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Diphtheria: A Disease of the Past or a Public Health Threat? Prevention Strategies in the 21st Century

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Abstract

Introduction and purpose: Diphtheria is an infectious, potentially fatal disease caused by the aerobic, Gram-positive bacillus *Corynebacterium diphtheriae*. For many years, it posed a significant health threat, particularly among children. The introduction of mass immunization programs led to a substantial decline in the number of cases, and in some countries, the disease was nearly eradicated. However, in recent years, a resurgence of diphtheria has been observed, which is linked to factors such as declining vaccination rates and increased human migration. The aim of this paper is to review the current knowledge on diphtheria, its epidemiological status, and strategies for its prevention.

Material and Methods: Bibliographic research was limited to papers published between 2019 and 2025. The articles were identified using the PubMed and Google Scholar search, using key terms.

Key terms: diphtheria, *Corynebacterium diphtheriae*, vaccination coverage, disease reemergence, vaccination hesitancy

Results: A review of the literature and epidemiological data indicates that, although diphtheria was once nearly eradicated, it continues to re-emerge in the population. This resurgence is primarily attributed to declining vaccination coverage and increased population migration. Such a trend poses serious consequences at both the individual and societal levels.

Prevention strategies to curb the spread of diphtheria include maintaining high vaccination coverage, promoting health education particularly regarding immunization and combating misinformation spread through social media.

Conclusions Problem highlights the urgent need for preventive strategies focused on increasing vaccination coverage, combating misinformation on social media, and improving access to immunization services. Only integrated and coordinated efforts can ensure that the disease remains under control.

Keywords: diphtheria, *Corynebacterium diphtheriae*, vaccination coverage, disease reemergence, vaccination hesitancy

Introduction

The resurgence of diphtheria, a potentially fatal bacterial disease, presents new challenges for public health. Since 2022, an increase in diphtheria cases has been observed across Europe [1]. Proven risk factors for diphtheria include lack of immunization, population migration, low levels of health education, and insufficient epidemiological surveillance [2]. With this upward trend continuing, the implementation of effective preventive strategies is essential to halt further spread.

The aim of this study is to review the current epidemiological situation of diphtheria and to propose methods for preventing its spread, as well as appropriate responses to potential outbreaks.

A literature review was conducted using articles published between 2019 and 2025. Relevant publications were selected using key terms such as *diphtheria*, *Corynebacterium diphtheriae*, *vaccination coverage*, *disease reemergence*, and *vaccination hesitancy* through Google Scholar and PubMed. A total of 31 articles were included in the final analysis.

1. Pathophysiology of Diphtheria

Diphtheria is an infectious, potentially life-threatening disease caused by the aerobic, Gram-positive bacillus *Corynebacterium diphtheriae*. Other toxigenic strains responsible for infection include *C. ulcerans* and *C. pseudotuberculosis* [3].

Humans are the primary reservoir of infection, although in rare cases, toxigenic strains of *C. ulcerans* and *C. pseudotuberculosis* can be transmitted through contact with infected animals such as horses, donkeys, and cats. Transmission typically occurs via respiratory droplets, and less commonly through direct contact with respiratory secretions. Asymptomatic carriers play a significant role in the spread of the infection.

The entry points for the bacteria include the nasal cavity or broken skin; less commonly, the mucous membranes of the genital tract and conjunctiva may be involved.

Diphtheria is characterized by acute upper respiratory tract infection, with the formation of grayish-brown pseudomembranes that adhere tightly to the mucosal surface. Attempted removal of these membranes may cause bleeding, which is a hallmark of the disease [4].

Diphtheria exotoxin enters the bloodstream and may disseminate to various internal organs, including the heart, kidneys, liver, and central nervous system, sometimes causing significant damage.

Cardiac complications may include myocarditis, arrhythmias, and acute heart failure. Such complications are associated with a high risk of permanent myocardial damage.

If the central nervous system is affected, peripheral nerve palsy, paralysis of the respiratory muscles and pharynx, soft palate palsy, muscle weakness, and neuropathy may occur [5].

The most common clinical form is pharyngeal diphtheria. Its symptoms include foul-smelling breath, excessive salivation, sore throat, swollen cervical lymph nodes, dysphagia, fever, muscle pain, and progressive weakness.

A particularly dangerous feature is the presence of pseudomembranes covering the tonsils, posterior pharyngeal wall, and soft palate, which may detach and cause airway obstruction, leading to suffocation.

Other clinical forms include laryngeal and nasal diphtheria. In laryngeal diphtheria, swelling of the larynx and narrowing of the glottic space result in dyspnea, cough and hoarseness. Without treatment, this condition can lead to asphyxiation. *Corynebacterium diphtheriae* causes symptoms of toxemia, meaning that the general condition of the patient is poor despite relatively low fever. Diagnosis is made by isolating *Corynebacterium diphtheriae* from patient swabs or by conducting a toxin production test.

Past infection does not confer lasting immunity. The overall mortality rate is approximately 10%, increasing to 20% in children and the elderly, and up to 50% in untreated cases.

All cases require hospitalization. Treatment is based on the rapid administration of diphtheria antitoxin along with appropriate antibiotic therapy. Supportive care is also essential. In cases where laryngeal diphtheria develops, airway management may be necessary [6].

2. Epidemiology of Diphtheria

Prior to the introduction of mandatory vaccination programs, diphtheria caused numerous local epidemics. In 1943 alone, one million people in Europe contracted the disease, resulting in 50,000 deaths. At the peak of the epidemic, the incidence rate reached 163 cases per 100,000 inhabitants.

Following the widespread implementation of vaccination programs in the second half of the 20th century—particularly the introduction of the combined DTP vaccine (diphtheria, tetanus, pertussis) the epidemiological situation of diphtheria significantly improved. In Poland, since the mid-1970s, only sporadic cases were reported, and no deaths were recorded [7].

Unfortunately, despite the initial success and near elimination of the disease in Europe, diphtheria has begun to re-emerge. Between 1991 and 1998, due to insufficient vaccination coverage among children and even lower booster coverage in adults, an epidemic outbreak occurred in Ukraine, resulting in 20,000 cases and 696 deaths [8].

According to data published by the ECDC, between January 22, 2022, and August 11, 2023, a total of 281 laboratory-confirmed diphtheria cases were identified in the European Union and European Economic Area. In

2022, 224 cases were reported, and 57 in 2023. Most infections were caused by *Corynebacterium diphtheriae*, with the remaining cases attributed to *C. ulcerans*.

Among the *C. diphtheriae* infections with available clinical data, cutaneous diphtheria was the most common manifestation (199 cases). There were also 18 respiratory cases, 3 mixed cutaneous-respiratory infections, and 3 isolated nasal diphtheria cases.

The highest number of cases was reported in Germany (208), followed by Belgium (37), the Czech Republic (10), Slovakia and the Netherlands (9 each), Sweden (5), Latvia (3), and one case each in Norway and Spain.

The report indicated four diphtheria-related deaths during the study period—two in 2022 (Germany and Slovakia) and two in 2023 (Belgium and Latvia). The majority of infected individuals were male, accounting for 85% of all reported cases [9].

In Poland, a full-blown case of diphtheria was registered in 2025 for the first time in years. The case involved a six-year-old unvaccinated child who returned from a summer trip to Africa—an endemic region for diphtheria [10].

3. Causes of Diphtheria Resurgence

The recent increase in diphtheria incidence is driven by multiple contributing factors. The most significant of these is the decline in vaccination coverage and adherence to national immunization schedules (NIP), particularly among children. Anti-vaccine movements have effectively reduced both pediatric vaccination rates and adult booster uptake. These groups frequently use the internet and social media to spread misinformation, including myths about the harmful effects of vaccines or their alleged overload on the immune system.

Vaccine-hesitant individuals often base their beliefs on isolated reports of adverse reactions and question the overall safety of immunization. Some people refuse vaccines due to fear of injections or a preference for non-conventional approaches to medicine, assuming that they are not at risk of infection. Such attitudes are frequently rooted in cognitive biases, particularly in the misjudgment of risk-benefit ratios.

The COVID-19 pandemic also played a key role in the decline of immunization rates by limiting access to healthcare and reducing attendance for scheduled vaccinations. Regional disparities in healthcare access further contribute to the problem. Many individuals avoiding vaccination exhibit low levels of trust in healthcare professionals and prefer so-called “natural methods” of disease prevention and treatment [11].

Migration and Humanitarian Crises

In response to the rise in diphtheria cases in Belgium in 2022 following the arrival of migrant groups, Doctors Without Borders (Médecins Sans Frontières) launched free medical consultations for newly arrived migrants. A roadside medical consultation point was set up to screen and treat suspected cases.

Over a three-month period, physicians identified 147 suspected cases of cutaneous diphtheria, of which 8 were confirmed as toxigenic *Corynebacterium diphtheriae* infections. In light of the increasing number of suspected cases, a targeted immunization campaign was initiated, and 433 individuals were selected for diphtheria

vaccination. This situation illustrates that even in the center of Europe, disparities in healthcare access persist, and that vaccination remains a critical tool for disease control [12].

Geographical Distribution

Diphtheria is present worldwide but remains endemic in several regions, as outlined in the table below:

Region	Countries
Asia and South Pacific	Cambodia, China, India, Vietnam, Philippines, Indonesia, Thailand, Pakistan, Papua New Guinea, Afghanistan, Bangladesh, Malaysia, Mongolia, Nepal, Myanmar, Laos
Africa	Egypt, Niger, Nigeria, Sudan, Algeria, Angola
Middle East and Central Asia	Turkey, Iraq, Iran, Yemen, Syria, Saudi Arabia
Central and South America	Dominican Republic, Brazil, Ecuador, Haiti, Bolivia, Paraguay

The highest numbers of reported cases originate from India, Nigeria, Yemen, Indonesia, Pakistan, and Bangladesh [13].

Bacterial Mutations and Resistance

Another contributing factor to the spread of diphtheria is genetic variation within *Corynebacterium diphtheriae*. A study conducted in Australia examined 57 strains isolated from the respiratory tract and skin, using whole genome sequencing to assess genetic variability and detect genes associated with antibiotic resistance and toxin production.

The findings revealed significant genetic diversity among strains. Nearly 40% of the skin infection strains showed resistance to tetracyclines or sulfonamides. A resistance gene for penicillins was found in 55% of isolates, although without expression of resistance to β -lactam antibiotics. An unmutated diphtheria toxin gene was identified in only three of the isolates [14].

The rise in antimicrobial resistance plays a critical role in the potential severity of infections. In some cases, it may lead to fatal outcomes. One such case involved a fatal respiratory diphtheria infection caused by a toxigenic *C. diphtheriae* strain resistant to penicillin and all other β -lactam antibiotics. Whole genome sequencing revealed a high level of resistance to penicillin, cephalosporins, and ceftriaxone. The genomic analysis identified a novel penicillin-binding protein responsible for resistance to both penicillin and cephalosporins [15].

4. Prevention Strategies in the 21st Century

Vaccination

Vaccination remains the cornerstone of diphtheria prevention. It is essential to immunize both children and adults with booster doses every 10 years. Immunization against diphtheria is administered via a combined vaccine that includes diphtheria, tetanus, and pertussis (DTP).

To minimize the number of injections thereby reducing stress and discomfort in children and optimizing costs most EU countries use multivalent vaccines. These offer protection against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type B, and hepatitis B in a single dose.

In Poland, the DTP vaccine is administered in a four-dose schedule at 2, 4, 6, and 16–18 months of age, followed by booster doses at 6, 14, and 19 years. A booster should be administered every 10 years thereafter. In other European countries, variations in vaccination schedules mainly concern the timing of boosters or the age of initiation [16]. For pregnant women, reduced-dose diphtheria toxoid vaccines are available [17].

The history of the DTP vaccine dates back over a century. In 1914, mixtures of diphtheria toxin and antitoxin were first introduced, and in 1926 the alum-precipitated diphtheria toxoid was registered [18]. Historical data demonstrate that mass immunization significantly reduced diphtheria incidence. In Poland, following the introduction of vaccination in 1954, the number of cases dropped from tens of thousands to single digits by 1981–2000. Currently, new diphtheria cases typically occur in unvaccinated children or individuals with waning immunity [19].

Modern Vaccines

Research into innovative vaccine approaches continues. One study involved cloning the full diphtheria toxin gene and fragments of toxin B into *E. coli*, with the expressed proteins proposed as vaccine candidates [20].

Early Detection

Early diagnosis is vital for controlling diphtheria. Diagnosis is based on clinical presentation and laboratory testing. Suspicion arises from characteristic symptoms such as acute throat and laryngeal pain, pseudomembranes in the oral cavity or pharynx, and hoarseness. These typically appear 2–5 days post-exposure, although the incubation period can extend to 10 days.

Laboratory confirmation involves isolating the pathogen from a nasopharyngeal swab or a deep wound swab in cases of cutaneous diphtheria. Preliminary identification can be performed using microscopy with Neisser or Albert staining. Definitive diagnosis requires culture on selective media such as tellurite or Loeffler agar [21,22]. PCR testing is crucial for detecting genes encoding the diphtheria toxin. The Elek test is also used to determine toxigenicity: a filter paper soaked with diphtheria antitoxin is applied to a bacterial culture, and the formation of a precipitation line confirms toxin production [23].

In cases involving suspected damage to distant organs (e.g., CNS), cerebrospinal fluid analysis may be required, or troponin measurement in cases of cardiac involvement [24].

Recent developments include an electrochemical genosensor for detecting toxigenic diphtheria strains. This

portable DNA-based device can detect as little as 20.8 nM of the target sequence in 5 minutes or 0.5 nM in 30 minutes, with sensitivities of 12.81 and 0.24 μM^{-1} , respectively [25].

Treatment

All diphtheria cases require hospitalization and isolation until two negative cultures taken 24 hours apart are obtained. Treatment includes etiologic and symptomatic therapy.

First-line treatment is administration of equine diphtheria antitoxin as soon as possible—ideally before bacteriological confirmation—because it neutralizes free circulating toxin but does not reverse toxin already bound to tissues. The antitoxin is administered intravenously using the Besredka method: 0.1 mL every 15 minutes up to 10 mL, then 0.25 mL increments until the full dose is administered, minimizing anaphylaxis risk [26].

Recommended dosages are as follows [27]:

Clinical Form	Antitoxin Dose
Pharyngeal or laryngeal	20,000–40,000 IU
Nasopharyngeal	40,000–60,000 IU
Severe or late treatment	80,000–120,000 IU

In cutaneous diphtheria, antitoxin use is debated. A dose of 20,000–40,000 IU may be considered if toxemia is present. Antibiotic therapy includes intramuscular procaine penicillin at 25,000–50,000 IU/kg/day in two divided doses or erythromycin at 40–50 mg/kg/day in four divided doses orally or intravenously for 14 days. Symptomatic treatment focuses on airway management: mechanical removal of pseudomembranes and early intubation are critical. Cardiac arrhythmias may require temporary pacing. If pharyngeal muscle paralysis occurs, feeding via a nasogastric tube is indicated. Invasive cardiac involvement (e.g., endocarditis) may necessitate valve replacement [24].

Some studies suggest human monoclonal antibodies as an alternative treatment. Using phage display techniques, researchers identified antibody clones from vaccinated volunteers that showed positive ELISA reactivity and neutralized diphtheria toxin in Vero cell assays, even at double-toxin concentrations—indicating promising therapeutic potential [28].

Post-Exposure Prophylaxis (PEP)

PEP should be implemented for individuals with recent contact with a suspected or confirmed diphtheria case. Action is recommended if exposure occurred within 7 days before symptom onset or up to 48 hours after antibiotic initiation. High-risk contacts include:

1. Household members (parents, siblings, grandparents)
2. Individuals sharing confined spaces (e.g., classmates, teachers)
3. Healthcare workers involved in patient care
4. Those with intimate physical contact (e.g., kissing)
5. Shared use of utensils or drinkware

6. Unvaccinated or incompletely vaccinated individuals

Preventive measures include:

1. Throat swab collection for diphtheria testing
2. Full immunization for unvaccinated individuals; missing doses for partially vaccinated
3. Booster dose for those whose last vaccination was >5 years ago
4. One vaccine dose for individuals with unknown immunization history
5. Protective antibody level is considered ≥ 0.1 IU/mL
6. Administration of benzathine penicillin: 600,000 IU IM (<30 kg) or 1,200,000 IU IM (≥ 30 kg); alternatively, erythromycin 40–50 mg/kg/day orally for 7–10 days [29].

The most effective protection against diphtheria remains full DTP immunization, offering 87–99% effectiveness. The majority of vaccinated individuals will not develop the disease; those who do generally experience a milder course [30].

In most European countries, diphtheria is a notifiable disease. Confirmed cases must be reported to public health authorities, and follow-up on treatment outcomes or carrier status is required for convalescents, ensuring public health safety and effective surveillance [31].

Conclusions

The complete eradication of diphtheria remains a significant challenge for public health. *Corynebacterium diphtheriae* continues to spread in regions where population immunity has been disrupted. This phenomenon is driven by multiple factors: anti-vaccine movements that reduce immunization coverage, waning immunity among adults which increases the risk of severe diphtheria globalization and population migration, armed conflicts, deteriorating and unstable sanitary conditions in certain areas, and current epidemiological conditions. Diphtheria has re-emerged in areas that had remained disease-free for years, indicating that it is no longer a disease of the past. Vaccination remains the most crucial and indisputable measure in the fight against diphtheria. Its effectiveness has been proven through scientific studies and decades of epidemiological surveillance. Vaccines provide direct protection to vaccinated individuals and contribute to herd immunity, benefiting society as a whole.

Maintaining this collective immunity requires regular booster vaccinations in adults and high coverage among children. Combating misinformation propagated by anti-vaccine movements is also essential. Educational programs should be implemented to raise public awareness of the critical role widespread vaccination plays in building and sustaining herd immunity.

Another key aspect is the preparedness of healthcare systems to respond to increasing diphtheria incidence. Efficient diagnostics, broad access to medications and diphtheria antitoxin, capacity for patient isolation, and a well-trained healthcare workforce are fundamental for effective disease management.

In summary, diphtheria remains a real and current threat. Implementing the aforementioned prevention strategies is essential to avoid the recurrence of the disease and prevent future local outbreaks reminiscent of those seen in the past.

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