The toxin consists of two fragments: B, which is responsible for binding to the host cell, and A, which inactivates elongation factor EF-2, thereby blocking protein synthesis and leading to cell death [1,5,7]. The result of the toxin's action is tissue necrosis, along with the characteristic pseudomembranes in the upper respiratory tract; damage may also extend to the myocardium, kidneys, and nervous system [3,15].

ROUTES OF TRANSMISSION AND RISK FACTORS

C. diphtheriae is primarily transmitted via exhaled droplets, for example, through coughing, but also through contact with the secretions of infected individuals, skin lesions, or contaminated objects [16]. Infection may also arise from close contact with animals that serve as reservoirs of the bacterium [17]. Medical risk factors include insufficient vaccination, immunosuppression, and low herd immunity levels. Non-medical risk factors include traveling to endemic regions, low socioeconomic status, living in overcrowded conditions (e.g., in prisons or shelters), and mass migration. Diphtheria infection does not correlate with gender or ethnicity, although it most commonly affects children under 12 years of age [1]. Adults are also susceptible, particularly those who have not received booster doses of the vaccine. The incubation period typically ranges from 2 to 5 days. The infectious period lasts throughout the clinical course of the disease and may continue for 2 to 3 weeks after symptoms resolve [6]. Asymptomatic carriers also constitute a significant source of infection, as they may unknowingly transmit the bacterium, especially in populations with low vaccination coverage [18,19,20,21,22,23,24].

CLINICAL PRESENTATION, DIAGNOSIS, AND TREATMENT OF DIPHTHERIA

Diphtheria typically develops within 2 to 5 days of infection. Symptoms include fever, sore throat, difficulty breathing and swallowing, cervical lymphadenopathy, and the presence of a characteristic grey, fibrous pseudomembrane in the throat. Advanced cases may lead to the development of so-called "bull neck," dyspnea, hoarseness, and signs known as "diphtheritic croup" [13,19]. Nasal diphtheria is characterized by a chronic, often bloody discharge and mild systemic symptoms [13]. The cutaneous form most commonly affects the legs and manifests as non-healing ulcers covered with a grey membrane, especially in areas of previous skin injury [25,26,27,28].

Complications result from the action of diphtheria toxin, which may damage the heart and nervous system. Myocarditis occurs in most severely ill patients and can present as heart failure, arrhythmias, electrocardiographic abnormalities, and even death during convalescence [4,7]. Neuropathies typically affect the soft palate, extraocular muscles, and cranial nerves, with limb paralysis occurring in later stages [29,30,31,32,33,34,35].

Diagnosis is based on clinical presentation, patient history (vaccination status, travels, and contact), and microbiological testing and is confirmed by the Elek test, PCR, or EIA for detecting the *tox* gene, as well as cultures on specialized media such as Löeffler or Tindale agar [1,7,11]. Differential diagnosis should consider other pharyngeal diseases, including streptococcal pharyngitis, infectious mononucleosis, epiglottitis, oral candidiasis, and retropharyngeal abscess [1,9,10].

Treatment includes administration of diphtheria antitoxin (DAT) and antibiotic therapy (erythromycin or penicillin G) and must be initiated as early as possible. The antitoxin only neutralizes circulating toxin, so its effectiveness depends on the timing of administration – delays significantly increase mortality [12,13,35,36,37,38,39,40]. Antibiotics shorten the period of infectivity and eradicate the bacteria, with alternatives such as linezolid or metronidazole being available in cases of resistance [1,14]. Patients should be isolated for at least 6 days or until two consecutive negative culture results are obtained [12]. The increasing antibiotic resistance of

C. diphtheriae, observed in Brazil, for example, highlights the need for continuous surveillance and therapy adjustment [41,42,43,44,45].

Early diagnosis and prompt treatment are crucial for prognosis. The highest mortality rates are observed in children under the age of 5 and adults over 40, as well as in cases with delayed treatment and cardiovascular involvement [1].

CONTEMPORARY EPIDEMIOLOGY AND GLOBAL SITUATION

Following the introduction of widespread DTP vaccination, there was a dramatic global decline in diphtheria cases. In the 1980s, nearly 100,000 cases were still being reported annually; for example, there were over 97,000 in 1980 alone [27]. The incidence significantly decreased over the following decade. However, in the mid-1990s, a serious diphtheria epidemic occurred in the countries of the former Soviet Union, resulting in over 150,000 reported cases and approximately 5,000 deaths. This outbreak demonstrated that large adult populations with no immunity and low childhood vaccination rates can lead to a rapid resurgence of the disease within communities. Thanks to international control efforts, including catch-up vaccination campaigns, the epidemic was contained by the late 1990s. Global incidence reached its lowest levels in the early 2000s. In subsequent years, the incidence remained relatively low, with annual global reports ranging from several thousand to just over ten thousand cases [28,32,46,47].

However, since around 2010, a renewed increase in global diphtheria cases has been observed. In the last decade, the number of reported cases has nearly quintupled (between 2010 and 2019) [27]. For example, in 2017, there were 8,819 reported cases – the highest since 2004 – and by 2019, the global figure exceeded 22,000 [27,28]. It is important to note that these numbers are based on WHO/UNICEF surveillance reports and are likely underestimated, meaning that the actual number of cases may be significantly higher. The rise in cases from 2010 to 2020 has been attributed not only to improved surveillance and case detection (particularly in endemic countries), but also to the emergence of outbreaks under specific conditions, such as armed conflicts, mass migrations, and a decline in vaccine confidence in certain populations. Despite the overall downward trend observed since the 1960s, diphtheria remains a significant public health concern on a global scale [28].

Epidemiological situation in different countries worldwide

The epidemiological situation of diphtheria varies significantly across regions. Currently, the disease remains endemic primarily in the developing countries of Asia and Africa. The highest numbers of cases are reported in Southeast Asia and Africa [27,29,30, 46,47,48,49,50,51]. In contrast, in the Americas, diphtheria has been largely eliminated except in countries such as Haiti and the Dominican Republic, where outbreaks continue to occur [30]. In Europe, thanks to widespread vaccination, the situation remained stable for many years, with only a few dozen cases being reported annually [31]. However, even in these regions, diphtheria can resurge locally under favorable conditions.

There is a clear difference in epidemiological patterns between developed and developing countries. In high-income countries with organized immunization programs, diphtheria has largely faded from public awareness. In most countries of Western Europe, the disease is usually imported by travelers or migrants from endemic regions or is spread among unvaccinated subpopulations. Thanks to high vaccination coverage, the disease does not spread widely in these societies. According to available data, diphtheria is rare in high-income countries [27]. For instance, in the United States, respiratory diphtheria has been virtually absent over the past two decades, with the last case being reported in 2003, involving an American traveler [30]. In the European Union (EU), before 2022, an average of around 50 cases were reported annually (mostly isolated incidents), which, given the population of over 500 million, indicated near-elimination. A rise was observed in 2022–2023, when 281 cases were reported in Europe, mainly among migrants in reception centers. These cases largely involved individuals from endemic regions, including outbreaks in refugee facilities in Germany and Switzerland. However, no broader transmission to the general European population was recorded. This incident demonstrates that even developed countries must maintain epidemiological vigilance, because migration and travel can reintroduce diphtheria into local communities, but also that high vaccination rates prevent wider spread [32].

Diphtheria remains endemic in low- and middle-income countries and periodic epidemics are a major public health concern. Low primary DTP vaccination rates and limited access to healthcare allow the bacterium to continue circulating, particularly in densely populated, impoverished areas [27]. Most global diphtheria cases originate from developing countries. According to the World Health Organization (WHO), nearly all reported infections occur in Asia, Africa, and parts of the Americas. For example, India has reported thousands of cases annually for many years, accounting for a significant share of the global burden. Indonesia experienced recurring outbreaks in the past decade, with over 4,000 pediatric cases being reported in East Java province alone since 2011 [29]. Bangladesh faced a major outbreak among Rohingya refugees living in unsanitary conditions in 2017–2018. Yemen saw thousands of cases across several provinces during its ongoing civil war (2017–2018), driven by the collapse of vaccination and healthcare systems. Venezuela, affected by economic crisis, also experienced a diphtheria resurgence, with thousands of cases being reported since 2016 due to declining immunization rates and emigrating medical professionals [27]. Other examples include Pakistan and Nepal (outbreaks after 2010), Haiti (epidemic following natural disasters), and Ukraine, where dozens of cases were reported in 2017–2018 amid declining vaccine confidence [30]. These examples underscore that developing countries frequently struggle with diphtheria outbreaks, especially where underfunded health systems, conflict, and migration converge [27].

Factors contributing to diphtheria outbreaks

Despite the availability of an effective vaccine, *C. diphtheriae* can still cause local outbreaks when favorable conditions arise. One major factor is war and armed conflict. During wars, routine healthcare services and immunization programs collapse and civilians are often exposed to overcrowded shelters and poor hygiene. This creates an ideal environment for diphtheria transmission. Notable examples include the outbreak in Yemen (2017–2018) and clusters in Syria during the civil war. In such contexts, the lack of routine vaccinations and limited access to treatment, including DAT, often results in high mortality. The WHO emphasizes that diphtheria is particularly likely to re-emerge in settings of conflict or political instability, where overcrowding, interrupted vaccination schedules, and collapsed health infrastructure intersect [27].

Another major contributor is migration and population displacement. Mass population movements can introduce pathogens from endemic areas into regions where diphtheria has not been reported for years. This is especially true for refugees and migrants from countries with low vaccination coverage. Displacement camps with poor living conditions are prone to outbreaks, such as the diphtheria epidemic among Rohingya refugees in Bangladesh [27]. Even small-scale movements, such as air travel by infected individuals, can lead to more cases. Europe faced this challenge in 2022, when most newly reported cases involved migrants in reception centers [32].

Low vaccination coverage and immunity gaps also increase the risk of outbreaks. Communities with insufficient diphtheria vaccination rates are vulnerable, particularly where large proportions of children or adults remain unvaccinated or lack immunity. The post-Soviet epidemic illustrated how a significant group of unprotected adults, combined with disrupted childhood vaccination programs, created ideal conditions for the rapid spread of disease [28]. Today, countries where coverage with a third dose of the DTP vaccine (DTP3) remains below the recommended 90% threshold frequently experience outbreaks. According to WHO estimates, in 2021, approximately 14.5 million infants worldwide did not receive even the first dose of DTP due to limited access or vaccine hesitancy. This "zero-dose" population represents a key reservoir for potential infection [33]. Pockets of incomplete vaccination are found in all countries, including high-income ones, highlighting the importance of achieving and maintaining high vaccination coverage across all population groups [27].

Weak and underfunded healthcare systems also play a critical role. Inadequate infrastructure and disrupted preventive programs facilitate the resurgence of infectious diseases. Inadequate epidemiological surveillance means that outbreaks may go undetected until they escalate. A specific issue in diphtheria management is the limited global supply of diphtheria antitoxin, with ongoing shortages complicating outbreak response [29].

In a world where *C. diphtheriae* still circulates in some populations, it is crucial to identify the most vulnerable groups. The highest-risk group includes unvaccinated or incompletely vaccinated individuals, particularly children who have not completed the full DTP series. The absence of vaccine-induced immunity means that even occasional contact with the pathogen can lead to disease. During outbreaks, most cases occur among unvaccinated individuals – for instance, during one outbreak in Indonesia, 76% of affected children had not completed DTP immunization [29]. However, diphtheria can affect any age group if immunity is lacking. Communities that refuse vaccination (due to religious or ideological reasons) often form clusters of susceptible individuals [30].

Another at-risk group is adults who have not received recent booster doses. Because vaccine-induced immunity against diphtheria wanes over time, booster doses are recommended every 10 years [31]. Adults who have not received a booster in the past decade may have insufficient antibody levels. In the United States, in 2017, only 63.4% of adults reported having received a tetanus-diphtheria (Td) vaccine within the last 10 years and only 31.7% had received the Tdap vaccine, which also protects against pertussis [44]. This includes elderly individuals vaccinated long ago or exposed to diphtheria in childhood, whose immunity may have diminished over time. In populations where wild-type diphtheria has not circulated for years, adults lack natural immune boosting. This was the case for adults in post-Soviet countries during the 1990s, where an entire generation not covered by previous mass vaccination campaigns became a susceptible reservoir [28]. Thus, unprotected adults, whether they have never been vaccinated or are overdue for a booster, constitute a key risk group, particularly when exposed to imported infections.

Travelers to endemic regions are also at risk. They may be exposed to infection if not adequately vaccinated. This applies to tourists, humanitarian workers, and military personnel alike [30]. Risk is also elevated in populations living in poor sanitary conditions. Diphtheria spreads more easily in settings with close human contact and limited hygiene, such as overcrowded environments that facilitate droplet transmission or contact with contaminated surfaces [30]. Outbreaks among refugees, prisoners, or slum dwellers are especially concerning [34].

Healthcare personnel and caregivers are also at risk during outbreaks. When diphtheria clusters occur, individuals caring for patients, such as doctors, nurses, and paramedics, may be exposed to the disease. Standard protocol includes verifying their vaccination status and administering prophylactic antitoxin or antibiotics if exposure is suspected. While medical staff in developed countries are usually vaccinated, such protection may be lacking in resource-poor settings. Nevertheless, the main drivers of transmission are patients and those they interact with, not well-protected healthcare professionals [35,36].

Epidemiological challenges and controversies

Despite the availability of effective vaccines, new challenges have emerged in recent years that hinder full control of diphtheria. One such challenge is the rise of vaccine hesitancy. In many countries, a decline in public trust in vaccination has been observed, driven by misinformation and fear of adverse reactions. In high-income countries, anti-vaccine movements have contributed to reduced childhood immunization rates, creating clusters of susceptible individuals vulnerable to the re-emergence of diseases previously under control. In developing countries, logistical, cultural, and religious barriers also play a significant role in limiting vaccine coverage. This phenomenon affects diphtheria vaccination as well. According to the WHO, vaccine hesitancy has become one of the global threats capable of reversing prior successes in diphtheria elimination [38]. For example, in Ukraine, between 2010 and 2016, DTP3 vaccination rates dropped to alarmingly low levels due to the spread of anti-vaccine sentiment, contributing to a resurgence of polio and raising concerns about a potential diphtheria epidemic. Similar trends, although on a smaller scale, have been observed in Western Europe and the United States, where local declines in child vaccination rates increase the risk of diphtheria transmission in the event of bacterial importation. Combating misinformation and educating the public about vaccine safety and efficacy remains a critical priority to sustain herd immunity [37].

In many parts of the world, basic immunization programs still do not reach all children. Geographic isolation (e.g., remote villages) and economic and social disparities prevent parts of the population from receiving required vaccinations. According to WHO data, global DTP3 coverage has stagnated at approximately 86% over the past decade, with no notable improvement [27]. Moreover, there was a marked setback between 2020 and 2021: global DTP3 coverage dropped from 86% in 2019 to just 81% in 2021 – the most significant decline in decades. In 2021, approximately 20 million children worldwide did not receive the full course of diphtheria vaccination, including 14.5 million who had not even started the schedule [33]. This issue primarily affects low-income countries, where healthcare systems face shortages of funding, personnel, and infrastructure. Access to vaccines can also be disrupted during crises, as in Venezuela, where currency shortages led to interruptions in vaccine supply. Likewise, in conflict zones, the distribution and transportation of vaccines may be severely constrained [27].

Interruptions or neglect in vaccination schedules also disrupt diphtheria control efforts. Program continuity can be compromised not only by vaccine refusal, but also by unforeseen events such as the COVID-19 pandemic. The consequences of the pandemic in 2020–2021 were devastating for routine childhood immunizations worldwide, as the suspension of clinical services and diversion of resources toward pandemic response caused delays and cancellations of many vaccination campaigns [27]. This led to the most significant drop in global immunization coverage since the 1990s, with DTP3 rates falling to their lowest levels in approximately 20 years [39]. Although a partial recovery was observed in 2022–2023 (reaching around 84% in 2023), pre-pandemic levels have not yet been fully restored [33]. This loss of continuity has resulted in a larger population of children susceptible to diphtheria and other preventable diseases.

The situation in Poland

Although Poland remained free of diphtheria cases for many years, recent developments have raised concerns about the potential re-emergence of the disease [40]. In 2021, the first confirmed case of diphtheria in over two decades was reported, alarming the medical and epidemiological communities. The patient was a 41-year-old Ukrainian man living in poor social conditions in Poland. He was diagnosed with the cutaneous form of diphtheria caused by a toxigenic strain of *C. diphtheriae*. The patient was homeless, suffered from chronic alcoholism and epilepsy, and lacked vaccination, all of which created favorable conditions for infection. This incident marked the actual return of diphtheria to Poland after more than 20 years without any reported cases [40]. In 2023, a fatal case of respiratory diphtheria was described in a Polish woman who had traveled to Germany and died from an infection caused by a toxigenic *C. diphtheriae* mitis biotype strain. Genetic analysis (next-generation sequencing – NGS) identified the strain as ST574, resistant to cotrimoxazole, and likely part of an undetected diphtheria cluster in Poland. Researchers suggested a possible link between this fatal case and the earlier cutaneous diphtheria case in a homeless man from the same region [41]. These incidents demonstrate that despite Poland's historical success in immunization programs, diphtheria remains a potential epidemiological threat, especially in the context of migration and the emergence of unvaccinated populations [41]. This phenomenon is not unique to Poland: similar challenges are being observed in other Central and Eastern European countries. According to the European Centre for Disease Prevention and Control (ECDC), between 2022 and 2023, a total of 281 confirmed diphtheria cases were reported in the European Union / European Economic Area (EU/EEA), most of them in Germany (206), followed by Belgium (37), Czechia (10), Slovakia (9), and the Netherlands (9). Most infections occurred in men aged 15–44 and residing in migrant reception centers, often in unsanitary conditions. Most cases reported in Czechia and Slovakia were cutaneous diphtheria and were associated with migrant populations; Slovakia recorded one fatal case in 2022. While countries such as Hungary and Romania did not report major outbreaks during this period, their geographical location and role in migration routes mean that future cases cannot be ruled out [32,46]. A shared priority across the region is to maintain high vaccination coverage, effective epidemiological surveillance, and international cooperation in identifying and controlling potential outbreaks [37].

PREVENTION AND THE IMPORTANCE OF VACCINATION

Vaccination is the cornerstone of diphtheria prevention. Vaccines contain diphtheria toxoid – an inactivated form of the toxin that stimulates antibody production [1]. These are usually administered in combination with tetanus toxoid and pertussis antigens: DTaP (for children), Tdap (for adolescents and adults), and DT or Td (for individuals with contraindications to pertussis vaccines) [1]. According to Centers for Disease Control and Prevention (Advisory Committee on Immmunization Practices) guidelines, individuals over the age of 11 should receive a Tdap dose followed by Td booster doses every 10 years [14]. Vaccine-induced immunity may wane after 10–15 years, meaning that many adults have suboptimal antibody levels and require boosters [43]. Infection prevention also includes isolating infected individuals and providing prophylactic treatment to those with whom they have contact. Epidemiological surveillance plays a key role in the early detection and containment of outbreaks. Thanks to vaccination, diphtheria has been nearly eliminated in many countries [18].

MODERN DIAGNOSTICS AND PREVENTION OF DIPHTHERIA

Modern diagnostic approaches to diphtheria use advanced technologies. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry allows for the rapid identification of *C. diphtheriae* strains based on protein profiles, though it does not assess toxigenicity [7]. Toxin production is confirmed using the lateral flow immunoassay (LFIA) strip test – a rapid immunoassay with high sensitivity and specificity [16]. Innovative molecular methods such as loop-mediated isothermal amplification (LAMP) can detect the *tox* gene without a thermocycler, making them suitable for field settings [17]. Research is also ongoing on biosensors that combine toxin detection with a signal output [17]. Classic diagnostics are supported by identification systems such as API Coryne, RapID CB Plus, and BBL Crystal, which provide rapid biochemical assessments [7].

Innovation in vaccines has brought about BR-TD-1001, a modern Td vaccine with high efficacy and safety for adolescents and adults [18]. DTP programs, introduced globally through the WHO's Expanded Programme on Immunization (EPI) in the 1970s, have played a vital role in reducing diphtheria mortality [19,20,21]. Over time, combination vaccines (e.g., pentavalent formulations), booster doses, and maternal vaccinations were implemented [22]. The "cocooning" strategy, which involves vaccinating the close contacts of infants, helps reduce transmission [23]. Epidemiological investigations remain essential for controlling outbreaks, particularly in low-coverage countries [24]. In response to global shortages of equine DAT (eDAT), next-generation therapies are in development, including the human monoclonal antibody S315, which offers high efficacy and long-lasting protection [25], and recombinant scFv antibody fragments, which eliminate the risk of allergic reactions associated with animal-derived sera [26].

Future prospects

Despite the success of immunization programs, diphtheria continues to pose a potential epidemiological threat. Several key areas require strengthening in the future. Firstly, epidemiological surveillance must be further developed. The European Diphtheria Surveillance Network (EDSN) supports EU countries in monitoring and diagnostics, but additional investment in infrastructure and training is needed, especially in resource-limited settings [47]. Secondly, there is a need for alternative treatment options. Given the limited global availability of diphtheria antitoxin, research into monoclonal antibody therapies may offer more effective solutions in the future [48]. New vaccine technologies, especially thermostable formulations, could significantly improve vaccine supply to hard-to-reach areas and thus raise immunization coverage [49]. Parallel efforts should advance research on *C. diphtheriae* carriage and herd immunity, to better understand transmission dynamics even in vaccinated populations [50]. Lastly, public education is crucial. Increasing skepticism toward vaccination necessitates effective communication strategies to raise awareness and rebuild trust in immunization [51].

CONCLUSIONS

Diphtheria is an infectious disease caused by *C. diphtheriae*, with its primary pathogenic factor being diphtheria toxin. Although the global incidence of diphtheria has significantly decreased due to widespread vaccination, recent years have seen a resurgence of cases in areas with low vaccination coverage and in regions affected by humanitarian crises. This underscores the need for continuous epidemiological surveillance and maintenance of high herd immunity. This review provided the historical and microbiological context for diphtheria, focusing on risk factors, transmission routes, and both global and local epidemiological trends. It also discussed the role of vaccination in reducing disease burden, the importance of preventive measures, rapidly identifying outbreaks, and actions to prevent transmission. While diphtheria is now rare in developed countries, it remains a global threat and has re-emerged in the form of local outbreaks, particularly in populations with reduced immunity. Therefore, ongoing monitoring, rapid epidemiological response, and updated vaccination strategies – including for adult populations – are essential.

All authors declare that they have contributed significantly to the work and that no ghostwriting or guest authorship took place.

Authors' contribution

Study design – M. Sulasz, J. Fiegler-Rudol
Data collection and interpretation – M. Sulasz, J. Fiegler-Rudol, K. Lau, J. Kasperczyk
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