Analysis of *Streptococcus pneumoniae* in Bangladesh: 2009-2021

INTERNSHIP PROJECT

SUPERVISED BY

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Abstract:

The aim of the study is to investigate the trends in the distribution and impact of invasive pneumococcal disease (IPD) from 2009-2021 in Bangladesh. We used a dataset of <5 years children with various symptoms (pneumonia, meningitis etc.) and outcomes (death, discharge, referred etc.) who had all tested positive for *Streptococcus pneumoniae* (Spn), the causative agent of IPD. The dataset has been scrutinized to understand the tendency of different Spn serotypes to cause meningitis, identify severe serotypes that cause death, correlate age and serotype, and identify the geographical distribution of Spn. Through this analysis, we also investigated the impact of the 10-valent pneumococcal vaccine (PCV-10) on IPD cases in Bangladesh. Customized python scripts were used for this analysis and all the visualization was performed in Datawrapper and Google colab platform. Bangladesh suffers from a high burden of IPD-related mortality, morbidity and disability cases, however PCV introduction has had a major impact. 7/10 Spn serotypes covered by Spn were to reduce after vaccine introduction. Further, serotype 2 caused one of the most severe infections with high mortality and symptom of meningitis. In future vaccine formulations, covering serotype 2 would be extremely beneficial to Bangladesh and will likely further significantly reduce the mortality associated with this disease.

Introduction:

Invasive pneumococcal disease (IPD) is an acute and serious infection caused by *Streptococcus pneumoniae* (Spn) that predominantly affects children under five years of age. Globally, this pathogen causes over 9 million cases and 300 thousand deaths every year, majority of which occur in low-and-middle-income countries. According to the most recent 2015 estimates, 48% of the 8.9 million pediatric pneumococcal pneumonia cases that occur each year globally occur in the Southeast Asian region. Bangladesh, a densely populated country in this region, has the tenth highest pneumococcal pneumonia mortality burden in under-five year old children worldwide and nearly 40% of deaths from lower respiratory tract infection in under-five year old children in Bangladesh are attributed to Spn [1].

In Bangladesh, more than 50 different serotypes have been detected to cause IPD cases and 78% of them occur within the first year of life from 2007 to 2013 the most common serotypes were 2 (16%), 1 (10 %), 6B (7%), 14 (7%) and 5 (7%). Potential serotype coverage for meningitis and non-meningitis cases was 45% and 49% for PCV-10. The distribution of serotypes causing IPD in Bangladeshi children is diverse, limiting the proportion of IPD cases PCV can prevent. To reduce burden of invasive pneumococcal disease, Bangladesh introduced the 10-valent Pneumococcal conjugate vaccine (PCV10) in the national routine vaccination in March 2015.[2]. PCV introduction is expected to have major benefits as the country has a high burden of IPD-related mortality, morbidity and disability [2].

The objective of this project is to describe the changes in serotypes and clinical manifestations of children who were admitted to Bangladesh Shishu Hospital and Institute (BSHI, formerly known as Dhaka Shishu Hospital from 2009 to 2021 and tested positive for IPD through culture, PCR or ICT diagnostic tests. This analysis allowed us to determine the impact of PCV-10 introduction on the prevalence of IPD in children in Bangladesh. We also scrutinized the data to understand the tendency of different Spn serotypes to

cause meningitis, the temporal changes of serotypes because of PCV-10, identify severe serotypes that cause death, correlation between age and serotype, and the geographical distribution of Spn.

Result:

Overview of the dataset:

In the dataset, there were 789 possible IPD cases from 2009 to 2021, among them 457 cases were also diagnosed with meningitis. Seven features or variables were considered for this analysis: Year, Age, Case Definitions, Zilla, Outcome, Hospital Duration, Serotypes.

Distribution of serotypes:

Among the cases, we identified 77 different serotypes. Here, we omitted 5 serotypes such as ND, NTD, NoPCV13, QNS, NON TYPABLE. To observe the serotype distribution, we created a bar graph by displaying each serotype as its own bar whose height (Y-axis) represents the number of individuals belonging to that category (figure 1). From left to right the height of the bars are decreasing and a peak could be seen for serotype 1 and 2. Taken together, this tells us that these two serotypes are the cause for the most IPD cases.

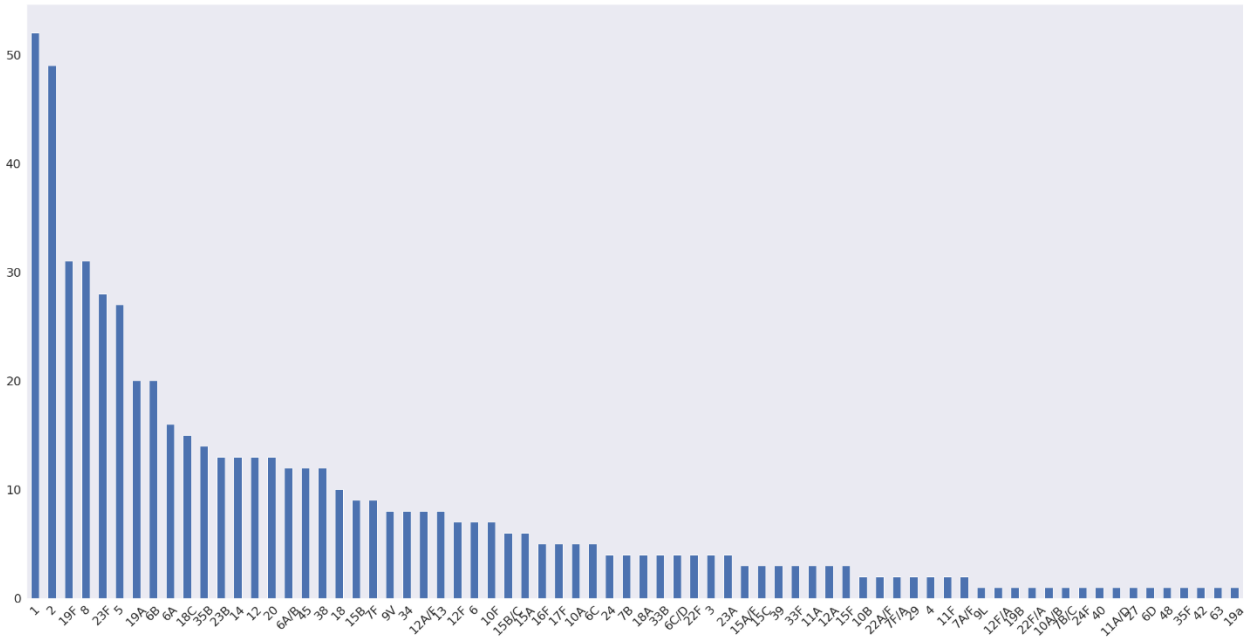


Figure 1: Distribution of *Streptococcus pneumoniae* (Spn) serotypes in Bangladesh.

Propensity of different Spn serotypes to cause meningitis:

We found 457/790 IPD cases exhibited symptoms for meningitis. Here, we calculated the probability of causing meningitis for each serotype and sorted them in ascending order and created a scatter plot for visualizing the percentage. The propensity to cause meningitis for Spn serotypes is shown in Figure 2. The serotypes that are more likely to cause meningitis are 2 (91.84%, total case: 49), 5 (85.71%, total case: 28), 8 (70.96%, total case: 31), 1 (34.545%, total case: 55).

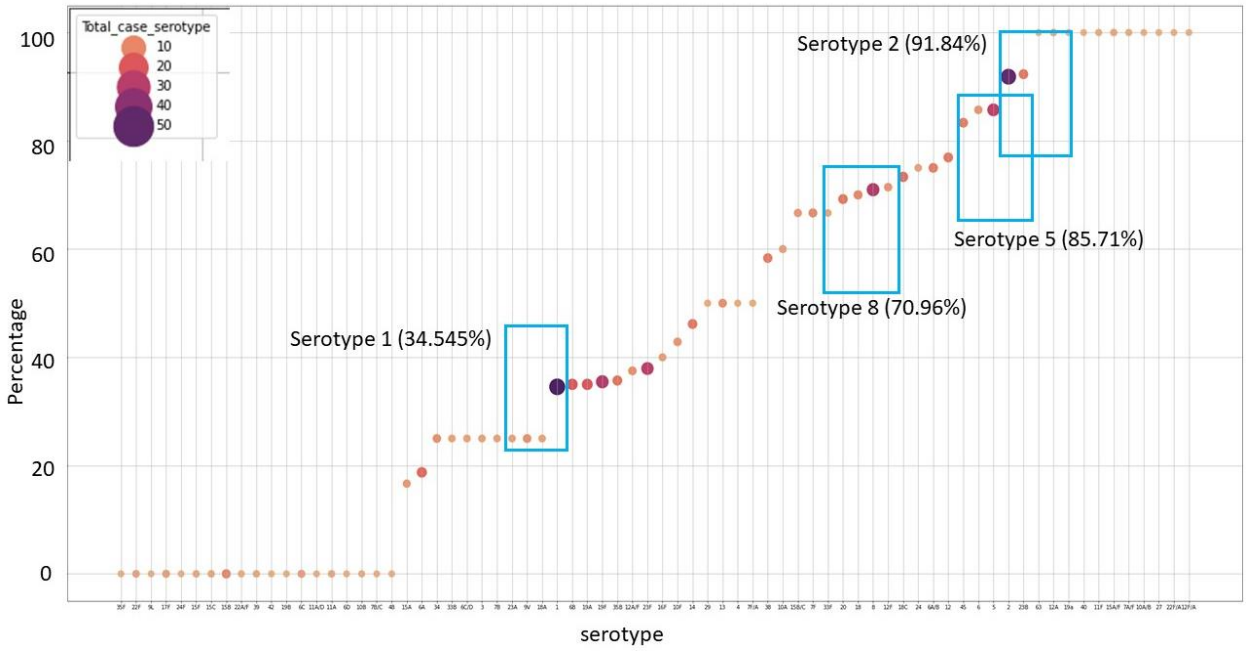
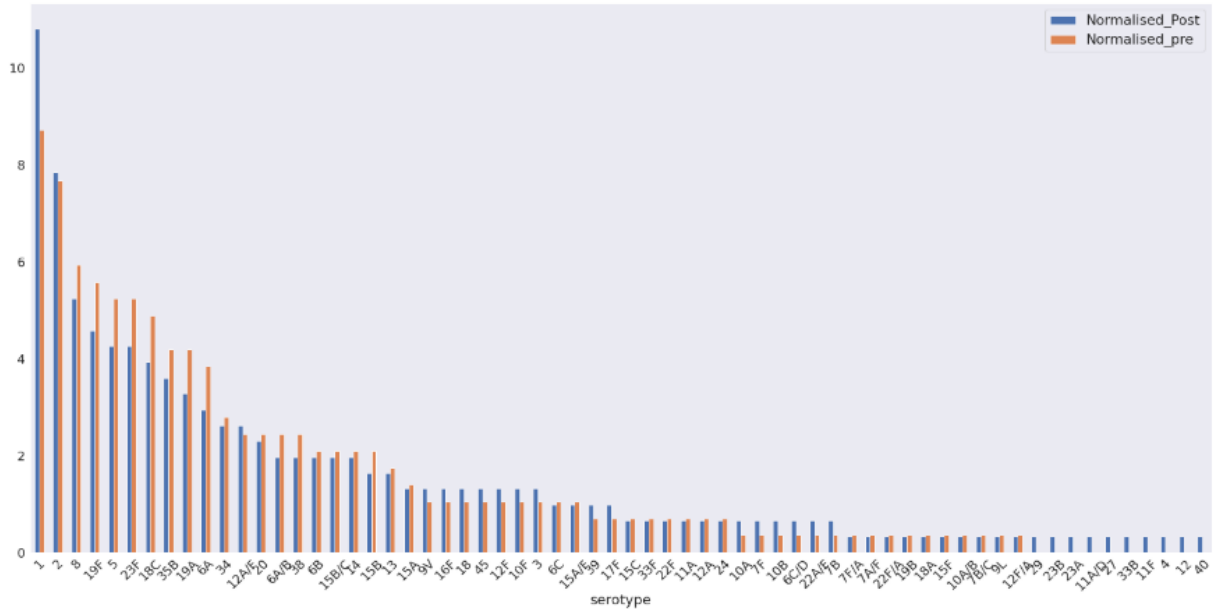


Figure 2: Propensity to cause meningitis for Spn serotypes

Temporal changes in serotype distribution:

PCV-10 was introduced in March 2015 and provides protection against the following ten serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. Therefore, we divided the dataset into two portions, namely pre-PCV (2009-March 2015) and post-PCV (April 2015-2021). In Figure 3 (upper panel), the normalized scenario of pre and post cases for each serotype have been shown. In Figure 3 (lower panel), the effect of PCV-10 vaccine for the different serotypes is shown and was calculated by subtracting pre cases from post cases. The vaccine is working significantly for 19F, 5, 23F, 18C, 6B and 14



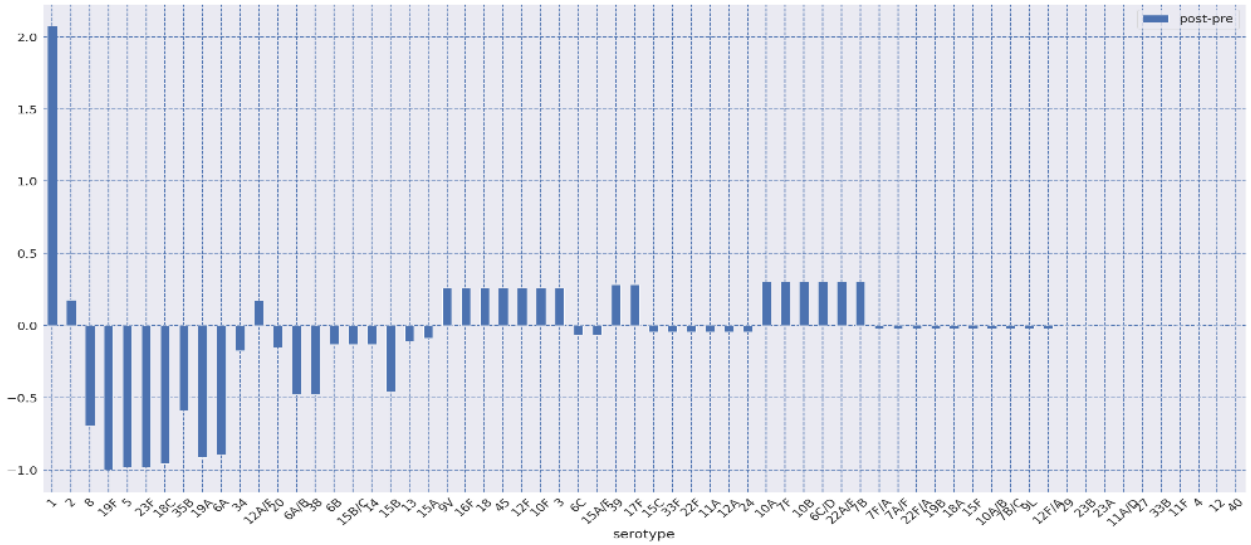
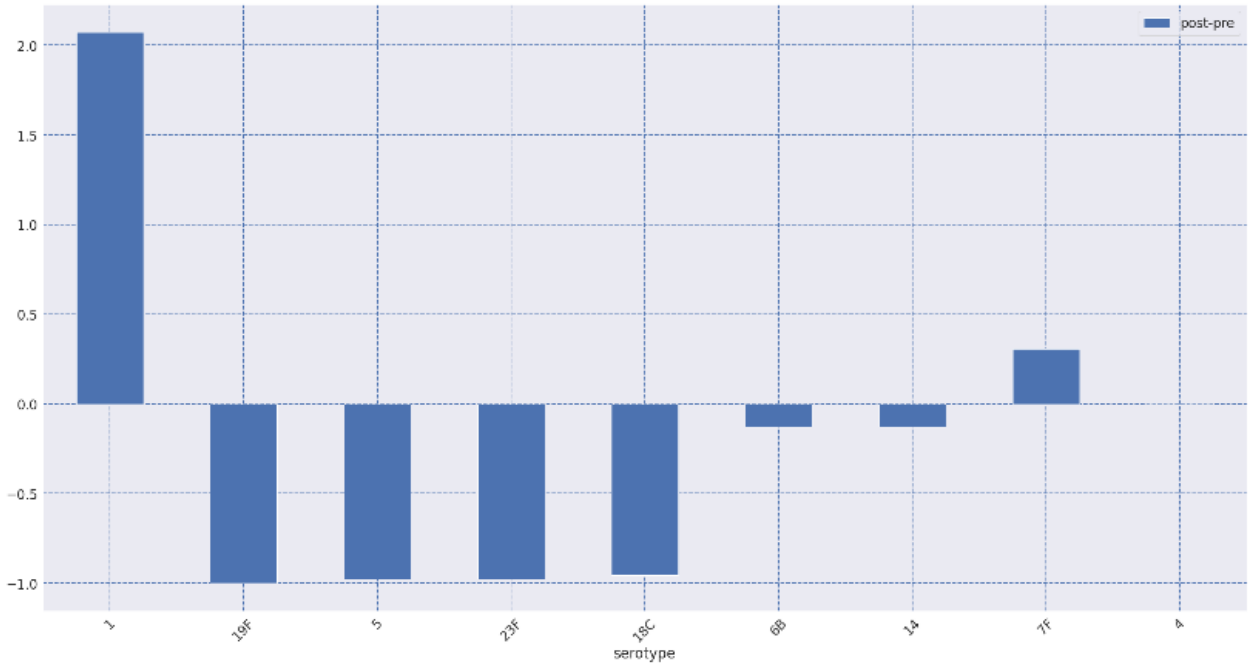


Figure 3: impact of PCV10 on the distribution of Spn serotypes. Frequency of serotypes pre-PCV and post-PCV (Normalized, upper panel). Frequency of serotypes: Post-Pre (Normalized, lower panel)

To estimate the impact of vaccination effect on the 10 serotypes covered by the vaccine, we focused on the proportions for these two cases for specifically (Figure 4, upper panel). The reduction was seen for 19F, 5, 23F, 18C, 6B and 14. However, no reduction was seen for Serotype 1 and 7F. The temporal analysis highlighted the change of each serotype with years from 2009 to 2021 (Figure 4, lower panel)



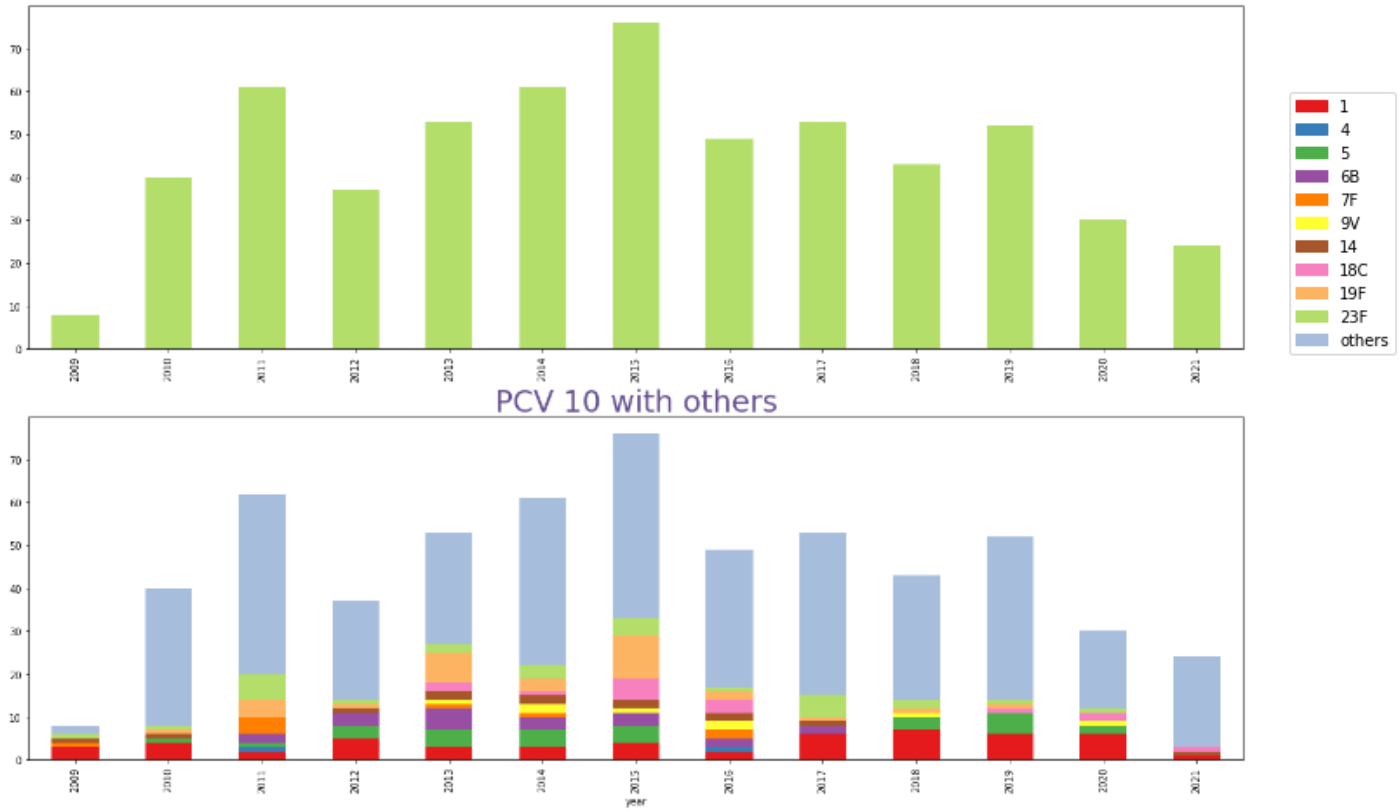


Figure 4: Impact of PCV-10 on 10 serotypes covered by the vaccine. A) PCV-10: Post-Pre (Normalized, upper panel), distribution of overall Spn and PCV-10 (lower panel)

Death and severity of different Spn serotypes:

We calculated the probability of death and severity for each serotype and sorted them in ascending order. Then creating a scatter plot, we visualized the percentage separately. The tendency of causing death for Spn serotypes is shown in Figure 2 (upper panel) and for severity the scatter plot is displayed in figure 2(lower panel). The serotypes that are more likely to cause death are 19F (19.35484%), 5 (10.71429%), 2 (6.1224%), 1 (3.6363%). And for severity the percentages are: 19F (29.03%), 2(24.48%), 5 (21.42%), 1 (12.72%).

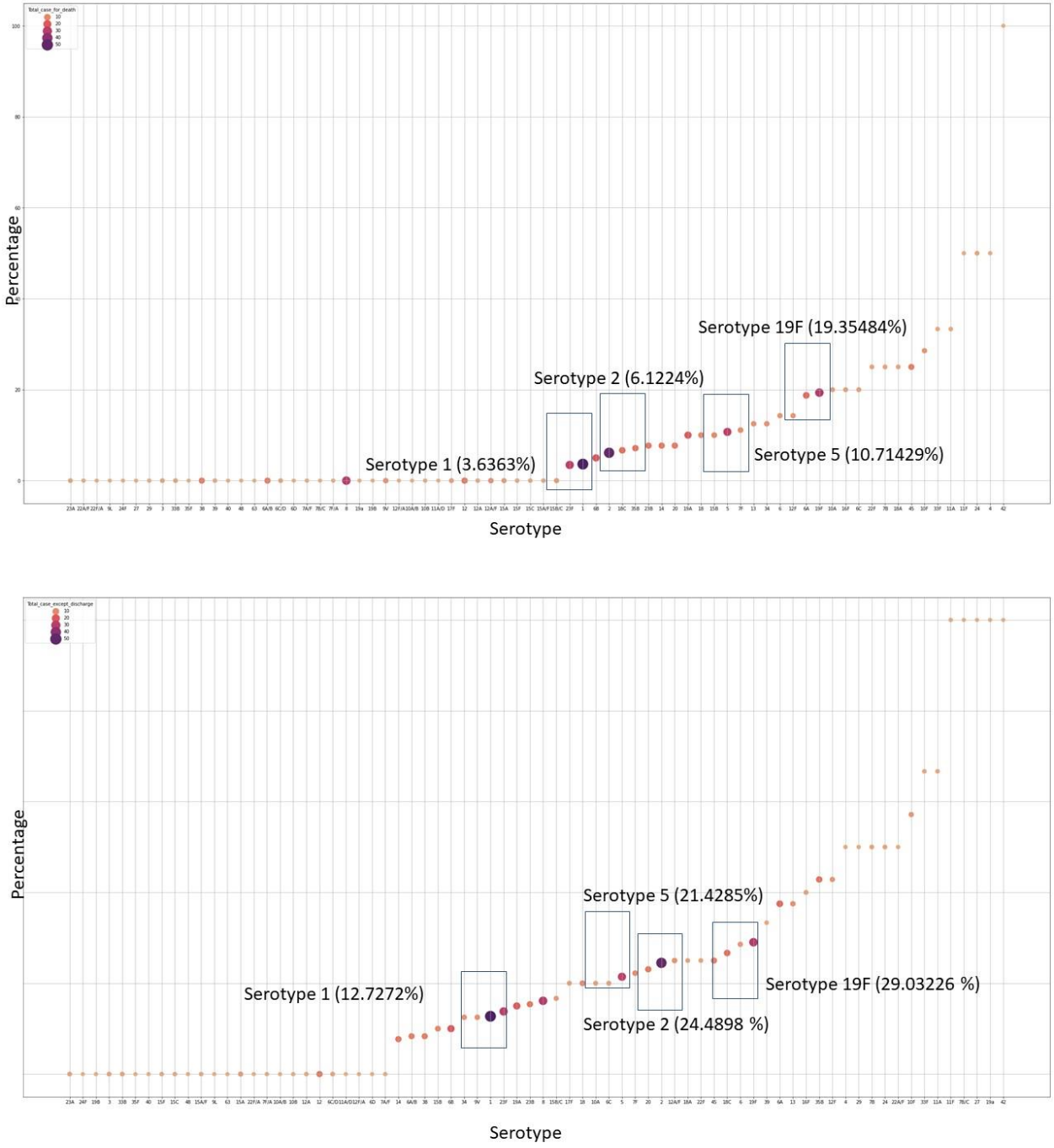


Figure 5: For death (upper panel), for severity (lower panel)

Correlation between age and serotype:

To investigate the relationship between age and different serotypes, we obtained the hospital records of children admitted to our surveillance network, whose ages range from 0 to 177 in month. In Figure 6

(upper panel), we have the age distribution for all the different serotypes is shown including all cases from 2009 to 2021. A large variation is seen for different serotypes.

To investigate the impact of PCV-10 on age range of different serotypes, we considered all cases (Figure 6, upper panel) and compared Pre and Post-PCV10 (Figure 6, lower panel). Here, we can see a transition of age group for serotypes of 1, 7F, 12F, 17F, 18, 38, 24, 18C, 9V, 7B, 6C and from all the serotypes the PCV10 serotypes are being shown by highlighted boxes.

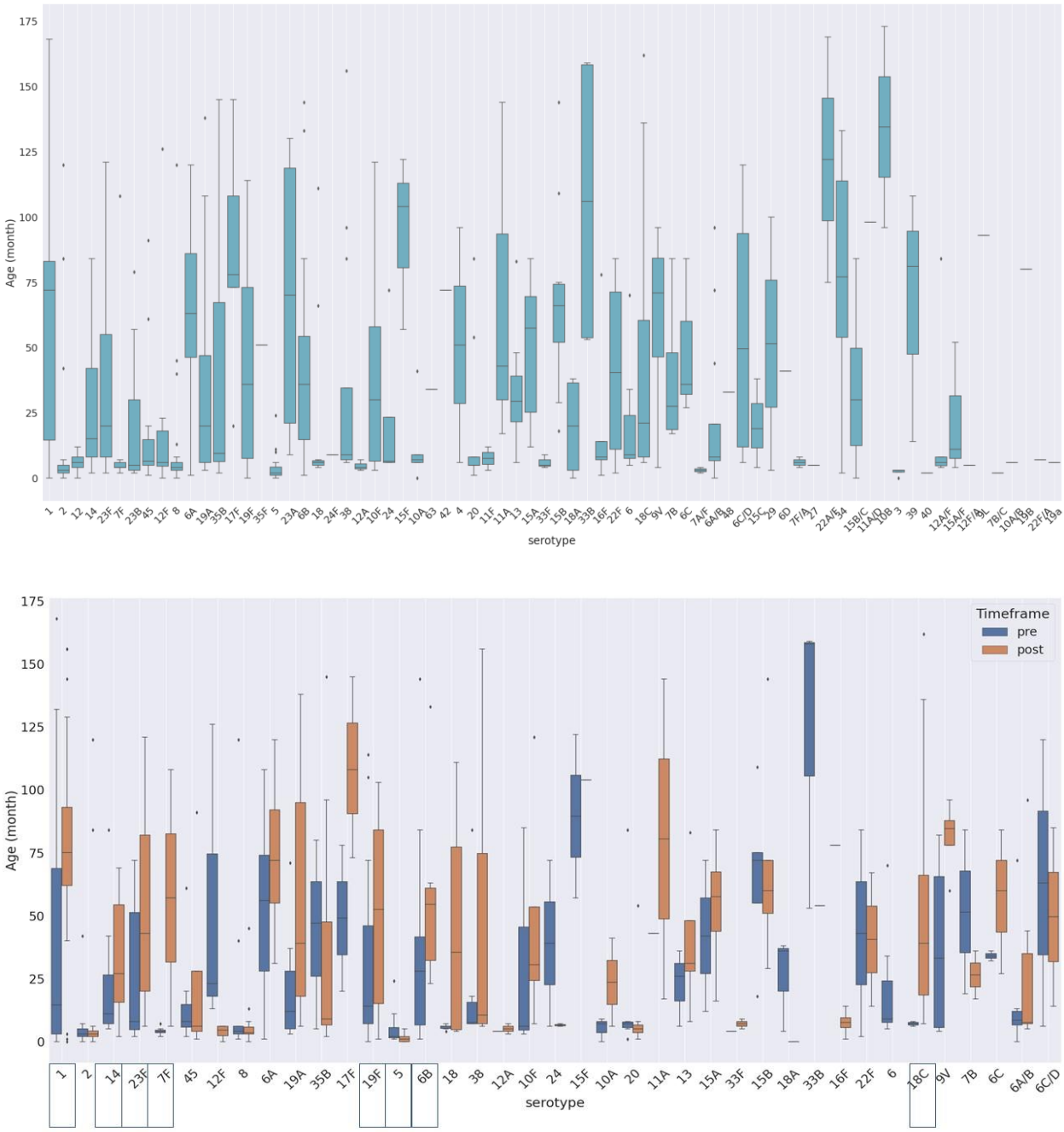


Figure 6: All cases (upper panel), Pre Vs. Post (lower panel)

Geographical distribution of IPD cases in Bangladesh:

To investigate the geographical distribution of IPD cases in Bangladesh, we used Datawrapper to obtain a district-wise plot of cases admitted to the CHRF hospital network (Figure 7). The highest number of samples came from Dhaka district (n=255). Dhaka district is the most populated district in Bangladesh. The districts (Gazipur, Brahmanbaria, Narayanganj, Comilla, Chandpur and Noakhali) to the east of Dhaka provided more cases than the districts to the west (Tangail, Manikganj and Faridpur). This is likely due to better transportation facilities and larger population in these districts in comparison to the western districts.

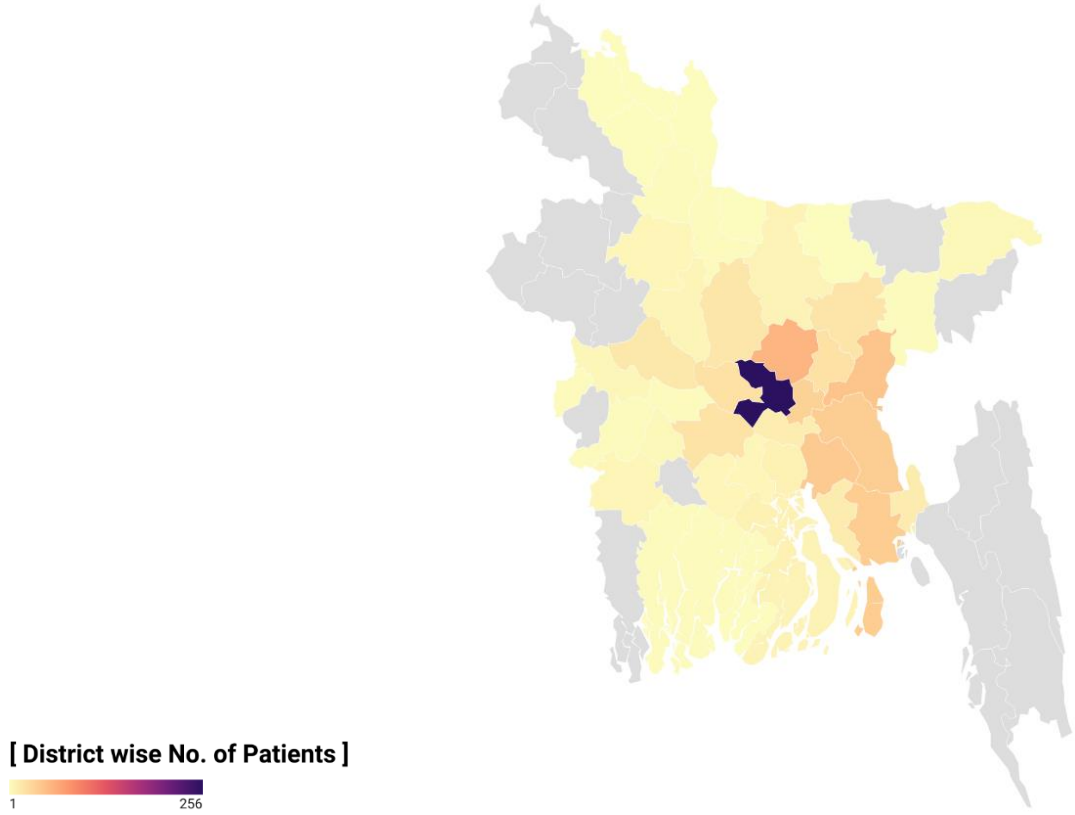


Figure 7: Geographical distribution of IPD cases in Bangladesh

Discussion:

The aim of the current study was to undertake an epidemiological analysis of invasive pneumococcal disease (IPD) in Bangladesh over a 13-year period (2009-2021). The data was collected at the largest pediatric hospital in the country, Bangladesh Shishu Hospital and Institute (BSHI) located in the capital city Dhaka, and allowed us to investigate the impact of PCV-10 introduction in 2015, serotype distribution and clinical features (age distribution, clinical manifestation, outcome) of IPD cases in the country.

Considering severity, 19F (29.03%), 2(24.48%), 5 (21.42%), 1 (12.72%) have larger percentage sequentially (Figure 5, lower panel). The serotypes that have higher record for death are serotypes 19F (19.35484%), 5 (10.71429%), 2 (6.1224%) and 1 (3.6363%) (Figure 5, upper panel). On the other hand, meningitis causing serotypes are 2 (91.84%, total case: 49), 5 (85.71%, total case: 28), 8 (70.96%, total case: 31), 1 (34.545%, total case: 55) (Figure 2). So, serotype 2 and 5 are the most severe and cause high rates of meningitis. Of these two serotypes, 5 is included in PCV-10 while 2 is not.

A positive Impact of PCV-10 can be seen for 4, 5, 6B, 14, 18C, 19F, 23F (Figure 4, upper panel). however, as the vaccine is only given to the younger children (<5 years), the elder children remained unprotected from IPD. This can be a probable cause for change in age transition seen for 1, 7F, 12F, 17F, 18, 38, 24, 18C, 9V, 7B, 6C serotypes (Figure 6, lower panel pre and post PCV10 introduction).

Surprisingly, we also observed that the proportion of serotype 1 has increased after the introduction of PCV-10 in Bangladesh (Figure 3, lower panel). An increase in age distribution is also seen (from median: 12 to median: 75 months) for Serotype 1 after introduction of PCV-10 (Figure 6, lower panel). Given, the age is negatively linked with death, the severity and mortality linked with Serotype 1 could likely have reduced, even though the proportion has increased since PCV-10. Further investigations are required to confirm this hypothesis.

While introduction of PCV-10 has been effective in Bangladesh, it does not cover serotype-2, that remains one of the largest contributors of mortality amongst IPD cases in Bangladesh. It's severe (6.1225%), deadly (24.4898%) and one of the leading causes of meningitis amongst IPD cases (91.84%). Addition of serotype-2 to future vaccine formulations would be extremely beneficial to Bangladesh and will likely further significantly reduce the mortality associated with this disease.

This study has also some limitations. Though CHRF works with four hospitals, in the surveillance network we have used data from only one hospital. For another region (district, country etc.) with different demographic characteristics making decisions relying on this study can be misleading. Furthermore, in our analysis, we excluded cases with serotypes ND, NTD, NoPCV13, QNS, NON TYPABLE. In spite of those limitations, the strength of this study is that the data has been scrutinized through statistical analysis and visualizing each feature. The insights obtained from this analysis are important for policy makers making decisions regarding current and future vaccine policies in the country.

Reference:

1. McCollum ED, Ahmed S, Roy AD, et al. Effectiveness of the 10-valent pneumococcal conjugate vaccine against radiographic pneumonia among children in rural Bangladesh: A case-control study. Vaccine **2020**; 38:6508–6516.

2. Saha SK, Hossain B, Islam M, et al. Epidemiology of Invasive Pneumococcal Disease in Bangladeshi Children Before Introduction of Pneumococcal Conjugate Vaccine. Pediatr Infect Dis J **2016**; 35:655–661.