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Invasive Pneumococcal Disease in Children Under Five Years in a Tertiary Care Center, Saudi Arabia

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Abstract **Original Research Article**

Background: The problem of invasive pneumococcal disease (IPD) has been one of the leading health issues causing morbidity and mortality in young children, even when pneumococcal conjugate vaccines have been used widely. Limited data exists on clinical features, vaccination, and antimicrobial susceptibility, and outcomes of IPD among Saudi Arabian children. ***Objective:*** To characterize the epidemiology, clinical manifestation, vaccination history, and antimicrobial resistance trends, as well as the outcomes of invasive Streptococcus pneumoniae infection among children under the age of five years in a tertiary care unit in Saudi Arabia. ***Methods:*** The study was a retrospective observational one, which was carried out in the Prince Sultan Military Medical City, where it reviewed cases of invasive Streptococcus pneumoniae infection in children aged 0-5 years, which were confirmed by microbiology between January 2009 and January 2019. Medical records were analyzed to obtain demographic, clinical, radiological, laboratory, microbiological, vaccination, treatment, and outcome information. The IBM SPSS version 26 was used to perform descriptive statistical analysis. ***Results:*** Sixty-seven children who were diagnosed with invasive pneumococcal infection were detected. Males were 55.2 percent of the cases, and the highest age of infection was two years. In 73.1 percent of patients, the blood cultures were positive. The presenting symptom of fever was the most frequent (65.7%); 43.3% and 44.8% of children did not have respiratory or gastrointestinal symptoms, respectively. In 34.3% of cases, neurological manifestations were observed. Those with pneumococcal vaccination data were 43 patients, and of them, 37.2 were unvaccinated during the time of infection. Ceftriaxone was the most susceptible to antimicrobials (82.1%), whereas penicillin was found to be less susceptible in a significant percentage of the isolates. There was an in-hospital mortality of 19.4% patients. ***Conclusion:*** Invasive pneumococcal disease has remained a major cause of morbidity and mortality among children below five years in Saudi Arabia. Unaffiliated vaccination, comorbidities, unusual clinical manifestations, and the development of antimicrobial resistance are significant problems. To enhance the outcomes, it is necessary to strengthen immunization rates, early detection of invasive disease, and antimicrobial stewardship.

Keywords: Pneumococcal/invasive pneumonia; Streptococcus pneumoniae; Pediatrics; Vaccination; Antimicrobial resistance.

INTRODUCTION

Streptococcus pneumonia is one of the leading infectious causes of pneumonia, meningitis, and sepsis in children worldwide (O'brien *et al*., 2009). Pneumococcal pneumonia is considered one of the leading causes of childhood mortality in developing countries. Approximately 1 million children die every year because of pneumococcal diseases, and about 90% of these deaths occur in low-income countries (Foster & Baltimore, 2010).

Invasive pneumococcal infections are often fatal, with fatality ranging between 11% and 60%. In low-income countries, death from pneumococcal meningitis is close to 59%, and among survivors, about 25–50% suffer severe neurological complications (Rudan & Campbell, 2009).

Invasive Pneumococcal Diseases (IPD) are considered life-threatening diseases; any patient infected with Streptococcus pneumonia has been identified traditionally in sterile locations, including blood, cerebrospinal fluid, or pleural fluid ((CDC), 2024;

O'brien *et al*., 2009). Although Pneumococcal Conjugate Vaccines (PCVs) have been widely used, S. pneumoniae remains one of the most significant bacterial causes of morbidity and mortality in this susceptible age group worldwide. The low- and middle-income countries have a disproportionate burden of IPD. It has been one of the main causes of children under five years old dying each year (Nimpa *et al*., 2025). Related to Mortality before the introduction of the vaccine, the World Health Organization projected a figure of about 800,000 deaths a year because of pneumococcal disease in children (O'brien *et al*., 2009).

PCVs' effectiveness of pneumococcal conjugate vaccines (PCVs) in the prevention of vaccine-type invasive pneumococcal disease (IPD). It also states, however, that there are still areas with a high level of IPD, with some areas showing a figure that represents more than 100 cases per 100,000 children. This implies that vaccination programs may not work as effectively and cover all areas and locations, which may be dependent on the availability of health care, vaccination coverage, and differences in the prevalent strains of pneumococcus (Mohanty *et al*., 2023).

Asymptomatic nasopharynx colonization is the start of the pathogenesis of IPD. The migration of bacteria in the bloodstream or other sterile organs in young children occurs due to underdeveloped immunity and high rates of carriage by the bacteria in the upper respiratory tract (Keller *et al*., 2016).

The process of the introduction of PCV7, and then PCV10 and PCV13 formulations, has caused a paradigm shift in the epidemiology of the disease. Although these vaccines have almost eliminated the serotypes targeted, the phenomenon that is currently of critical public health concern is the so-called serotype replacement, which is the development of non-vaccine serotypes such as 19A or 3 (Sgrulletti *et al*., 2025). Moreover, clinical management is complicated further by the emergence of antimicrobial resistance in the isolates of S. pneumoniae, which highlights the need to persist in surveillance and create next-generation vaccines (Barbieri *et al*., 2022).

Data for invasive pneumococcal disease incidence in low-income countries are scarce, probably because of multiple factors, such as inadequate laboratory facilities, suboptimal specimen collection, and, most importantly, pre-hospitalization use of antibiotics among children. Because of these limitations, the incidence of invasive pneumococcal disease is often underestimated in these countries. Since pneumococcal pneumonia is considered a main cause of mortality in resource-poor nations, the use of an effective vaccine would be helpful. Pneumococcus is an encapsulated diplococcus with over 94 serotypes; nonetheless, 70–80% of invasive pneumococcal disease cases are caused by 13 main serotypes included in the conjugated vaccine (McIntosh & Reinert, 2011).

Understanding the serotype epidemiology of the invasive pneumococcal disease (IPD) among children is necessary for vaccine development and introduction policies (Johnson *et al*., 2010). Furthermore, antimicrobial resistance among pneumococcal isolates is one of the new challenges in the treatment of pneumococcal infections (O'brien *et al*., 2009).

This study aimed to describe the clinical and microbiological image of Invasive Pneumococcal Disease (IPD) in children under five years in a tertiary care facility in Saudi Arabia. In particular, the study aimed to identify the incidence and clinical outcomes of infections, the serotypes of circulating Streptococcus pneumoniae to identify the coverage of the current Pneumococcal Conjugate Vaccines (PCVs), and the antimicrobial susceptibility of the isolated strains. Through the analysis of these aspects, the research was supposed to present the necessary local information to inform empirical antibiotic therapy and inform people on the strategies of health in relation to national immunization programs in the Kingdom.

METHOD

This study is a retrospective review of data collected from the PSMMC microbiology lab database over 10 years, from January 2009 to January 2019. After obtaining approval from the Research Ethics Committee of the Scientific Research Center of the Medical Services Department for Armed Forces, a retrospective study of microbiology data will be performed at PSMMC.

Data will be used from the microbiology database from 2009 to 2019 looking for positive blood, cerebrospinal fluid and pleural fluid positive for streptococcus pneumonia to determine the most common serotypes associated with invasive infection in children less than five years of age in PSMMC. All patients' data will be subject to the terms of confidentiality that ensure the patient data privacy (e.g., names and file numbers) will be confidential.

The data is characterized by isolation of bacteria from the sterile site (blood, cerebrospinal fluid, pleural fluid, or bronchoalveolar lavage). The monitored data consisted of demographics, comorbidities, clinical presentation, lab results, radiological images, vaccination history, antimicrobial sensitivity, treatment history, and outcomes. The missing data were noted and did not go through certain analyses. IBM SPSS version 27 was used to do a statistical analysis. The descriptive statistics were in frequencies and percentages. The statistically significant p-value was taken as less than 0.05.

RESULTS

This study included 67 children aged ≤5 years and with microbiologically confirmed invasive Streptococcus pneumoniae infection used in the study. All of them were detected by the culture of sterile sites that were noted in the microbiology database during the 10-year period of study.

Demographic Characteristics

There were 37 (55.3) and 30 (44.7) males and females among the included children, respectively. The age of infection varied between 2 days to 5 years, with 2 years having the highest percentage of 20.9, then 3 years (10.4) and 5 years (4.5).

Table 1: Demographic characteristics of children

Variable	Frequency (n)	Percentage (%)
Male	37	55.3
Female	30	44.7
Age ≤ 2 years	26	38.8
Age 3–5 years	41	61.2

Microbiological Cause of Sepsis.

The most common source of isolation was blood culture, which was positive in 49 cases (73.1%). A positive result was reached in 5 cases (7.5%), of combinable blood and cerebrospinal fluid (CSF) cultures, and in 9.0 cases, it was in bronchoalveolar lavage. CSF and pleural fluid were all 4.5% of the isolates.

Table 2: Source of positive cultures

Sample Type	Frequency (n)	Percentage (%)
Blood	49	73.1
Blood + CSF	5	7.5
Bronchoalveolar lavage	6	9.0
CSF	3	4.5
Pleural fluid	3	4.5

Comorbidities

Most of the patients had underlying medical conditions. The percentage of the number of children with no comorbidity recorded was only 14 (20.9%). Multifactorial comorbidity was common and comprised of congenital heart disease, chronic lung disease, prematurity, genetic syndromes, sickle cell disease, neurological, and chronic liver or kidney disease. It was prevalent with several comorbidities.

Table 3: Presence of comorbidities in children with IPD

Comorbidity Status	Frequency (n)	Percentage (%)
None	14	20.9
At least one comorbidity	53	79.1

Clinical Presentation

ever was present in approximately 65.7% of children with invasive pneumococcal disease. Many patients lacked typical organ-specific symptoms, with about one-third presenting without respiratory symptoms and nearly half without gastrointestinal symptoms. When present, cough and shortness of breath were the most common respiratory manifestations, while vomiting and decreased oral intake were the leading gastrointestinal complaints. Neurological manifestations, including convulsions or altered level of consciousness, were observed in roughly one-third of cases, indicating a substantial burden of severe disease at presentation.

Table 4: Clinical presentation at admission

Symptom	Frequency (n)	Percentage (%)
Fever		
Yes	44	65.7
No	23	34.3
Respiratory symptoms		
No respiratory symptoms	29	34.3
Cough	8	11.9
Shortness of breath	6	9.0
Gastrointestinal symptoms		
No GI symptoms	30	44.8
Vomiting	7	10.4
Decreased oral intake	7	10.4
Neurological		
Convulsions / altered consciousness	23	34.3

Radiological Findings

In the vast majority of patients, chest radiography or CT chest was conducted. Aberrant results were not unusual and a great variety of aberrant pulmonary findings was noted. Bilateral pulmonary infiltrates, ground-glass opacities or peribranchial infiltrations were often reported. The imaging was reported to be normal in 10 patients (14.9%), and not done in 12 cases (17.9%).

Table 5: Chest imaging findings

Radiological Finding	Frequency (n)	Percentage (%)
Abnormal findings	45	67.2
Normal imaging	10	14.9
Imaging not performed	12	17.9

Laboratory Findings

There was often a high level of inflammatory markers. ESR was measured in a subset of the patients and was found to be elevated in most instances. The count of white blood cells and C-reactive protein was basically elevated, which indicates that there was high systemic inflammation.

Vaccination Status

The pneumococcal vaccination information was accessible for 43 patients (64.2%). Of these, 16 children (37.2) had not received any pneumococcal doses of vaccinations when they were infected. Four doses of vaccines were reported on 14 patients (32.6).

Table 6: Pneumococcal vaccination status at time of infection

Number of PCV doses	Frequency (n)	Percentage (%)
0 doses	16	37.2
1 dose	4	9.3
2 doses	2	4.7
3 doses	7	16.3
4 doses	14	32.6

Antimicrobial Susceptibility

Most Streptococcus pneumoniae isolates were susceptible to penicillin (70.1%) and ceftriaxone (82.1%). Resistance or intermediate susceptibility was observed among penicillin isolates; however, no resistance or intermediate susceptibility to ceftriaxone was reported in the available data.

Table 7: Antimicrobial susceptibility patterns of *S. pneumoniae* isolates

Antibiotic	Susceptible n (%)	Resistant/Intermediate n (%)
Penicillin	47 (70.1)	13 (19.4)
Ceftriaxone	55 (82.1)	-

Neurological Investigations

The brain MRI was conducted in 17 patients (25.4%), and abnormalities were noted in a number of them, such as subdural collections and ventricular dilatation. EEG was done in 19 patients (28.4%), and the majority of the studies reported a lack of epileptiform activity.

Presentation Neurological Manifestations

The presence of neurological symptoms was reported in 23 children (34.3%). The most common neurological presentation was convulsions, which occurred in 5 patients (7.5%), and the reduced level of consciousness was observed in 2 patients (3.0%). The rest of 44 children (65.7%) did not report any neurological symptoms on presentation.

Table 8: Neurological manifestations among children with IPD

Neurological symptom	Frequency (n)	Percentage (%)
Any neurological symptom	23	34.3
Convulsions	5	7.5
Decreased level of consciousness	2	3.0
No neurological symptoms	44	65.7

Brain MRI Findings

Abnormal findings were found in 7 patients out of 10 (10.4%) with subdural collections, ventricular dilatation, arachnoid cysts, and cerebral volume loss. In 1 patient (1.5%), MRI was found to be normal whereas it was not done in 42 (62.7) patients.

Table 9: Brain MRI findings

MRI result	Frequency (n)	Percentage (%)
Abnormal MRI findings	7	10.4
Normal MRI	1	1.5
MRI not performed	42	62.7

Electroencephalography (EEG) Results

The EEG was performed in 19 children (28.4%). Abusive EEG results were reported in 3 patients (4.5%), one of them being generalized cortical dysfunction, and the other focal slows. In 2 patients (3.0%), normal EEG records were found. EEG was not done to 46 patients (68.6%).

Table 10: EEG findings among children with IPD

EEG result	Frequency	Percentage (%)
Abnormal EEG	3	4.5
Normal EEG	2	3.0
EEG not performed	46	68.6

Inflammatory Markers (ESR)

The 20 patients (29.9) had Erythrocyte sedimentation rate (ESR) values available. Out of these, ESR had been myocardially raised in most of them. ESR was not done or not reported in 47 patients (70.1%).

Pneumococcal Serotype Data

The number of patients reporting serotype data was 2(6,14).

Clinical Outcomes

A significant percentage of patients were reported to have in-hospital complications. During hospitalization, thirteen children (19.4) died. The survivors had a recovery rate of 34 (50.7) patients without reported complications.

Table 11: Clinical outcomes of children with IPD

Outcome	Frequency (n)	Percentage (%)
Death	13	19.4
Survived without complications	34	50.7
Survived with complications	20	29.9

DISCUSSION

Streptococcus pneumoniae is a gram-positive, alpha-hemolytic, catalase-negative diplococcus that remains a leading cause of invasive bacterial infections in children, including bacteremia, meningitis, and severe pneumonia (McDevitt *et al*., 2020; O'brien *et al*., 2009). Despite the global implementation of pneumococcal conjugate vaccines (PCVs), invasive pneumococcal disease (IPD) continues to impose a substantial burden of morbidity and mortality, particularly among young children and those with underlying medical conditions (Olarte & Jackson, 2021; Troeger *et al*., 2018). Data describing the contemporary epidemiology and outcomes of IPD in Saudi Arabian children, however, remain limited.

In this 10-year retrospective study, we evaluated the clinical characteristics, vaccination status, antimicrobial susceptibility, and outcomes of IPD among children younger than five years at a tertiary care center in Saudi Arabia. Our findings demonstrate that IPD remains associated with significant disease severity and adverse outcomes. The in-hospital mortality rate in our cohort was 19.4%, which is higher than that reported in several earlier regional studies (Almazrou *et al*., 2016; Memish *et al*., 2010). This finding underscores the ongoing clinical burden of IPD and may reflect referral bias to a tertiary center, delayed presentation, high comorbidity burden, or severe disease at onset.

A notable proportion of children in our cohort had underlying medical conditions, with nearly four-fifths presenting with at least one comorbidity. Congenital heart disease, chronic lung disease, prematurity, genetic syndromes, and hematologic disorders were frequently observed. Previous studies have consistently identified comorbid conditions as major predictors of severe disease, complications, and mortality in children with IPD (Pallares *et al*., 1995). The high prevalence of comorbidities in our population likely contributed to the observed severity and outcomes.

The pneumococcal vaccination information was accessible for 43 patients (64.2%). Of these, 16 children (37.2) had not received any pneumococcal doses of vaccinations when they were infected. Four doses of vaccines were reported on 14 patients (32.6). Other study findings have been reported in earlier Saudi studies, where low vaccine coverage was associated with increased susceptibility to IPD (Memish *et al*., 2010). Although vaccine failure and infection with non-vaccine serotypes may explain some cases, incomplete vaccination remains a preventable risk factor for invasive disease (Brooks & Mias, 2018).

Clinically, fever was the most frequent presenting symptom (65.7%); however, a substantial proportion of children presented without respiratory (34.3%) or gastrointestinal symptoms (44.8%). Atypical presentations of IPD have been described previously and may delay diagnosis, particularly in high-risk pediatric populations (Lynch & Zhanel, 2009). Neurological manifestations, including convulsions and altered level of consciousness, were observed in more than 34.3 % of cases. Central nervous system involvement is a well-recognized complication of IPD and is associated with increased mortality and long-term sequelae (Sáez-Llorens & McCracken, 2003; van de Beek *et al*., 2021).

Comparisons with previous regional studies reveal important differences. Almazrou *et al*. reported a very low prevalence of IPD in Saudi children before widespread PCV implementation, with extremely low vaccination coverage (Memish *et al*., 2010). In contrast, our study reflects a later post-PCV period in which vaccination is available but remains incomplete. Similarly, Memish *et al*. reported lower mortality rates in earlier surveillance studies conducted in Riyadh and Jeddah (Almazrou *et al*., 2016; Sáez-Llorens & McCracken, 2003). The higher mortality observed in our cohort may be attributed to differences in study populations, healthcare utilization, or disease severity.

Studies from neighboring countries, including Kuwait, have documented increasing resistance to penicillin and cephalosporins among pneumococcal isolates, as well as rising rates of multidrug resistance (Johny *et al*., 2010). Although multidrug resistance was not extensively evaluated in our study, the observed resistance patterns align with regional trends, emphasizing the importance of antimicrobial stewardship programs.

This study has several limitations. Its retrospective design may have resulted in missing or incomplete data, particularly regarding vaccination history, serotype distribution, and long-term outcomes. Additionally, as a single-center study, the findings may not be generalizable to all regions of Saudi Arabia. Nevertheless, this study provides valuable insight into the contemporary burden and outcomes of invasive pneumococcal disease in young children.

CONCLUSION

Invasive pneumococcal disease remains a serious and potentially fatal condition among children under five years of age in Saudi Arabia. High mortality rates, frequent comorbidities, incomplete vaccination, and emerging antimicrobial resistance highlight the need for strengthened immunization strategies, early recognition of atypical presentations, and robust antimicrobial stewardship. Multicenter prospective studies are warranted to better define national disease burden, serotype distribution, and long-term sequelae.

REFERENCES

- (CDC), C. f. D. C. a. P. (2024). *Pneumococcal Disease: Pink Book.* https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-17-pneumococcal-disease.html
- Almazrou, Y., Shibl, A. M., Alkhlaif, R., Pirçcon, J.-Y., Anis, S., Kandeil, W., & Hausdorff, W. P. (2016). Epidemiology of invasive pneumococcal disease in Saudi Arabian children younger than 5 years of age. *Journal of epidemiology and global health*, *6*(2), 95–104.
- Barbieri, E., Porcu, G., Hu, T., Petigara, T., Senese, F., Prandi, G. M., Scamarcia, A., Cantarutti, L., Cantarutti, A., & Giaquinto, C. (2022). A Retrospective Analysis to Estimate the Burden of Invasive Pneumococcal Disease and Non-Invasive Pneumonia in Children< 15 Years of Age in the Veneto Region, Italy. *Children*, *9*(5), 657.
- Brooks, L. R., & Mias, G. I. (2018). Streptococcus pneumoniae's virulence and host immunity: aging, diagnostics, and prevention. *Frontiers in immunology*, *9*, 1366.
- Foster, M., & Baltimore, R. (2010). Pneumonia remains leading cause of child mortality worldwide. *Infectious Diseases in Children*, *23*(8), 18.
- Johnson, H. L., Deloria-Knoll, M., Levine, O. S., Stoszek, S. K., Freimanis Hance, L., Reithinger, R., Muenz, L. R., & O'Brien, K. L. (2010). Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS medicine*, *7*(10), e1000348.
- Johny, M., Babelly, M., Al-Obaid, I. a., Al-Benwan, K., & Udo, E. E. (2010). Antimicrobial resistance in clinical isolates of Streptococcus pneumoniae in a tertiary hospital in Kuwait, 1997–2007: Implications for empiric therapy. *Journal of Infection and Public Health*, *3*(2), 60–66.
- Keller, L. E., Robinson, D. A., & McDaniel, L. S. (2016). Nonencapsulated Streptococcus pneumoniae: emergence and pathogenesis. *MBio*, *7*(2), 10.1128/mbio. 01792–01715.
- Lynch, J. P., & Zhanel, G. G. (2009). Streptococcus pneumoniae: epidemiology, risk factors, and strategies for prevention. Seminars in respiratory and critical care medicine,
- McDevitt, E., Khan, F., Scasny, A., Thompson, C. D., Eichenbaum, Z., McDaniel, L. S., & Vidal, J. E. (2020). Hydrogen peroxide production by Streptococcus pneumoniae results in alpha-hemolysis by oxidation of oxy-hemoglobin to met-hemoglobin. *Msphere*, *5*(6), 10.1128/msphere. 01117–01120.
- McIntosh, E. D. G., & Reinert, R. R. (2011). Global prevailing and emerging pediatric pneumococcal serotypes. *Expert review of vaccines*, *10*(1), 109–129.
- Memish, Z. A., El-Saed, A., Al-Otaibi, B., Al Shaalan, M., Al Alola, S., & Thaqafi, A. O. (2010).

Epidemiology of invasive pneumococcal infection in children aged five years and under in Saudi Arabia: a five-year retrospective surveillance study. *International Journal of Infectious Diseases*, *14*(8), e708–e712.

- Mohanty, S., Podmore, B., Cuñado Moral, A., Matthews, I., Sarpong, E., Lacetera, A., & Qizilbash, N. (2023). Incidence of pneumococcal disease from 2003 to 2019 in children≤ 17 years in England. *Pneumonia*, *15*(1), 2.
- Nimpa, M. M., Ntambue, A., Ngandu, C., Danovaro-Holliday, M. C., Bita Fouda, A., Cikomola, A. M.-W., Mukendi, J.-C., Mwamba, D., Aluma, A. D. L., & Yapi, M. D. (2025). Effects of Pneumococcal Vaccination in Children Under Five Years of Age in the Democratic Republic of Congo: A Systematic Review. *Vaccines*, *13*(6), 603.
- O'brien, K. L., Wolfson, L. J., Watt, J. P., Henkle, E., Deloria-Knoll, M., McCall, N., Lee, E., Mulholland, K., Levine, O. S., & Cherian, T. (2009). Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *The Lancet*, *374*(9693), 893–902.
- Olarte, L., & Jackson, M. A. (2021). Streptococcus pneumoniae. *Pediatrics in Review*, *42*(7), 349–359.
- Pallares, R., Liñares, J., Vadillo, M., Cabellos, C., Manresa, F., Viladrich, P. F., Martin, R., & Gudiol, F. (1995). Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *New England Journal of Medicine*, *333*(8), 474–480.
- Rudan, I., & Campbell, H. (2009). The deadly toll of S pneumoniae and H influenzae type b. *The Lancet*, *374*(9693), 854–856.
- Sáez-Llorens, X., & McCracken, G. H. (2003). Bacterial meningitis in children. *The Lancet*, *361*(9375), 2139–2148.
- Sgrulletti, M., Mastrototaro, M. F., Beni, A., Mantuano, G., Costagliola, G., Santilli, V., Montin, D., Rizzo, C., Martire, B., & Marseglia, G. L. (2025). Toward Universal Protection: A Comprehensive Review of Pneumococcal Disease, Emerging Vaccination Challenges and Future Perspectives. *Vaccines*, *13*(12), 1237.
- Troeger, C., Blacker, B., Khalil, I. A., Rao, P. C., Cao, J., Zimsen, S. R., Albertson, S. B., Deshpande, A., Farag, T., & Abebe, Z. (2018). Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet infectious diseases*, *18*(11), 1191–1210.
- van de Beek, D., Brouwer, M. C., Koedel, U., & Wall, E. C. (2021). Community-acquired bacterial meningitis. *The Lancet*, *398*(10306), 1171–1183.