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Reported Bacterial Infectious Diseases in Saudi Arabia: Overview and Recent Advances

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Abstract

Epidemiological surveillance is a critical tool to monitor the population's health and facilitate the prevention and control of infectious disease outbreaks. Bacterial infections are well known as one of the leading causes of global infection-related morbidity and mortality. Our study summarizes the number of bacterial infectious diseases in Saudi Arabia, along with an overview and recent advances in treatment or prevention modalities against these reported bacterial infections. This study only covers the reported bacterial infectious diseases in the Saudi Monthly Epidemiology Reports between 2018 and 2021. The results revealed that brucellosis, tuberculosis and salmonellosis were the most frequently reported bacterial infectious diseases in Saudi Arabia. Generally, males were more affected by bacterial infections than females. There was a variation in the distribution of bacterial infectious diseases between Saudi and non-Saudi citizens. Brucellosis and Salmonellosis infections were more common among Saudi citizens, while Tuberculosis was more common in non-Saudis. Interestingly, there was a decline in the incidence rates of numerous bacterial infectious diseases during the Coronavirus Disease 2019 (COVID-19) pandemic and COVID-19 restrictions. However, this decline in the incidence rates might be a result of underreporting during the national lockdown. Some bacterial infectious diseases were rarely reported in Saudi Arabia, including Syphilis, Diphtheria, and Guillain-Barré syndrome.

1. Introduction

Infectious diseases have long been recognized as a leading cause of illness and death and a global priority for public health [1]. According to the World Health Organization (WHO), lower respiratory infections and diarrheal diseases were among the top 10 leading causes of death worldwide [2]. A global burden of disease study published in 2020 indicated that 20% of global deaths were related to infections [1]. Bacterial infections are remarkably involved in global infection-related deaths; however, more data is needed to present a comprehensive global estimate of mortality associated with bacterial infections. In a recent study that estimated global mortality, 13.6% of all global deaths and 56.2% of all sepsis-related deaths were due to 33 bacterial pathogens. The leading bacterial pathogens associated with global death are *Staphylococcus aureus (S. aureus), Escherichia coli* (*E. coli*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Klebsiella pneumoniae* (*K. pneumoniae*), and *Pseudomonas aeruginosa* (*P. aeruginosa*) [3].

The United States Centers for Disease Control and Prevention (CDC) established the Active Bacterial Core surveillance, which provides estimates on invasive bacterial infections of public health importance in the United States (US) and provides an infrastructure to track disease trends and facilitate public health research [4]. In Saudi Arabia, epidemiologic data on bacterial infections are crucial to implement targeted prevention efforts. This is particularly important as each year, the country hosts millions of pilgrims in the cities of Makkah and Madinah for Hajj and Umrah, which increases the risk of disease transmission [5].

Knowing the burden of specific bacterial infections is an initial core step toward public health goals such as implementing strategies to reduce the rate of common bacterial infections, improving infection control and antimicrobial stewardship measures, prioritizing vaccine deployment, and guiding building a stronger

healthcare system against these infectious diseases. Therefore, this study aims to highlight the current Saudi epidemiology surveillance data and describe the bacterial infectious diseases reported in the Kingdom between 2018 and 2021, along with the recent advances in treatment or prevention modalities against these infections.

2. Methodology

The Saudi Field Epidemiology Program's surveillance data and epidemiology reports were utilized to depict the changing epidemiology of infectious diseases in Saudi Arabia from 2018 to 2021 [6], along with a detailed graphical analysis of the cases during the same period. The data were extracted from the Saudi Monthly Epidemiology Reports, and the cumulative numbers of cases and demographics (sex, nationality, age) were calculated using Microsoft Excel software (version 16.75.2). Only the bacterial infectious diseases that were reported between the years 2018 and 2021 are covered in this study. The surveillance data was visualized using GraphPad Prism 9 software (version 9.5.1). Furthermore, a literature review was conducted to identify published articles from 2018 to 2023 on recent advances for treating or preventing bacterial infections, with a focus on bacterial infectious diseases reported in Saudi Arabia.

3. Reported Bacterial Infectious Diseases in Saudi Arabia

Saudi Arabia faces various challenges in preventing and controlling bacterial infectious diseases, due to its large and diverse population of about 34 million people, who live in different regions and conditions. Each year, a large mass gathering occurs in Makkah and Madinah, Saudi Arabia, when over 7 million people from all over the world arrive in the country to perform Hajj and Umrah [7]. During the Hajj and Umrah seasons, the potential for infectious disease outbreaks is remarkably high as a result of the crowded conditions [5]. Upper respiratory tract infections are particularly the most common infectious diseases occurring during Hajj and Umrah, followed by gastrointestinal infections. Supposedly, any inappropriate prescription of antibiotics during Hajj and Umrah would raise antibiotic resistance globally [8]; hence, huge efforts are being exerted to reduce the overuse of antibiotics during these events [9]. However, despite these challenges, Saudi Arabia has shown remarkable achievements in reducing the burden of disease and improving the access and quality of health care in recent years. It has also invested in strengthening its public health systems and building capacity for disease outbreak response, surveillance, laboratory systems, and workforce development. Furthermore, it has implemented various preventive and control measures for bacterial infectious diseases, such as vaccination campaigns, screening programs, infection prevention and control practices, antimicrobial stewardship programs, and public awareness campaigns [10].

Monitoring the burden of infectious diseases and their epidemiology is crucial for maintaining the population's health by controlling disease outbreaks and facilitating disease prevention. National surveillance data is essential in tracking trends in disease rates and, most importantly, the impact of control measures such as vaccination programs in the elimination and eradication of certain infectious

diseases [11]. Infectious disease surveillance is required to facilitate the control of infectious diseases. Well-conducted surveillance relies on criteria that include simplicity, flexibility, timelines, data quality, acceptability, sensitivity, representativeness, and reliability [12]. However, some challenges compromise the usefulness of surveillance data, including lack of reporting, lack of representativeness of the reported infections, and lack of timeliness [13].

In Saudi Arabia, a monthly epidemiology report is published by the Public Health Deputyship of the Ministry of Health, the Assistant Agency for Preventive Health, the Saudi Field Epidemiology Training Program (FETP), and the Public Health Operations Center, to monitor the incidence and distribution of infectious diseases by the Kingdom's regions and population demography (i.e., sex, age, and nationality). This monthly epidemiology report clearly states that it is limited to the confirmed infectious cases that have been reported by Public Health guidelines (2017) on Surveillance and Preventive Measures for Communicable Diseases [6] only. Consequently, there is a lack of data regarding the incidence rates of infections caused by certain bacterial pathogens, including *S. aureus, E. coli, S. pneumoniae, K. pneumoniae*, and *P. aeruginosa*.

Bacterial infections have a significant impact on human health; they can cause severe morbidity and mortality, particularly in susceptible populations such as children, infants, the elderly, and those with compromised immune systems. Due to the costs of diagnosis, treatment, and prevention, they can also represent a considerable economic burden [14]. Table 1 shows the details of the bacterial infectious diseases reported in Saudi Arabia from 2018 to 2021 and the percentages of reported sex and nationalities throughout the study period. These infections include Brucellosis; TB (both pulmonary and extra-pulmonary); Salmonellosis; Typhoid and Paratyphoid fever; Meningitis; Shigellosis; Pertussis; Cholera; Tetanus; Leprosy; Haemophilus influenzae; Syphilis; Diphtheria; and Guillain-Barré syndrome (an immune-mediated neurological disorder that can be caused by *Campylobacter jejuni* bacterial infection). The most common bacterial infection in Saudi Arabia is Brucellosis, followed by Tuberculosis (both pulmonary and extrapulmonary), and Salmonellosis. Figure 1 shows the trends and patterns of bacterial infections in Saudi Arabia throughout the study period (2018–2021). The results will be discussed in the next sections.

Table 1
The total number of reported bacterial infectious diseases (2018–2021) in Saudi Arabia and the percentages of reported sex and nationalities. (Data presented for sex & nationality is based on the total number of reported cases.)

Bacterial Infectious disease	Total in 2018	Total in 2019	Total in 2020	Total in 2021	Reported Sex		Reported Nationality	
					% Male	% Female	% Saudi	% Non-Saudi
Brucellosis	**5213**	**4219**	**2302**	**2193**	76.5%	23.5%	67.8%	32.2%
Tuberculosis (TB)	**3907**	**3596**	**2717**	**3154**	69.5%	30.5%	40.9%	59.1 %
I. Pulmonary TB	**2991**	**2751**	**2109**	**2393**	70.1%	29.9%	39.8%	60.2 %
II. Extra-Pulmonary TB	**916**	**846**	**608**	**761**	67.5%	32.5%	44.5%	55.5%
Salmonella infection	**2061**	**2568**	**1450**	**2208**	53.5%	46.5%	74.6%	25.4%
Typhoid-Paratyphoid fever	**391**	**612**	**287**	**277**	63.3%	36.7%	42.8%	57.2%
Meningitis	**228**	**246**	**123**	**94**	58.3%	41.7%	74.9%	25.1 %
I. Meningitis Meningococcal	**5**	**6**	**8**	**8**	59.3%	40.7%	70.4%	29.6 %
II. Meningococcemia	**0**	**2**	**1**	**1**	75.0%	25.0%	100%	0%
III. Meningitis - Pneumococcal	**27**	**29**	**6**	**5**	59.7%	40.3%	70.1%	29.9 %
IV. Meningitis- Haemophilus influenzae type B	**10**	**5**	**1**	**1**	64.7%	35.3%	94.1%	5.9%
V. Meningitis - Other	**186**	**204**	**107**	**79**	57.8%	42.2%	74.9%	25.1%
Pertussis	**24**	**207**	**77**	**29**	45.1%	54.9%	90.4%	9.6%
Shigellosis	**68**	**75**	**36**	**54**	51.9%	48.1%	76.0%	24.0%
Cholera	**53**	**41**	**12**	**14**	70.0%	30.0%	28.8%	71.2 %
I. Cholera - O1	**41**	**30**	**4**	**3**	74.4%	25.6%	10.4%	89.6 %
II. Cholera - O139	**0**	**0**	**2**	**0**	50.0%	50.0%	50.0%	50.0%
III. Cholera - non-O1 non-O139	**12**	**11**	**6**	**11**	62.5%	37.5%	62.5%	37.5%

Bacterial Infectious disease	Total in 2018	Total in 2019	Total in 2020	Total in 2021	Reported Sex		Reported Nationality	
					% Male	% Female	% Saudi	% Non-Saudi
Tetanus	**16**	**30**	**15**	**10**	90.1%	9.9%	11.4%	89.6 %
I. Non-neonatal Tetanus	**12**	**22**	**13**	**5**	96.2%	3.8%	13.7%	86.3%
II. Neonatal Tetanus	**4**	**8**	**2**	**5**	73.7%	26.3%	10%	90%
Leprosy	**29**	**17**	**14**	**20**	76.3%	23.8%	21.3%	78.8%
Haemophilus influenzae type B: Encephalitis	**2**	**1**	**1**	**1**	100%	0%	100%	0%
Syphilis	**0**	**0**	**9**	**0**	88.9%	11.1%	75.0%	25.0%
Diphtheria	**1**	**2**	**0**	**0**	66.7%	33.3%	33.3%	66.7%
Guillain-Barré syndrome	**6**	**4**	**1**	**3**	64.3%	35.7%	64.3%	35.7%

4. The Distribution of Reported Bacterial Infectious Diseases Among Saudi and non-Saudi Citizens

Knowing the distribution of bacterial infectious diseases would help in directing infection control measures toward the persons concerned and ensure that all people receive appropriate health education and access to the appropriate medical services. Figure 2 presents the distribution of bacterial infectious diseases between Saudi and non-Saudi citizens. Tuberculosis, Cholera, Tetanus, and Leprosy are remarkably higher in non-Saudi than Saudi citizens. These infections are highly associated with low income, low health awareness, and poor living conditions. Some of these infections are preventable, primarily with vaccines like tetanus [15]. Tetanus can affect anyone, but its incidence rates are remarkably higher in people who have never been vaccinated and those who missed their booster shots [16]. In Saudi citizens, Brucellosis is the most common bacterial infectious disease, followed by Salmonellosis. The high rate of brucellosis is probably due to the cultural practice of consuming unpasteurized raw milk from sheep and camels and direct contact with the infected animals [17]. Salmonellosis is also highly linked to consuming unpasteurized raw milk. Therefore, it is critical to increase awareness of the serious health risks associated with drinking unpasteurized milk and debunk unpasteurized milk myths. Furthermore, Meningitis, Pertussis, and Shigellosis were reported in Saudi citizens more than non-Saudis. Figure 2 reveals variations in the distribution of bacterial infectious diseases among different citizens. Consequently, maintaining the population's health requires implementing targeted prevention measures.

5. The Distribution of Reported Bacterial Infectious Diseases Among Different Sexes

One of the essential epidemiological factors that influence infectious diseases is sex differences. Previous studies have demonstrated an apparent sexual dimorphism in bacterial infections in both animals and humans, [18]. Sexual dimorphism has been shown to influence susceptibility to conditions, infectious disease pathogenesis, disease frequency and severity, and response to therapy and vaccinations [19]. Generally, females are less susceptible to infections than males as they develop higher immune responses to diseases and vaccination. The differences in hormonal, genetic and environmental factors have mainly attributed to the sexual dimorphism in bacterial infections [20]. In Fig. 3, it is clearly shown that bacterial infectious diseases in Saudi Arabia were more frequently reported in males than females. The total number of bacterial infectious diseases reported between 2018 and 2021 was 26271 cases in males and 12430 cases in females. However, Pertussis cases were slightly higher among females. Interestingly, our results are consistent with a recent study that evaluated the sex differences in age-specific pertussis incidence rates from multiple countries between the years 1990 to 2017. The study revealed that pertussis affected females more commonly than males, particularly in infants and young children. It has been suggested that sex differences in pertussis incidence rates are likely due to chromosomal and hormonal factors not environmental or related to differences in exposure [21].

6. Overview of the Reported Bacterial Infectious Diseases and the Recent Advances

6.1. Brucellosis

Brucellosis is a widespread zoonotic infection caused by gram-negative bacteria of the *Brucella* species [22]. Of the genus Brucella, *B. melitensis, B. canis, B. suis*, and *B. abortus* are mainly the species that affect human and animal health. Brucellosis primarily infects cattle, pigs, sheep, and dogs. The disease is acquired by humans via direct contact with infected animals, inhaling airborne particles or eating contaminated animal products, especially unpasteurized milk, or cheese. Moreover, brucellosis is one of the common laboratory-acquired infections and is considered a serious biosafety issue [23]. *B. melitensis* (from sheep) and *B. suis* (from pigs) have significant human pathogenicity, while *B. abortus* (from cattle) and *B. canis* (from dogs) have moderate human pathogenicity. Fortunately, disease transmission from person to person is relatively rare [24]. The clinical manifestations of Brucellosis are relatively mild and nonspecific; therefore, a detailed patient history is critical in diagnosing infection. The symptoms of Brucella infection are fever, fatigue, malaise, and anorexia; some may persist for prolonged periods. The disease is managed by administering doxycycline for 45 days and streptomycin for 15 days [25].

Brucellosis has been known and recognized since the early 20th Century and is still common in several countries. Annually, the WHO reports over 500 thousand confirmed human brucellosis cases globally. Some countries have successfully maintained effective preventive strategies and were able to eradicate the disease from their areas, such as the United States, Northern Europe, Australia, New Zealand, and

Japan. However, Brucella infections remain a public health concern in endemic areas, including the Middle East, the Mediterranean, and parts of Africa, Asia, and Latin America [26]. In Saudi Arabia, brucellosis was the most reported bacterial infectious disease between 2018 and 2019 (Fig. 1). The high incidence rates of brucellosis occur particularly in Saudi citizens (Fig. 2). In 2018, there were 5,213 confirmed cases of Brucellosis. Interestingly, the number of cases dropped remarkably in 2020 and 2021, with 2,302 and 2,193 cases respectively. This recently reduced incidence in the years 2020–2021 indicates a significant improvement in the prevention and control measures for Brucellosis. Brucellosis affected males more than females, as shown in Fig. 3. Brucellosis cases in Saudi Arabia were remarkably high in adults. The incidence of Brucellosis over the study period was 3.3% (n = 459) in the 0–4-year age group, 11.2% (n = 1555) in the 5–14 age group, 25.6% (n = 3550) in the 15–29 age group, 47.6% (n = 6606) in the 30–59 age group, and 12.3% (n = 1710) in the elderly (60 years and above).

Numerous studies have investigated the risk factors associated with the high prevalence of Brucellosis in Saudi Arabia. These studies revealed that most brucellosis patients had a history of direct animal contact or ingestion of raw milk products. Veterinary practitioners and cattle owners have an increased risk of infection [27]. Prevention of Brucella infection is primarily based on surveillance using serological tests and elimination of risk factors. Brucellosis elimination in animals is the best strategy to eradicate the disease effectively. Vaccination of animals is highly recommended in endemic areas with high prevalence rates. However, in humans, prevention of infection is primarily based on increasing awareness of the disease, applying food-safety measures by avoiding the consumption of undercooked meat and unpasteurized dairy products and maintaining good hygiene. Moreover, it is important to establish a comprehensive biosafety system in laboratories to eliminate the risk of laboratory-acquired Brucellosis. [28].

The *Brucella* organism is known for its ability to escape the host immune responses via the interference of complement pathway and Toll-like receptors (TLRs) signaling pathways and numerous molecular and cellular pathways that contribute to disease. Recently, it has been identified that circulating microRNAs have a crucial role in the immunopathogenesis of brucellosis as it modulates several events, including inflammatory responses and immune defense. Circulating microRNA are stable and easy to find, which makes them excellent noninvasive diagnostic biomarkers for detecting microbial infection. Moreover, recent findings suggest that microRNA-based drugs, with their immune-modulatory capabilities, have potential applicability in treating Brucellosis [29]. However, the microRNA-based drugs have not yet translated into FDA-approved candidates for phase 3 clinical trials [30].

6.2. Tuberculosis

Tuberculosis (TB) remains a worldwide public health concern, as 1.6 million people died from this disease in 2021. TB infection is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) is transmitted from person to person through the air and mainly affects the lungs [31]. The pathogenesis of TB is complicated and remains to be fully understood. Most TB cases show no clinical symptoms and are described as Latent TB, where the bacilli persist in the human body without becoming active (dormant bacilli). Patients with latent TB cannot transmit the disease to others. Active TB develops once the latent

infection is activated. Excessive host adaptive immune responses potentially cause significant inflammatory responses leading to necrosis and cavitation, which is considered the hallmark of active TB infection. The clinical manifestations of active pulmonary TB are a chronic cough with blood-containing sputum in some cases, chest pain, weight loss, elevated temperature, and night sweats [32]. TB can also affect organs other than the lungs, such as the brain, kidneys, joints and the spine, which is described as extrapulmonary TB (EPTB), and can cause a wide range of symptoms depending on the targeted site [33]. TB is a curable and preventable disease. For nearly 100 years, Bacille CalmetteGuèrin (BCG) has been the only vaccine available against TB around the globe. Despite its age and extensive use of the vaccine, there is still considerable debate on how long immunity lasts after its administration in infancy, as well as its efficiency in preventing TB. BCG is widely used in many countries where TB is common, but it is not routinely recommended in the United States, where the disease is relatively uncommon. The effects of BCG vaccination show that the risk of acquiring TB infection in children declined by 20%, and the risk of developing active TB declined by 60% [34].

Anyone can get TB, although some individuals are at higher risk than others. Most TB cases occur in Sub-Saharan Africa, Asia, and Eastern Europe, and it has been estimated that 10.6 million people fell ill with TB in 2021, including 1.2 million children. The most significant number of newly diagnosed TB cases in 2021 occurred in the South-East Asia region (46% of cases), followed by the African region (23% of cases) and the Western Pacific (18% of cases). In the United States, the incidence rates of TB have steadily declined since 1992. In 2021, the United States reported 7,882 cases of TB, with an incidence rate of 2.4 per 100,000 persons [31]. In Saudi Arabia, there were 3,154 cases of TB reported in the same year (Fig. 1). In Saudi Arabia, TB is one of the most reported bacterial infectious diseases, where more than 2,000 people get infected with pulmonary TB yearly, while EPTB cases range from 600 to 900 annually. The incidence of TB is remarkably higher among non-Saudi than Saudi citizens, as shown in Fig. 2. Most of the TB infections in Saudi Arabia affect adults more than children. The incidence of pulmonary and extrapulmonary TB over the study period in the 30–59 age group was 50.4% (n = 5165) and 47.5% (n = 1488), respectively. In the 15–29 age group, the incidence of pulmonary and extrapulmonary TB was 34.8% (n = 3565) and 36.4% (n = 1139), respectively. While in children under the age of 5, it ranges from 1.3–2.5%. Saudi Arabia faces a challenge in the spread of TB as it is highly contagious and difficult to control, especially during mass gatherings like Hajj and Umrah [5]. Eradicating TB infection will require global efforts to maintain and strengthen the current TB control programs while focusing on identifying and treating latent TB infections [35]. In June 2016, Saudi Arabia adopted the World Health Organization's (WHO) strategic plan to eradicate TB infections (i.e., End-TB strategy). This strategy aims to end the global TB epidemic to reach a world free of TB, with zero deaths, zero diseases, and zero suffering from TB [36].

Despite the importance of an effective mycobacteriological diagnosis of TB disease, there are some significant limitations to the current traditional methods [37]. Culture is still considered the gold standard of TB diagnosis, although it is labor-intensive and time-consuming. Smear microscopy on the other hand is a quick and easy method to perform, its low sensitivity and negative predictive value (NPV) as well as the number of samples necessary limit its clinical effects [37]–[39]. For these reasons, the World Health

Organisation (WHO) in 2021 updated the TB screening guidelines and recommended the use of the molecular WHO-recommended rapid diagnostics (mWRDs) and biomarker-based tests as initial techniques for screening of presumptive TB [40]. The mWRDs for the diagnosis of TB are defined as diagnostic tests that employ molecular or biomarker-based techniques for the diagnosis of TB. The latest, rapid, and sensitive molecular tests recommended for the initial detection of *M. tuberculosis* complex (MTBC) and drug resistance (DR) include Xpert MTB/RIF Ultra and Xpert MTB/RIF (Cepheid, Sunnyvale, United States of America [USA]); Truenat MTB, MTB Plus and MTB-RIF Dx tests (Molbio Diagnostics, Goa, India); and loop-mediated isothermal amplification (TB-LAMP; Eiken Chemical, Tokyo, Japan) [40]. Furthermore, for HIV-infected presumptive-TB patients, the WHO recommended using the biomarker-based lateral flow lipoarabinomannan assay (LF-LAM) test (Alere Determine TB LAM Ag, USA) to assist in diagnosing TB. A positive LF-LAM result indicates the bacteriological confirmation of TB in these patients, and this test is also included as a WHO-recommended diagnostic test (WRD) [41].

The follow-on tests to detect the multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB include line-probe assays (LPAs) for detection of resistance to rifampicin and isoniazid (GenoType MTBDRplus, Bruker/Hain Lifescience, Nehren, Germany; NTM + MDRTB Detection Kit, NIPRO Corporation, Osaka, Japan) and to fluoroquinolones and second-line injectables therapies (GenoType MTBDRsl, Bruker/Hain Lifescience, Nehren, Germany). The two new classes added as follow-on tests comprise the low complexity automated nucleic-acid amplification tests (NAATs) for the detection of isoniazid, fluoroquinolones, ethionamide and amikacin resistance (first in class: Xpert MTB/XDR [Cepheid, Sunnyvale, USA]) and the high complexity reverse hybridization NAAT for the detection of pyrazinamide resistance (first in class: Genoscholar PZA-TB II [NIPRO Corporation, Osaka, Japan]) [40], [41]

TB infection can be treated with antibiotics. Based on the CDC, a recent randomized controlled trial in 2021 showed that a 4-month treatment regimen consisting of rifapentine, moxifloxacin, isoniazid, and pyrazinamide was as effective as the standard 6-month regimen in curing drug-susceptible pulmonary TB [42]. Multi-drug Resistant (MDR) TB requires more aggressive and prolonged therapy than drug-susceptible tuberculosis. MDR TB is defined when the organism is resistant to at least isoniazid and rifampin anti-TB drugs. Extensively drug-resistant (XDR) TB can also occur when the organism presents additional resistance to the most effective anti-TB medications. Management of drug-resistant TB and extensively drug-resistant TB remains very challenging due to decreased efficacy and increased toxicity [43].

The conventional anti-TB treatment strategies require a lengthy drug regimen with frequent and multiple drug dosing, which results in low patient compliance. Consequently, this leads to treatment failure, TB recurrence, and drug-resistant TB emergence. Therefore, there is an urgent need to identify improved interventions to effectively reach and kill all *M. tuberculosis* bacteria, maximizing the potential to shorten treatment. Over the past 10 years, the anti-tuberculosis drug pipeline has gained momentum with promising drug candidates. The anti-TB drug pipeline involves repurposed and repositioned antibiotic classes and new drugs with novel mechanisms of action [44]. Three novel drugs in Phase III clinical trials are bedaquiline, delamanid, and pretomanid. Bedaquiline is an oral diarylquinoline that targets the ATP

synthase. The pretomanid and delamanid drugs belong to the nitroimidazole chemical class that poison multiple essential pathways [45]. The researcher prioritizes good drug regimens that substantially facilitate global efforts to control TB [44].

6.3. Salmonella infection (Nontyphoidal)

Salmonellosis is a gastrointestinal infection caused by *Salmonella* that belongs to the *Enterobacteriaceae* family. Contaminated food and water are significant sources of transmission of Salmonella infection. Infection is characterized by acute abdominal cramps, elevated body temperature, diarrhea, nausea, and vomiting [46]. The onset of symptoms usually occurs 12–36 hours after ingestion of *Salmonella*, and the disease lasts for about a week. Most cases of Salmonella infection are mild, but sometimes the disease can be severe and life-threatening. Children under the age of 5 years are the most likely to acquire Salmonellosis infection. *Salmonella* bacterium is one of the four global causes of diarrheal diseases [47]. According to the CDC, it is estimated that 1.35 million people get infected with *Salmonella*, from which 26,500 patients get hospitalized, and 420 deaths occur in the United States annually. In 2019, the CDC published a report on Antibiotic Resistance Threats in the United States and considered "drug-resistant nontyphoidal Salmonella" a severe threat to human health [48].

Salmonellosis is one of the most highly reported bacterial infectious diseases in Saudi Arabia, where around 2,000 people get infected annually. Previous studies have demonstrated that Salmonellosis is particularly prevalent during the Hajj and Umrah seasons [49], [50]. In 2020, there was a remarkable decline in reported cases of Salmonellosis. This reduction occurred during the Coronavirus Disease 2019 (COVID-19) Pandemic and COVID-19 restrictions and this reduction might be as a result of underreporting during the national lockdown. However, in 2021, the number of Salmonellosis cases increased remarkably after easing lockdown and COVID-19 restrictions measures, as shown in Fig. 1. Salmonellosis was reported in Saudi citizens more remarkably than non-Saudis, as shown in Fig. 2, which could be due to the local cultural practice of consuming unpasteurized raw milk from sheep and camels. Figure 3 shows no difference between the number of cases of Salmonellosis between males and females. Most Salmonellosis confirmed cases in Saudi Arabia during the study period were in children under the age of 5 (45.7%, n = 3782). The incidence was 10.8% (n = 897) in the 5–14 age group, 12.6% (n = 1040) in the 15–29 age group, 22.7% (n = 1881) in the 30–59 age group, and 8.3% (n = 684) in the elderly (60 years and above).

The management of Salmonellosis is rehydration and electrolyte replacement. Due to the increased antibiotic resistance of *Salmonella*, using antibiotics is not recommended for healthy individuals with mild to moderate symptoms [47]. However, antibiotics should be used in high-risk patients such as children, older people, and immunocompromised patients to prevent invasive disease. Moreover, antibiotics are recommended when the infection spreads to body parts other than gastrointestinal [48].

Currently, there is no effective vaccine against Salmonellosis. Numerous non-typhoidal salmonella vaccines are currently in preclinical or early phase of clinical trials to protect against invasive salmonellosis. The vaccine pipeline includes live-attenuated, subunit-based, and recombinant antigen-

based candidates [51]. Preventive measures help to reduce the chances of getting food-borne Salmonellosis [48]. The United States Food and Drug Administration (FDA) has published guidelines for the Food Safety and Inspection Service to control measures for all stages of the food chain, from agricultural production to food preparation at home [52]. Recently, there has been an increased interest in Salmonella biosensors, primarily in combination with nanomaterials, for detecting *Salmonella* in water and food. Biosensors are real-time diagnostics tools that translate biological signals into measurable analytical results. They are known as promising diagnostic tools due to their sensitivity, specificity, and accuracy [53], [54].

6.4. Typhoid-Paratyphoid Fever

Typhoid and paratyphoid fever are types of *Salmonella* infections that are clinically different from common Salmonellosis, in which they are characterized by severe and life-threatening systemic syndrome with fever and abdominal cramps. Typhoid and paratyphoid fever are called enteric fever [55]. The bacterium that is responsible for causing enteric fever is *Salmonella enterica*. Serotype Typhi is the leading cause of Typhoid fever, while Paratyphi A, Paratyphi B, and Paratyphi C serotypes cause paratyphoid fever. Enteric fevers can be transmitted mainly via consuming contaminated water or food (fecal-oral route). Interestingly, humans are the only source of *S. Typhi* and *S. Paratyphi A*, and there are no significant animal or environmental reservoirs [56].

Worldwide, the estimate is that typhoid fever affects 26 million persons, while paratyphoid fever affects 5 million people yearly, collectively leading to 215 thousand deaths [56]. In 2017, around 76% of enteric fevers were caused by *S. Typhi* [57]. Enteric fever is highly prevalent in low-income and middle-income countries with poor hygiene and sanitation and is rare in developed countries. According to the CDC, from 2008 to 2015, the United States reported approximately 350 confirmed typhoid fever and 90 confirmed paratyphoid fever caused by *S. Paratyphi A* annually. More than 80% of typhoid fever and 90% of paratyphoid fever cases in the United States occur among people who traveled to high-risk regions, especially in southern Asia areas (primarily India, Pakistan, or Bangladesh) [56]. In Saudi Arabia, during 2018–2021, around 300 confirmed cases of typhoid and paratyphoid fever were reported each year (Fig. 1). In 2019, typhoid and paratyphoid fever incidence remarkably increased compared to the previous year, subsequently dropping by half in 2020. As previously mentioned, gastrointestinal infection rates declined during the COVID-19 pandemic due to COVID-19 restrictions or underreporting of cases during the national lockdown. Generally, the number of cases is relatively higher in non-Saudi than in Saudi citizens (Fig. 2). However, in 2020, the incidence rate was higher among Saudi citizens, which is probably due to travel restrictions during the COVID-19 pandemic. In 2021, there were 277 confirmed cases of typhoid-paratyphoid fever. Most confirmed cases throughout the study period (2018–2021) were adults. The incidence of Typhoid and Paratyphoid fever over the study period was 11.1% (n = 173) in the 0–4-year age group, 16.2% (n = 253) in the 5–14 age group, 25.9% (n = 405) in the 15–29 age group, 43.5% (n = 681) in the 30–59 age group, and 3.4% (n = 53) in the elderly (60 years and above).

Typhoid and paratyphoid fever are usually treated with antibiotics to shorten the clinical symptoms of enteric fever and reduce mortality risk. Fluoroquinolone antibiotics are considered effective in eradicating

bacteria from patients, which makes them the first line of therapy for infected adults [56]. However, in high-risk regions for enteric fever, most typhoid and paratyphoid infections were resistant to fluoroquinolone agents, synthetic quinolone, and nalidixic acid. Azithromycin or ceftriaxone can be considered the second choice of treatment for fluoroquinolone-non-susceptible or nalidixic acid-resistant infections [58].

There are licensed typhoid conjugate vaccines that received the WHO policy recommendation in 2017, but there is no vaccine against paratyphoid fever. However, *S. Typhi* vaccines are not 100% effective, and high bacteria inoculum can overwhelm their induced immunity [59]. Therefore, food and water safety precautions and frequent hand washing are highly recommended for preventing typhoid and paratyphoid fever [56]. In the vaccine pipeline, there are vaccine candidates in the clinical development against paratyphoid fever, including monovalent *S. Paratyphi A* candidate vaccine and bivalent vaccine candidates that target both typhoid and paratyphoid [59].

6.5. Meningitis

Meningitis is a devastating disease characterized by acute or chronic inflammation of the protective membranes surrounding the brain and spinal cord, collectively called the meninges. Different pathogens, including viruses, bacteria, fungi, parasites, and amoeba, can cause meningitis. Other non-infectious causes of meningitis are cancer, subarachnoid hemorrhage, sarcoidosis, and some specific drugs. Bacterial meningitis has the highest global burden and remains a significant public health challenge. Bacterial meningitis is a life-threatening infection and almost always leads to death within a few hours if left untreated [60]. Most patients recover from bacterial meningitis but can have permanent disabilities affecting their quality of life, such as brain damage, hearing loss, and learning disabilities. Several bacteria can cause meningitis, but the most common is *S. pneumoniae*. The transmission of bacterial meningitis occurs from person to person via inhalation of respiratory droplets or throat secretions during close contact. The most common symptoms of meningitis are a sudden onset of fever, headache, and neck stiffness. Other symptoms often include altered mental status (confusion), nausea, vomiting, and photophobia or inability to tolerate loud noises. The extended-spectrum cephalosporin (ceftriaxone and cefotaxime) and the β-lactam antibiotic (meropenem) are shown to be effective in treating all types of bacterial meningitis [61].

Among all bacteria, *N. meningitidis* has the potential to spread rapidly, leading to large epidemics. Several serogroups of *N. meningitidis* exist, but mainly 6 can lead to outbreaks (A, B, C, W, X, and Y). Meningitis caused by *N. meningitidis* is known as Meningococcal meningitis or Meningococcal disease. *N. meningitidis* can cause various invasive diseases, referred to as invasive meningococcal diseases (IMD), such as meningitis, septicemia, and arthritis [62]. IMD can result in high morbidity and mortality among children and older people. Meningococcal disease can affect anyone but occurs more frequently in children under 1 year old, followed by adolescents and young adults. In the United States, the incidence rates have decreased since the 1990s and have continued to be low. In 2019, the incidence rate was 0.11 cases per 100,000 people. In Saudi Arabia, meningococcal meningitis is relatively rare (Fig. 1). Each year,

around 7 cases of meningococcal meningitis were reported. Introducing routine vaccination programs could have contributed to minimizing disease spread [63].

N. meningitidis is also known to cause a rare infectious disease called meningococcemia, which indicates disseminating meningococci into the bloodstream and evading the inflammatory host response, resulting in endothelial damage, downregulation of fibrinolysis, and uncontrolled coagulation [62]. Meningococcemia is known for its rapid progression to severe and acute disease. It is characterized by upper respiratory tract infection, fever, petechiae, and purpura. Meningococcemia is common in young children and relatively rare in adults [64]. In 2021, only one case of meningococcemia was reported in Saudi Arabia (Fig. 1).

Pneumococcal meningitis refers to meningitis caused by S. *pneumoniae. S. pneumoniae* can cause other invasive diseases such as otitis and pneumonia. Based on United States statistics, *S. pneumoniae* causes more than 50% of all bacterial meningitis infections. It is considered the leading cause of bacterial meningitis in children under 5 years old. The mortality rate of pneumococcal meningitis in the US is about 22% among adults and 8% among children [65]. Historically, penicillin with vancomycin or chloramphenicol was the first-line therapy for pneumococcal meningitis. Due to the increased antibiotic resistance, penicillin-resistant pneumococcal strains are found worldwide. Therefore, antibiotic susceptibility testing and alternative antibiotics should be determined. The extended-spectrum cephalosporin (ceftriaxone and cefotaxime) and the β-lactam antibiotic (meropenem) are shown to be effective in treating pneumococcal meningitis [66]. Annually, it is estimated that pneumococcal meningitis affects 2,000 persons in the United States [65]. In Saudi Arabia, the incidence of pneumococcal meningitis is relatively low (Fig. 1). Interestingly, the number of confirmed cases of meningitis-pneumococcal remarkably dropped from 27 in 2018 to 5 in 2021. It is worth mentioning that meningitis outbreaks are usually associated with the Hajj and Umrah seasons. However, these mass gatherings were affected during the COVID-19 pandemic. Therefore, the decline in the incidence rate of pneumococcal meningitis during 2020–2021 might have been due to COVID-19 restrictions or underreporting of cases during the national lockdown.

Haemophilus meningitis is a form of meningitis caused by *H. influenzae*, usually *H. influenzae* type B (HIB). In the pre-vaccine era, *H. meningitis* was the leading cause of bacterial meningitis in children under 5. After introducing the HIB vaccine in 1985, the number of children infected with *H. meningitis* remarkably dropped [66]. In 2018, 10 confirmed cases of Haemophilus meningitis were reported in Saudi Arabia (Fig. 1). In 2019, the number of reported cases dropped to 5 and continued to decrease to one reported case in both years 2020 and 2021. As shown in Fig. 2, most reported cases were Saudi citizens and only one case was reported in non-Saudis throughout the study period (2018–2021).

The Saudi epidemiological surveillance also reports the number of meningitis infections (meningitis-other) caused by other than *N. meningitidis, S. pneumoniae, and H. meningitis*. However, the report does not specify what “Meningitis-other” includes. The incidence of meningitis-other is the highest among all cases of meningitis in the Saudi epidemiology report (Fig. 1). In 2018, there were 186 reported cases of

meningitis-other, which declined to 79 in 2021. Meningitis infections caused by other causes were remarkably higher among Saudi citizens (Fig. 2). It is essential to determine the exact cause to monitor the prevalence and epidemiology of all types of meningitis.

Other infectious meningitis can be caused by viruses, fungi, parasites, and amoeba; however, since this study only focuses on bacterial infections, each type of such meningitis will be defined briefly. Non-polio enteroviruses most commonly cause viral meningitis. The Mumps virus, Herpesviruses, Measles virus, Influenza virus, Arboviruses, and *Lymphocytic choriomeningitis* virus cause the remaining cases of viral meningitis [60]. The exact epidemiology of viral meningitis is unknown because it is an under-reported infection [67]. In most cases, patients get better on their own without specific therapy. However, the CDC estimated 25 to 50 thousand hospitalizations annually due to viral meningitis [60]. Sometimes, fungal infections can spread to infect the brain and spinal cord, leading to fungal meningitis, which can be caused by *Cryptococcus, Coccidioides, Blastomyces, Histoplasma*, and *Candida*. Fungal meningitis primarily affects immunocompromised patients and rarely occurs in healthy individuals [68]. Parasitic meningitis appears rarely compared to bacterial and viral meningitis. Three parasites cause a rare type of meningitis known as eosinophilic meningitis. These parasites are *Angiostrongylus cantonensis, Baylisascaris procyonis* and *Gnathostoma spinigerum*. Eosinophilic meningitis is characterized by at least 5% of eosinophils in the cerebrospinal fluid (CSF). Moreover, meningitis can be caused by an opportunistic free-living amoeba called *Naegleria fowleri* [66]. Amebic meningitis is known as *Primary amebic meningoencephalitis* (PAM). PAM is a rare brain infection but highly fatal. According to the CDC, there have been 154 cases of PAM reported between 1962 and 2020 in the United States, out of whom only four patients survived [60]. No effective treatment is recognized since almost all infections are fatal [69].

There is an urgent need to overcome meningitis-associated high mortality and morbidity rates. The conventional therapeutic approaches for meningitis are insufficient to deliver the desired pharmacological action due to their difficulties in crossing the blood-brain barrier (BBB). The BBB is a highly selective prime lining that protects the brain by blocking the admission of toxins, foreign substances, and most drugs into the brain. Scientists are exploring advanced technologies to overcome BBB issues and provide timely treatment with appropriate antibiotics [70]. The nanotechnology approaches have physical, chemical, and biological characteristics that offer the best opportunity for superior therapy for meningitis. Nanoparticle-based drug delivery systems can cross BBB through para-cellular transport, transcellular, endocytosis, and receptor-mediated transcytosis. Several nanoparticle-based drug delivery systems have been researched for managing bacterial meningitis, such as polymeric nanoparticles, functionalized polymeric nanoparticles, solid lipid nanoparticles (SLN), nano-emulsion, nano-transfersomes, liposomes, and nanostructured lipid carriers. Direct delivery of antibiotics to the brain via nanotechnology approaches has great potential in treating bacterial meningitis [71].

6.6. Shigellosis

Shigellosis is an acute bloody diarrheal infection caused by *Shigella* bacterium. There are four species of the genus *Shigella: S. dysenteriae* (Group A), *S. flexneri* (Group B), *S. boydii* (Group C), and *S. sonnei*

(Group D). The first three species include numerous distinct serotypes [72]. The transmission of shigellosis occurs via the fecal-oral route, either by direct contact with an infected person or indirectly by contaminated water or food. The infection can be acquired easily due to the low infective dose of as few as 10 organisms [73].

Worldwide, the incidence of shigellosis is estimated to be 165 million cases yearly, with approximately 600 thousand deaths annually. Most of these Shigellosis cases are attributed to food-borne transmission. Transmission of *Shigella* species is more common when there is insufficient hygiene and sanitation. *Shigella* species are endemic in many low to middle-income countries as almost all Shigellosis cases occur in these countries, mostly among young children under 5 years of age [73]. Shigellosis is known as the second-leading cause of fatal diarrhea. Worldwide, it is estimated to be responsible for more than 60 thousand deaths among children under five years old annually [74]. In the United States, *Shigella* is estimated to cause 450 thousand cases of the disease annually, with the majority of these reported cases being caused by *S. sonnei* (70%) [73]. In Saudi Arabia, the number of reported cases of Shigellosis over the study period from 2018 to 2021 was relatively low (Fig. 1), when the incidence rates ranged from 36 to 75. The highest number of Shigellosis infections was reported in 2019, dropping to 36 in 2020, then slightly increasing to 54 in 2021. Figure 2 reveals that Shigellosis cases were remarkably higher in Saudi than non-Saudi citizens.

According to the WHO, there was an outbreak of XDR shigellosis caused by *S. sonnei* species in late 2021, that was notified within the United Kingdom and several multiple other European countries in early 2022. This raises a public health concern due to the insufficient treatment options for MDR and XDR Shigellosis [75]. Treatment of Shigellosis includes hydration and electrolyte management in addition to antibiotics. The selection of antibacterial therapy should be based on antibiotic susceptibility testing due to the increased resistance of *Shigella* species to drugs. Usually, when an effective antibiotic is given, the patient's symptoms resolve within two days [72]. Currently, there is no clinically approved vaccine for shigellosis. However, several Shigellosis vaccines are under investigation at different preclinical and clinical development stages. The development of a vaccine against shigellosis is considered a priority by WHO to reduce morbidity and mortality, especially in children under 5 years of age [76].

6.7. Pertussis

Pertussis or whooping cough is a highly contagious respiratory infection caused by *Bordetella pertussis* (*B. pertussis*). In the 16th Century, the outbreak of whooping cough was first described by Guillaume de Baillou. In the 20th Century, pertussis was considered a common childhood-threatening disease and a significant cause of childhood deaths in the United States. During the pre-vaccine era, the reported cases of pertussis were more than 200 thousand annually. However, since the widespread use of the pertussis vaccine, the incidence has dropped by over 75% [77]. Pertussis remains endemic worldwide, even in countries with high vaccination coverage. According to the WHO, there were more than 151 thousand reported cases of pertussis globally in 2018 [78]. Pertussis incidence rates in Saudi Arabia over the study period were relatively low (Fig. 1), with only 24 confirmed cases reported in 2018. However, in 2019, there was a remarkable increase in its incidence rates to 207, then declining to 77 cases in 2020, and dropping

to 26 in 2021. As shown in Fig. 2, pertussis cases were remarkably higher in Saudi citizens than non-Saudis. Pertussis was reported more frequently in females than males. (Fig. 3). As mentioned previously, chromosomal and hormonal factors can contribute to the increased incidence rates of pertussis in females. Unfortunately, most pertussis cases in Saudi Arabia affect children in the 0–4 age group (88.9%, n = 295). CDC highly recommends the routine vaccination of children to protect against pertussis.

The pathogenesis of pertussis is primarily induced by the toxin produced by *B. pertussis*. Once the bacterium enters the human body, it will attach to the cilia of the respiratory epithelial cells and stimulate the toxin. Consequently, the cilia will be paralyzed, and the respiratory cells will be inflamed, leading to the interference of regular clearing of the pulmonary secretions. Moreover, the pertussis antigens allow the bacterium to evade the host immune system [77]. The classical clinical presentation of the disease typically begins 7–10 days after exposure, with mild upper respiratory tract symptoms (catarrhal stage), followed by the paroxysmal stage, characterized by coughing paroxysms. In the last stage (convalescent stage), the coughing will be resolved gradually, but paroxysms often recur with subsequent respiratory infections [79]. Secondary bacterial pneumonia is a relatively common complication of pertussis and is considered a major cause of Pertussis-related mortality, especially among young infants. Neurologic complications such as seizures and encephalopathy rarely occur. However, young infants are at the highest risk for developing neurological complications [77].

The management of pertussis is primarily supportive; however, several antibiotics are available for treating this infection. Macrolide agents (azithromycin, clarithromycin, and erythromycin) are the drugs of choice for treating pertussis. Nevertheless, antibacterial agents have yet to be shown to improve the clinical course if not initiated before the disease commences (convalescent stage) [80]. Post-exposure antibacterial prophylaxis is recommended for all close contacts of confirmed cases, especially infants who have the highest risk of developing pertussis-related complications [81].

Despite the broad coverage provided by current commercial acellular vaccines (aPVs), some limitations exist, such as weak immune response and short-term protection. Therefore, several delivery vehicles have been developed to improve the protection against pertussis infection. Among many delivery vehicles, outer membrane vesicles (OMVs) have been most thoroughly studied against *B. pertussis*. Several gram-negative bacteria, including *B. pertussis*, can naturally produce extracellular OMVs. OMVs are known to contain numerous immunogenic endogenous antigens, which have significant advantages in vaccine development [82]. Previous studies have demonstrated that OMVs derived from *B. pertussis* can protect against intranasal pertussis challenges in mice through intraperitoneal, intranasal, subcutaneous, and pulmonary routes. The immune response evoked by the pulmonary route induced a more robust mucosal immune response than other immune routes, effectively inhibiting bacterial colonization in the respiratory tract [83]. Nasal mucosal immunity is remarkably vital for pathogenic respiratory infections. To illustrate, pathogenic respiratory bacteria cause colonization and invasion of the respiratory tract, and nasal mucosal immunity is an ideal approach for preventing respiratory infections and blocking the chain of transmission by inducing both mucosal and humoral immune responses [84].

6.8. Cholera

Cholera is a highly virulent diarrheal infection caused by the bacterium *Vibrio cholerae* (*V. cholerae*). The first cholera pandemic emerged during the 19th Century in India and spread worldwide, with 6 subsequent pandemics that resulted in millions of deaths across all continents [85]. Currently, cholera is considered an endemic in several countries with poor sanitation and inadequate hygiene [86]. Cholera infection occurs by ingesting contaminated food or water and requires 12 hours to 5 days to demonstrate clinical symptoms. Occasionally, patients may show no symptoms, although they can transmit the disease to others. Symptoms, when occurred, may range from mild to severe watery diarrhea with severe dehydration. If untreated, cholera can cause death within hours due to severe dehydration and electrolyte imbalance [85].

The bacterium *V. cholerae* has several serotypes, but only two serotypes (cholera-O1 and cholera-O139) were responsible for the outbreaks. V. cholerae serotype O1 caused the recent Cholera outbreaks, while serotype O139 has only been identified in sporadic cases—however, O1 and O139 serotypes cause similar illnesses without any significant difference. The global burden of cholera disease is undetermined because most of the cases are not reported [85]. According to the CDC, cholera infection affects 1.3 to 4 million people worldwide and causes 21 to 143 thousand deaths yearly [87]. In 2020, the WHO indicated that the number of cholera cases has continued to be high, with 24 countries reporting 323,369 confirmed cases and 857 deaths [85]. In Saudi Arabia, there were 14 cholera cases in 2021 (Fig. 1). During 2018–2019, Cholera (O1) was the most reported serotype, followed by Cholera (non-O1 and non-O139). However, during 2020–2021, Cholera (non-O1 and non-O139) became the most reported serotype. Cholera (O139) is rarely reported in Saudi Arabia. Figure 2 reveals that cholera (O1) cases were remarkably higher in non-Saudi than in Saudi citizens. However, the incidence rates of cholera (O1) dropped since the COVID-19 pandemic and travel restrictions started.

Despite all the previous efforts to control cholera, the number of cases remains high globally. Cholera is a paramount public health concern that needs an urgent multifaceted approach to prevent infection and reduce the number of deaths. Controlling cholera begins with economic development and universal access to clean water and adequate sanitation. Other interventions should be implemented in cholera hotspots, such as increasing awareness of cholera and control measures to ensure safe water, basic sanitation, and good hygiene practices [88]. Cholera disease is managed through rehydration and electrolyte replacement. During epidemics, antibiotics are recommended for patients with severe illnesses requiring hospitalization. Antibiotics improve symptoms, facilitate patients' recovery, and reduce the time spent in the hospital. The first-line therapy for treating cholera infections in children and adults is doxycycline. Other alternative drugs as ciprofloxacin and azithromycin, are recommended for patients who are resistant to doxycycline [89]. In cholera hotspots, drug resistance to the first line of therapy and MDR frequently leads to more severe illness. Two oral vaccines against cholera have been known as an adjunct approach for prevention and controlling cholera infections, including a killed whole-cell monovalent (O1) vaccine and a killed modified whole-cell bivalent (O1 and O139) vaccine [87].

6.9. Tetanus

Tetanus is an acute life-threatening disease acquired through infection of a cut or wound with the exotoxin produced by the bacterium *Clostridium tetani* (*C. tetani*) [90]. This bacterium is spore-forming, where the spores are ubiquitous in the environment, particularly in the soil and the intestines and feces of humans and animals like cattle, horses, sheep, cats, dogs, rats, and chickens. Moreover, spores are found on skin surfaces and rusty objects such as nails, needles, and screwdrivers [16].

Tetanus occurs worldwide, and it can affect anyone. In the pre-vaccine era, there were more than 500 reported cases of tetanus annually in the United States. Since tetanus toxoid vaccines were introduced into routine childhood vaccines, the incidence rates of tetanus steadily decreased. In the mid-1970s, about 50–100 cases were reported annually in the United States. In 2018, tetanus affected 23 persons; no deaths were reported in the United States. Worldwide, tetanus infection is more severe and significant in infants than adults [91]. In 2015, more than 34 thousand deaths were reported in newborns due to neonatal tetanus, a 96% reduction since 1988, primarily due to scaled-up immunization with the tetanus-toxoid-containing vaccines (TTCV) [16]. In Saudi Arabia, about 10–30 tetanus cases were reported each year over the study period (Fig. 1). The number of neonatal tetanus cases ranges from 2 to 8 annually. In 2021, 5 neonatal tetanus cases were reported. Generally, tetanus affected non-Saudis more frequently than Saudi citizens (Fig. 2). The incidence rates of tetanus decreased during the COVID-19 pandemic and travel restrictions.

Tetanus disease is characterized by muscle stiffness that usually begins in the jaw and neck, leading to generalized rigidity and convulsive spasms of skeletal muscles. The disease may affect the autonomic nervous system, and seizures may occur [91]. It also can cause serious complications, including laryngospasms that interfere with breathing, fractures of the spine or long bones due to persistent contractions and convulsions, hypertension or abnormal heart rhythm caused by the hyperactivity of the autonomic nervous system, nosocomial infections, pulmonary embolism, aspiration pneumonia, and death [92]. These typical clinical manifestations of tetanus are caused when tetanus toxin interferes with the release of neurotransmitters to block inhibitor impulses at several sites within the central nervous system. Usually, the incubation period is about one week, and most cases occur within 14 days of infection. Fortunately, tetanus cannot be transmitted via contact with an infected person [91].

Based on the clinical manifestations, several forms of tetanus have been recognized. The most reported form is generalized tetanus (more than 80% of cases). In this form, the disease is usually characterized by its descending pattern that starts with lockjaw, followed by neck stiffness, difficulty swallowing, muscle rigidity, and generalized spasms. The spasms may occur frequently and continue for four weeks. Full recovery may take several months [93]. The second form is localized tetanus, a distinctive form that causes persistent contraction of muscles in the same injury area [94]. The rarest form is cephalic tetanus which is limited to muscles and nerves in the head area. Usually, cephalic tetanus occurs following injuries to the head [95]. Neonatal tetanus is a serious form of generalized tetanus that affects newborn infants through contaminated umbilical stumps or because the mother has not been sufficiently immunized [96].

Management of tetanus infection requires hospitalization, aggressive wound care, and tetanus immune globulin (TIG) administration to remove the unbound tetanus toxin, a tetanus toxoid booster, antispasmodic drugs, and antibiotics. Patients who present with unclean wounds, who have not been sufficiently immunized, or who have an unknown history of prior doses of tetanus toxoid should receive TIG and the tetanus toxoid vaccine. The early doses of the tetanus toxoid vaccine may prime the immune system, while TIG provides temporary immunity by removing the unbound tetanus toxin [97].

Over the past century, chemically inactivated tetanus toxoid (CITT) has remained clinically effective and broadly used. However, chemical detoxification of bacterial toxin with formaldehyde alters the tetanus toxin (TT) structure with unknown effects on antigenicity. A recent study has reported a novel high-potency tetanus vaccine alternative to CITT via recombinant production of a genetically inactivated tetanus vaccine [98]. A recombinant full-length TT was engineered with eight individual amino acid mutations (8MTT) to inactivate light chain catalysis, translocation, and host receptor-binding while reserving 99% amino acid identity to native TT. Then, 8MTT was purified as a soluble protein to more than 90% purity. Mouse immunization showed 8MTT to be nontoxic and elicits a potent immune response. Developing a recombinant, genetically inactivated tetanus vaccine aligns with dedicated biosafety level, modern manufacturing, and regulatory requirements [99].

6.10. Leprosy

Leprosy, or Hansen's disease, is a chronic skin and peripheral nerve infection caused by *Mycobacterium leprae* (*M. leprae*) [100]. This bacterium is challenging as it multiplies inside the individual's body very slowly, and can take up to 20 years to manifest signs of infection [101]. Leprosy is a curable disease and is not highly contagious. The *M. leprae* bacterium is transmitted directly through untreated patients' droplets during close and frequent contact [100]. Leprosy disease affects the skin, peripheral nerves, eyes, and nasal mucosa. *M. leprae* attacks the nerves causing a lack of pain and sensation, eventually leading to injuries. Untreated, the bacterium will damage the individual's nerves leading to permanent disabilities. Early diagnosis and treatment are critical with leprosy to prevent the progression of the disease and improve the quality of the patient's life [101]. The current recommendation for treating leprosy is using a multi-drug therapy regimen that consists of dapsone, rifampicin, and clofazimine for 6 months or 12 months. Once the treatment begins, the patient will no longer transmit the disease to others [102].

In 1990, the WHO set goals for eliminating leprosy globally by the end of the 20th Century. Their aim is a prevalence of less than 1 per 10 thousand population. Despite governments' and healthcare providers' efforts and commitment, leprosy is a neglected tropical disease (NTD) that is still ubiquitous in tropical countries, especially in underdeveloped and developing countries. Annually, more than 200 thousand people get diagnosed with leprosy worldwide. In the United States, about 150 persons are infected with *M. leprae* each year [100]. While in Saudi Arabia, around 20 persons get infected with leprosy each year (Fig. 1). Throughout the study period (2018–2021), the highest number of leprosy cases was reported in 2018, while the lowest was reported in 2020. In 2021, there were 20 reported leprosy cases. The incidence rates of leprosy were higher in non-Saudi than in Saudi citizens (Fig. 2). The WHO recommends

continuing screening contacts and administrating single-dose rifampicin as a chemoprophylaxis to break the chain of transmission and eliminate the disease [102].

Prevention of leprosy infection can be accomplished via prophylactic immunization and chemoprophylaxis. Several vaccines are used as prophylactic immunizations before or after exposure to prevent infection and disease progression. BCG is the only vaccine to prevent Leprosy infection [103]. Previous studies demonstrated the role of BCG immunization in enhancing cell-mediated immunity and providing significant protection against Leprosy [104], [105]. For chemoprophylaxis, clinical trials have been conducted to assess the effectiveness of Rifampicin, Dapsone/ Acedapsone, and a multi-drug regimen (Rifampicin, Ofloxacin, and Minocycline) [103]. Interestingly, one study investigated the effect of combining prophylactic immunization and chemoprophylaxis. It demonstrated that administration of the BCG vaccine and Rifampicin showed additive protective effects and reduced leprosy infection by 80%. The study highlighted the role of combined prevention strategies in reducing the incidence of leprosy and eliminating the disease [106].

6.11. Haemophilus influenza

Haemophilus influenzae (*H. influenzae*) disease is an infection caused by several recognized strains of *H. influenzae*, but the most common one is HIB. This bacterium is an opportunistic pathogen that usually lives in the human's nose and throat, causing no harm but sometimes can travel and infect other parts of the body. *H. influenzae* is responsible for numerous localized and invasive infections that often cause severe complications, particularly among infants and children [107]. Invasive *H. influenzae* is described when the bacteria invade parts of the human body that are typically free from microbes, leading to encephalitis, meningitis, pneumonia, epiglottitis, cellulitis, infectious arthritis, and bloodstream infection [108]. In the pre-vaccine era, HIB was the primary cause of bacterial meningitis and other invasive bacterial infections, primarily among infants and children younger than 5 years old. In the early 1990s, an effective vaccine against HIB was licensed and recommended for use in children younger than 5 years of age [107].

H. influenzae infection occurs worldwide, and humans are the only reservoir. Transmission of *H. influenzae* occurs via direct contact through inhalation of respiratory droplets from an infected person. Infants can acquire *H. influenzae* infection during delivery through aspiration of amniotic fluid or contact with genital tract secretions. Elders and children younger than 5 years are more likely to get infected with *H. influenza* [107]. Since introducing the HIB vaccine in the early 1990s, invasive *H. influenzae* infections among older people and children have dropped by 99% in the United States. However, the incidence rates of non-HIB and nontypable *H. influenzae* are increasing [109]. In 2019, the incidence of invasive infections in all age groups was 0.04 cases per 100 thousand for HIB, 0.52 cases per 100,000 for non-HIB, and 1.34 cases per 100 thousand for nontypable *H. influenzae*. In children younger than 5 years, the incidence of invasive infections was 0.15 cases per 100 thousand for HIB, 1.18 cases per 100 thousand for non-HIB, and 1.62 cases per 100 thousand for nontypable *H. influenzae*. For individuals 65 years or older, the incidence of invasive infections was 0.06 cases per 100 thousand for HIB, 1.33 cases per 100 thousand for non-HIB, and 4.88 cases per 100 thousand for nontypable *H. influenzae* [110]. In Saudi

Arabia, the Saudi epidemiological surveillance only reports the number of meningitis and encephalitis cases caused by HIB. Other invasive HIB cases were not reported. Figure 1 shows that invasive HIB (encephalitis) is extremely rare in Saudi Arabia. In 2021, only one case of invasive HIB (encephalitis) and one case of invasive HIB (meningitis) were reported.

The management approach for treating *H. influenzae* infection usually includes the administration of antibiotics and supportive measures. A third-generation cephalosporin antibiotic should be administered once the patient is diagnosed with *H. influenzae* infection while waiting for the culture and sensitivity results [107]. Drug resistance is one of the major concerns when treating *H. influenzae* infection. *H. influenzae* bacteria contain penicillin-binding proteins (PBPs) involved in peptidoglycan metabolism. Beta-lactam antibiotics act by binding to PBPs to inhibit peptidoglycan synthesis. Some *H. influenzae* strains have mutations in their PBPs that resist the action of beta-lactam antibiotics by producing beta-lactamases. Therefore, it is necessary to monitor the response to the treatment and alter the choice of antibiotic accordingly [111].

6.12. Syphilis

Syphilis is a chronic Sexually Transmitted Disease (STD) caused by the Spirochaete bacterium *Treponema pallidum* (*T. pallidum*) [112]. Although syphilis is a curable disease, it can cause serious health issues without adequate therapy. If left untreated, syphilis could last several years. The disease has been classified into early and late syphilis. Early syphilis is divided into primary, secondary, and early latent syphilis, while late syphilis is divided into tertiary and late latent syphilis [113].

Since the advent of penicillin in the mid-1940s, the incidence of syphilis cases has declined remarkably worldwide. However, towards the end of the 20th Century, an increase in the number of cases was reported in the United States, especially among adolescents and men who have sexual activity with other men (MSM) [112]. The number of syphilis cases reported worldwide ranges from 5 to 12 million annually [114]. MSM account for more than 40% of all primary and secondary stages of syphilis incidents in the 2020 STD Surveillance Report. Moreover, recent studies reported a strong association between syphilis and an increased risk of infection with the Human Immunodeficiency Virus (HIV) among MSM [112], [115]. Recently, the rate of syphilis infections increased remarkably among reproductive-aged women between 2014 and 2018, especially among drug abusers. Consequently, there has been a dramatic increase in trans-placental fetus infections during pregnancy (i.e., congenital syphilis) in the United States. Therefore, the CDC continues to alert the public about congenital syphilis and calls for immediate action [116]. In Saudi Arabia, STDs such as syphilis are not common due to the conservative nature of the population and their practice of the Islamic faith. No Syphilis infection was reported in years 2018, 2019 and 2021; however, 9 cases were reported in 2020 (Fig. 1). Most syphilis cases were reported in non-Saudi citizens (Fig. 2).

T. pallidum is known for its highly invasive nature to disseminate via the bloodstream and invade multiple organs and tissues. Therefore, eliminating vascular dissemination is crucial for the syphilis vaccine to achieve successful protection. In 2017, progress was made to inhibit the dissemination of

Treponema subspecies *pallidum* with *T. pallidum*-lipocalin-domain containing Tp0751. Tp0751 can bind to multiple host components of the vasculature, including fibrinogen, laminin, collagen, and fibronectin. Tp0751 subunit vaccine candidate exhibits a remarkably decreased bacterial organ burden in *T. pallidum*-challenged animals compared with unimmunized animals. Furthermore, Tp0751 is proven to induce sterile protection against *T. pallidum* infection. This promising viable Syphilis vaccine candidate is years away [117].

Interestingly, there have been some studies supporting the possibility of syphilis prevention through a biomedical approach [112]. In a randomized controlled pilot study, prophylactic administration of a daily dose of 100 mg doxycycline reduced the combined odds of syphilis, chlamydia, and gonorrhea infections by more than 70% in a group of thirty HIV-infected MSM [118]. An open-label randomized sub-study involving 116 MSM showed a 73% reduction in syphilis incidence with post-exposure prophylaxis with a 200 mg dose of doxycycline [119].

6.13. Diphtheria

Diphtheria is an acute bacterial infection caused by toxigenic *Corynebacterium diphtheriae* (*C. diphtheriae*). The disease only occurs when the bacterium gets infected by corynebacteriophages carrying the tax gene required for pathogenicity. The toxin-producing strains of *C. diphtheriae* are responsible for the local and systemic manifestations of diphtheria [120]. The disease can be classified based on the site of infection, either respiratory or non-respiratory. It is transmitted easily through direct contact or the air through respiratory droplets [121].

Historically, diphtheria has been one of the threatening childhood infections leading to deaths in 20% of cases in children under 5 years old. In the 20th Century, the WHO incorporated the triple vaccine DPT which is a class of vaccine combination against three infections (Diphtheria, Pertussis, and Tetanus), and it has been part of the WHO Expanded Program on Immunization (EPI) [121]. Since the production of the effective diphtheria vaccine and expanding the program of immunization, the disease burden of diphtheria decreased, with cases declining by more than 90% worldwide [122], [123]. In Saudi Arabia, diphtheria infection is extremely rare due to vaccination programs. Only one case of diphtheria was reported in 2018, two cases were reported in 2019, and none were reported in both years 2020 and 2021.

The management of Diphtheria varies depending on the site of infection. Respiratory diphtheria infection is usually treated with diphtheria antitoxin to eliminate the circulating toxin from the body and stop the progression of the disease. In the United States, the FDA has not licensed diphtheria antitoxin. However, the CDC is authorized to dispense diphtheria antitoxin as an investigational new drug (IND). Antibacterial agents are recommended in treating respiratory and non-respiratory diphtheria infections. Usually, the disease becomes non-contagious after 48 hours of initiating antibiotic therapy [124].

6.14. Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an immune-mediated neurological disorder that causes acute flaccid paralysis. GBS is characterized by a sudden weakness of an individual's extremities in which the immune

system mistakenly attacks the peripheral nerves [125]. The symptoms of GBS usually start with an unexplained sensation in the hands or feet, and then these sensations tend to disappear. Significant weakness symptoms occur, affecting both sides of the individual's body as an ascending paralysis until it reaches the muscles controlling breathing [126]. The exact cause of this syndrome is still not known. Nonetheless, most cases usually happen following a respiratory or gastrointestinal infection. Several microbes are associated with GBS, including *Campylobacter jejuni* (*C. jejuni*), Zika virus, cytomegalovirus, Epstein-Barr virus, and recently Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Among these microbes, *C. jejuni* is the most reported to be associated with triggering GBS. In the case of *C. jejuni infection*, the strongest theory suggests a molecular similarity between the nerves and *C. jejuni* antigens, which leads to misrecognition by the immune system and the development of GBS [127]. In addition, other non-infectious factors may trigger GBS, such as vaccines and surgeries [128].

GBS is a rare condition that can affect anyone, and it is estimated to affect about one person in 100 thousand annually worldwide. In the United States, it is estimated that 3 to 6 thousand persons would develop GBS each year [129]. In Saudi Arabia, GBS is rarely reported. During the study period, its incidence rates ranged from 1–6 cases annually (Fig. 1). Interestingly, there was no increase in the incidence rates of GBS during the COVID-19 pandemic. In 2020, only one person developed GBS in Saudi Arabia, while 3 GBS cases were reported in 2021. During the COVID-19 pandemic, several cases were reported of patients who developed GBS after SARS-CoV-2 infection worldwide. A recent systematic review of 436 GBS cases of post-COVID-19 shows that there is no significant difference in clinical and laboratory findings between GBS post-COVID-19 and GBS due to other causes. Most patients in this study improved and recovered after receiving therapy [130].

GBS is a severe life-threatening condition that requires close monitoring of symptoms such as breathing, blood pressure, and heartbeat. Even though there is no cure for GBS, patients usually fully recover due to the acute nature of the disease. However, intravenous immunoglobulin and plasma exchange are the most important and influential immunotherapeutic drugs that facilitate recovery from GBS and improve the symptoms [125]. Recently, monoclonal antibody therapy has been investigated for treating GBS. Monoclonal antibody therapy is a form of targeted drug therapy that uses monoclonal antibodies to bind mono-specifically to the epitope of the target with their Fab antigen-binding region. Monoclonal antibodies are used to diagnose and treat multiple diseases, including autoimmune diseases, neurological disorders, and cancer. Among many marketed monoclonal antibodies, eculizumab is a humanized monoclonal antibody that targets complement protein C5 resulting in potent inhibition of complement activation. Currently, eculizumab is in phase III, a multicenter, double-blind, placebo-controlled, randomized study to evaluate the efficacy and safety of eculizumab in patients with severe GBS in Japan [131].

A novel treatment for GBS called ANX005 was granted fast-track designation from the United States FDA. ANX005 is a promising humanized recombinant antibody that inhibits the complement cascade via binding to C1q. Currently, ANX005 is being tested in phase III, a double-blind, placebo-controlled, randomized study to evaluate its efficacy, safety, pharmacokinetics, and pharmacodynamics in patients

with GBS. Furthermore, an open-label, single-arm study on patients with severe GBS is currently being conducted to investigate the safety and dosing of CK0801. CK0801 is a cord blood-derived T-regulatory cell product. T-regulatory cells play a role in maintaining immune homeostasis and limiting autoimmune responses via modulating innate and adaptive immune responses [131].

7. Conclusion

Monitoring the incidence and epidemiology of infectious diseases is essential for maintaining the health of the population. The role of infectious disease surveillance in controlling infectious disease outbreaks and facilitating disease prevention is crucial. Nonetheless, several obstacles, such as a lack of reporting, a lack of representativeness of the reported infections, and a lack of timeliness, diminish the utility of surveillance data. Our study summarized the burden of bacterial infectious diseases in Saudi Arabia obtained from the Monthly Epidemiology Report between 2018 and 2021. Brucellosis, tuberculosis and salmonellosis were the most frequently reported bacterial infectious diseases in Saudi Arabia. The most common sources were gastrointestinal and pulmonary infections, yet some infections were also linked to animal contact or sexual transmission. The reported bacterial infections were more prevalent in males; however, the rate of pertussis infections was slightly higher in females. These bacterial infections can cause severe morbidity and mortality, particularly in susceptible populations such as children, the elderly, and people with compromised immune systems. Essential strategies to prevent such infections are crucial and include raising awareness regarding disease transmission, increasing the rate of vaccination, applying food-safety measures by avoiding the consumption of undercooked meat and unpasteurized dairy products and improving access to safe drinking water, in addition to facilitating access to appropriate antibiotic therapy for treating these infections. Other strategies are also critical to decrease the burden and the consequences of bacterial infections as well as the rate of bacterial resistance, including the improvement of the diagnostic infrastructure and implementation of appropriate infection control and antimicrobial stewardship measures. Furthermore, our study revealed a clear lack of reporting and representation of some bacterial infections. Implementation of an improved public health surveillance system is necessary to overcome challenges associated with underreporting of communicable diseases. The future perspective of this research may focus on the mortality associated with bacterial pathogens to identify the greatest threats and set a public health priority.

Abbreviations

8MTT, Eight Individual Amino acid Mutations Tetanus Toxoid; aPVs, Acellular Vaccines; ATP, Adenosine Triphosphate, *B. abortus, Brucella abortus; B. canis, Brucella canis; B. melitensis, Brucella melitensis; B. pertussis, Bordetella pertussis; B. suis, Brucella suis;* BBB, Blood-brain Barrier; BCG, Bacille Calmette–Guèrin vaccine; *C. diphtheria, Corynebacterium diphtheria; C. jejuni, Campylobacter jejuni; C. tetani, Clostridium tetani;* CDC, Centers for Disease Control and Prevention; CITT, Chemically Inactivated Tetanus Toxoid; COVID-19, Corona Virus Disease - 2019; DR, Drug Resistance; *E. coli, Escherichia coli;* EPI, Expanded Program on Immunization; EPTB, Extrapulmonary Tuberculosis; FDA, The United States Food

and Drug Administration; FETP, Field Epidemiology Training Program; GBS, Guillain-Barré Syndrome; *H. influenzae, Haemophilus influenza; HIB, Haemophilus Influenzae type B;* HIV, Human Immunodeficiency Virus; IMD, Invasive Meningococcal Diseases; IND, Investigational New Drug; *K. pneumoniae, Klebsiella pneumoniae;* LF-LAM, lateral Flow Lipoarabinomannan Assay; LPAs, Line-probe Assays; *M. leprae, Mycobacterium leprae; M. tuberculosis, Mycobacterium tuberculosis;* MDR, Multi-drug Resistant; microRNAs, Micro-Ribonucleic acid; MSM, Men who have Sexual activity with other Men; MTBC/MTB, *Mycobacterium tuberculosis* Complex; mWRDs, Molecular WHO-recommended Rapid Diagnostics; *N. meningitides, Neisseria meningitides;* NAATs, Nucleic-acid Amplification Tests; NPV, Negative Predictive Value; NTD, Neglected Tropical Disease; OMVs, Outer Membrane Vesicles*; P. aeruginosa, Pseudomonas aeruginosa*; PAM, Primary Amebic Meningoencephalitis; RIF, Resistance to Rifampin; *S. aureus, Staphylococcus aureus; S. boydii, Shigella boydii; S. dysenteriae, Shigella dysenteriae; S. flexneri, Shigella flexneri; S. paratyphi, Salmonella paratyphi; S. pneumoniae, Streptococcus pneumoniae; S. sonnei, Shigella sonnei; S. typhi, Salmonella typhi;* SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SLN, Solid Lipid Nanoparticles; STD, Sexually Transmitted Disease; *T. pallidum, Treponema pallidum*; TB, Tuberculosis; TB-LAMP, Tuberculosis Loop-mediated Isothermal Amplification; TIG, Tetanus Immune Globulin; TLRs, Toll-like Receptors; TT, Tetanus Toxoid; TTCV, Tetanus-Toxoid-containing Vaccines; US, United States; *V. cholera, Vibrio cholera;* WHO, World Health Organization; WRD, WHO Recommended Diagnostic test; XDR, Extensively Drug-Resistant.

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Figures

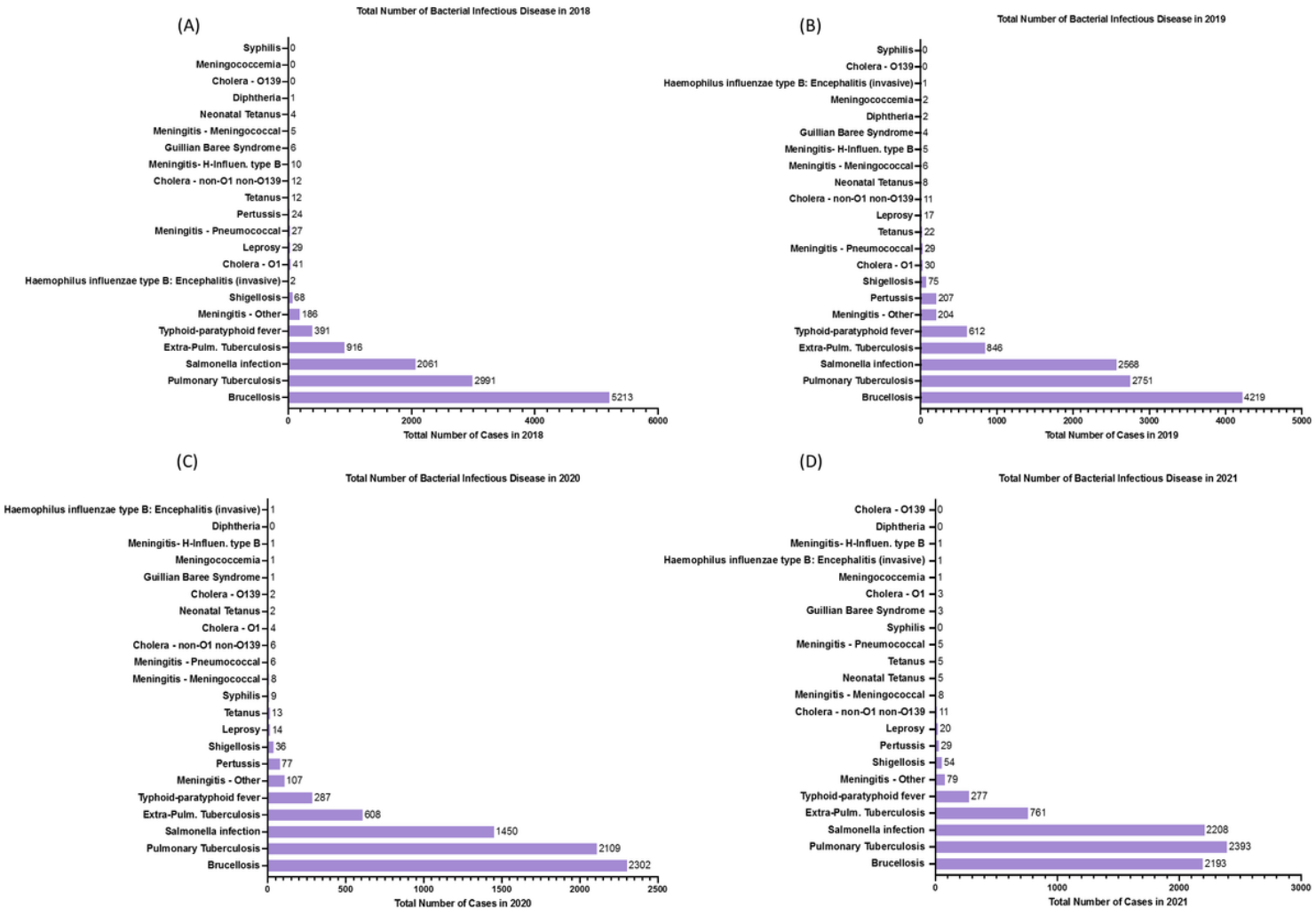

Figure 1

The total number of reported bacterial infectious diseases in Saudi Arabia from 2018 to 2021. Data presented based on the year. (**A**): Total number of reported bacterial infectious diseases in 2018. (**B**): Total number of reported bacterial infectious diseases in 2019. (**C**): Total number of reported bacterial infectious diseases in 2020. (**D**): Total number of reported bacterial infectious diseases in 2021.

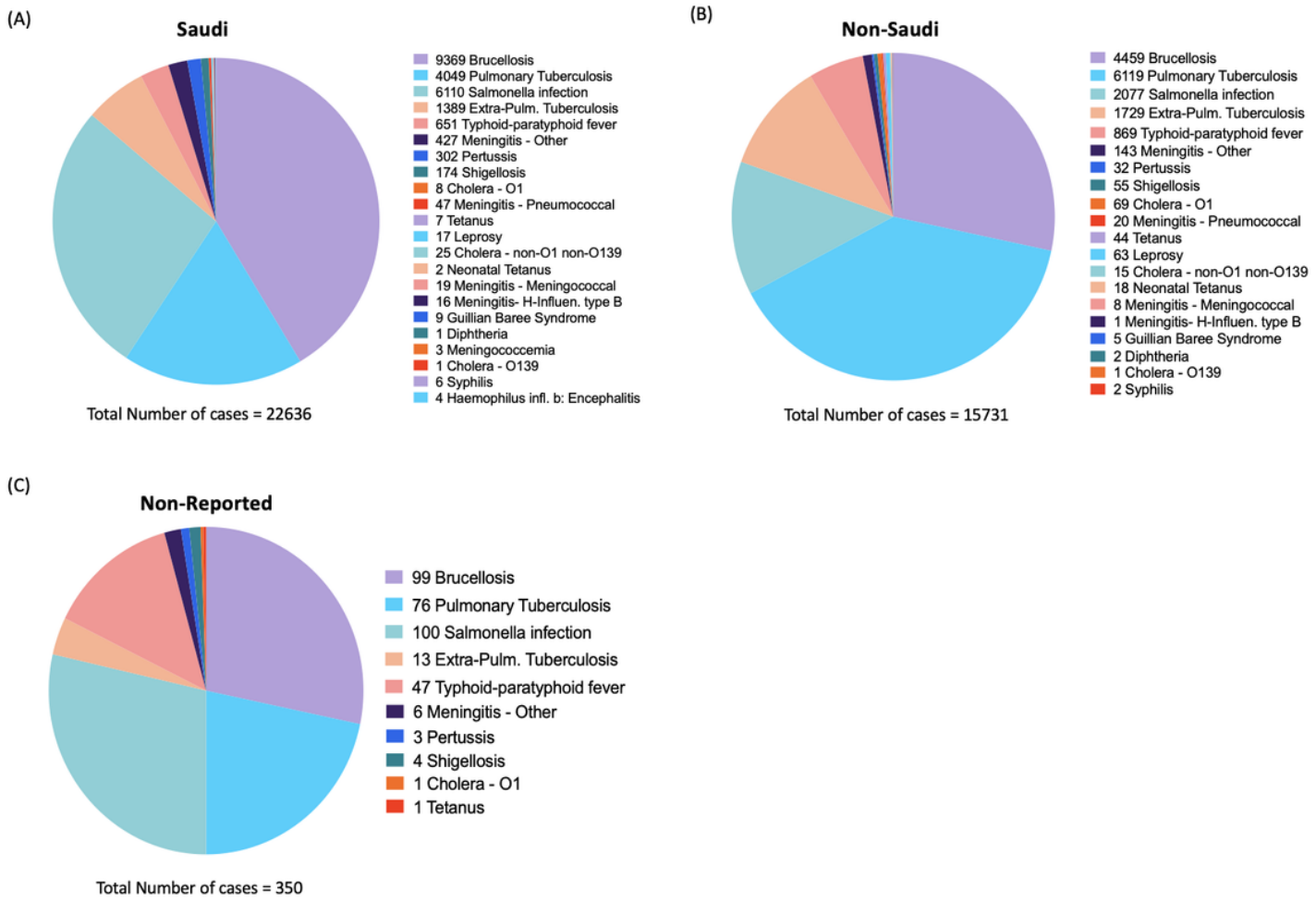

Figure 2

The total number of reported bacterial infectious diseases among Saudi and non-Saudi between 2018 and 2021. A: Distribution of bacterial infectious diseases in Saudi citizens. B: Distribution of bacterial infectious diseases in non-Saudi citizens. C: Bacterial infectious disease cases in unknown nationalities (not reported).

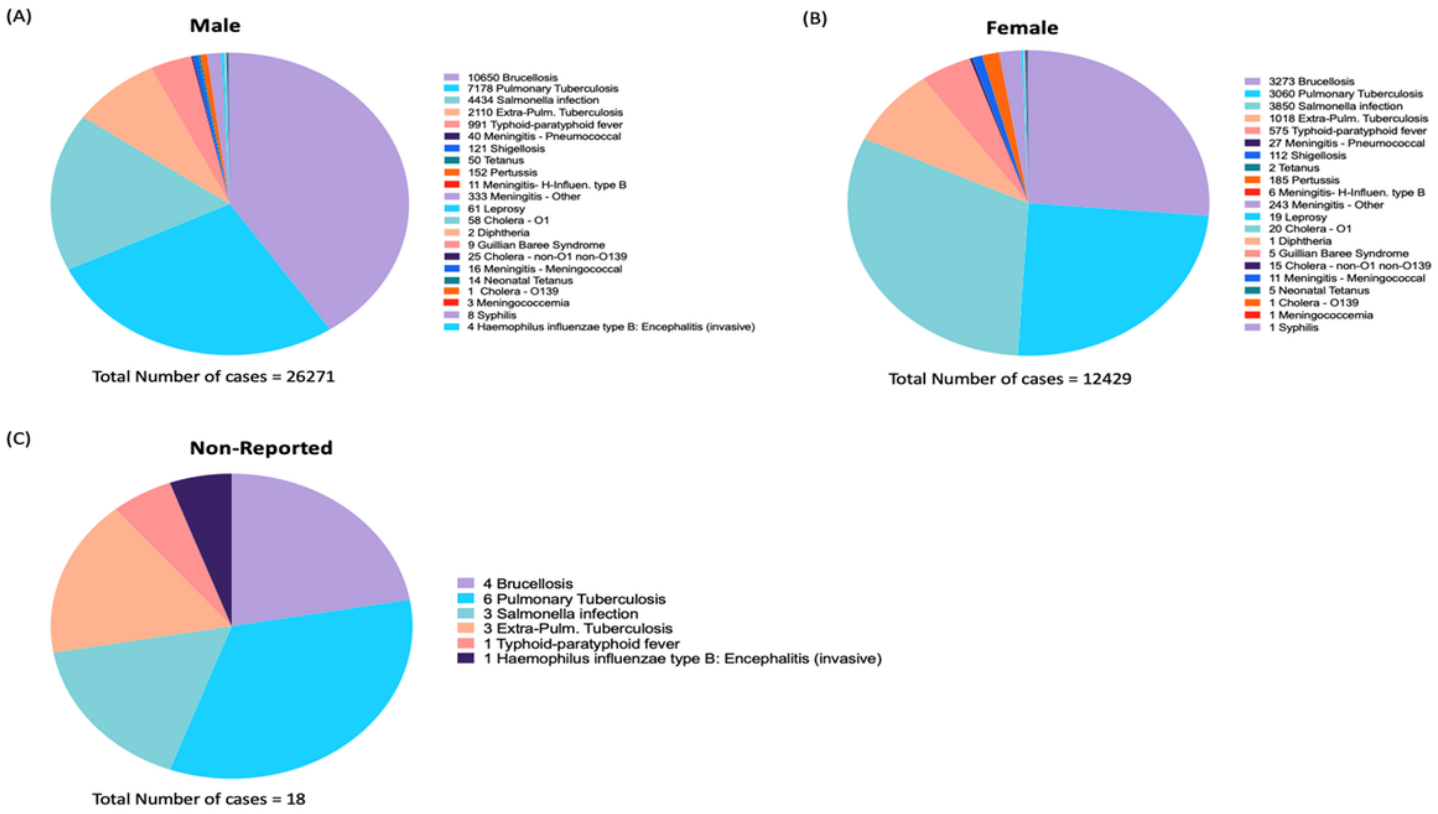

Figure 3

The total number of reported bacterial infectious diseases among males and females between 2018 and 2021. **A**: Distribution of bacterial infectious diseases in Males. **B**: Distribution of bacterial infectious diseases in Females. **C**: Bacterial infectious disease cases with missing information about sex (non-reported).