University of Latvia

Faculty of Medicine

INVASIVE PNEUMOCOCCAL DISEASE IN LATVIAN UNIVERSITY HOSPITAL

Diploma Thesis

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Abstract:

Background:

Streptococcus pneumonia belongs to the group of gram positive *cocci*, and it is an α-hemolytic organism. This bacteria is the most common cause of community-acquired pneumonia, but it can also manifest as invasive disease like sepsis and meningitis. Main described risk factors for invasive disease are immunosuppression, chronic disease, age, heavy alcohol or drug use, and splenectomy. Serotype specific vaccines are available for prevention of the disease and recommended for high risk patients.

Purpose:

The aim of the study was to characterize invasive pneumococcal disease in patients hospitalized in Pauls Stradins Clinical University Hospital.

Methodology:

The Hospital Microbiology Database and Medical Records were used to extract the necessary information. Serotyping was performed in National Reference Laboratory, Riga Eastern University Hospital.

Results:

Data on 33 patients hospitalized from January 2016 until April 2018 were included in the study. 60% of patients were females. The mean age of the women was 60 years and 65.5 years for the men. 24 patients suffered from sepsis, five from meningitis, and four suffering from sepsis and meningitis concurrently. A total of 63.6% (n=21) of the patients were discharged home and 36.4% (n=12) died. Serotyping data were available for 25 patients. Eight patients were infected with serotypes covered by both 10- and 13-valent vaccine, and four patients were infected with serotypes covered only by the 13-valent vaccine. 13 (52%) patients were infected with serotypes that are not covered by the vaccines. The most common serotype covered by the vaccines was 19A; 3 cases. The most common serotype not covered by the vaccines were 9N (2 cases) and

11A (2 cases). Detected prevalence of resistance in isolates was 6% to Penicillin, 27% to Trimetroprim/Sulfamethaxasole, 6% to Clindamycin, 6% to Erythromycin, 6% to Tetracycline and 9% to Oxacilin.

Conclusions:

Only 48% of the patients with serotyping available had pneumococcal serotypes covered by the available vaccine, which shows that there might be a selection of non-vaccine preventable strains after introduction of childhood vaccine.

Vaccination would prevent only half of the cases.

The antibiotic resistance doesn’t seem to be common in Latvian patients with invasive pneumococcal disease.

More extensive study is needed to understand the trends in the country.

Kopsavilkums

Ievads:

Streptokokus pneimonija ir gram pozitīva alfa hemolītiska baktērija. Šī baktērija ir visbiežākais ierosinātājs sadzīves pneimonijai, bet tā var arī izpausties ar sepsi vai meningītu. Galvenais riska faktors invazīvai slimībai ir imūnsupresija, hroniska slimība, vecums, pārmērīga alkohola lietošana vai narkotiku lietošana un splenektomija. Serotipiskas specifiskas vakcīnas ir pieejamas un rekomendējamas augsta riska pacientiem.

Darba Mērķis:

Pētījuma mērķis bija raksturot invazīvo pneimokoka slimību pacientiem, kuri tika ārstēti Paula Stradiņa Klīniskā Universitātes Slimnīcā.

Materiāli un Metodes:

Tika izmantota Slimnīcas Mikrobioloģiskā Datubāze un Pacientu Klīniskās Vēstures, lai iegūtu nepieciešamo informāciju. Seroloģiskā noteikšana tika veikta Nacionālā Mikrobioloģijas References Laboratorijā, Rīgas Austrumu Klīniskās Universitātes Slimnīcā.

Rezultāti:

Tika apkopti 33 pacientu dati, kas tika ārstēti no 2016. gada janvāra līdz 2018. gada aprīlim. 60% no šiem pacientiem bija vīrieši. Vidējais pacientu vecums sievietēm bija 60 gadi un vīriešiem 65,5 gadi. 24 pacienti slimoja ar sepsi, pieci ar meningītu un četri slimoja ar sepsi un meningītu vienlaicīgi. 63,6% (n=21) pacientu tika izrakstīti no slimnīcas un 36,4% (n=12) nomira slimnīcā. Seroloģiskie dati bija pieejami 25 pacientiem. Astoņi pacienti tika inficēti ar serotipu, ko būtu nosegusi 10 - un 13- valentā vakcīna un četri pacienti tika inficēti ar serotipu, ko būtu nosegusi 13- valentā vakcīna. 13 (52%) pacientu tika inficēti ar serotipu, kas netiktu nosegta ar vakcīnu. Visbiežākais vakcīnu nosegtais serotips bija 19A; trīs gadījumos. Visbiežākais vakcīnu nenosegtais serotips bija 9N (divos gadījumos)un 11A (divos gadījumos). Atklāta antibiotiku rezistence izolātos (don’t know about this either) bija novērojama 6% penicilīnam, 27%

Trimetoprimam/sulfametoksazolam, 6% Klindamicīnam, 6% Eritromicīnam, 6% Tetraciklīnam un 9% oksacilīnam.

Secinājums:

Tikai 48% no visiem pacientiem bija pieejama vakcīna, kas būtu nosegusi pneimokoka serotipu, kas norāda, ka ir bakterijas ar serotipiem, kuram nav pieejams vakcinas.

Vakcinācija būtu efektīva tikai pusei pacientu.

Antibiotiska rezistence nav bieži novērojama Latvijas pacientiem ar invazīvu pneimokoka slimību.

Apjomīgāks pētījums ir nepieciešams, lai saprastu situāciju valstī.

Introduction

S. pneumonia

Streptococcus pneumonia belongs to the group gram positive cocci, and it is an α-hemolytic organism. These lancet-shaped cocci are arranged in pairs, and often go by the name of diplococci. This bacteria is the most common cause of community-acquired pneumonia, and can also cause meningitis, sepsis, sinusitis and otitis media.[1]

The bacteria possess polysaccharide capsules that make up their most important virulence factor, and are of 85 antigenically distinct types. These capsules are interfering with phagocytosis in a way that favors invasion of the organism, and specific antibodies are needed to opsonize it in order to facilitate phagocytosis and resistance. These antibodies develop either as a result of infection or by administration of the vaccine consisting of pneumococcal polysaccharide conjugated to diphtheria toxoid.[2]

Invasive Disease Caused by Streptococcus pneumonia

Streptococcus pneumonia may cause invasive disease in the form of either bacteremia, sepsis or meningitis.

Sepsis

Sepsis can be characterized as a syndrome of abnormalities on a physiological, pathological and biochemical level that is induced by an infection. The newest definition of sepsis as stated by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) goes as follows:

“Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.”[3]

Meningitis

Meningitis is defined as inflammation of the meninges, and can be of different etiologies, like for instance bacteria or viruses. It is a very serious disease with high mortality rate, and should be diagnosed and treated promptly.

Transmission of the Disease

The organism is harbored in a proportion of 5% - 50% of the population, and it resides in the oropharynx. Resistance towards infection is high in healthy individuals, and the disease occurs with predisposing risk factors.[4]

Risk Factors for Disease by Streptococcus pneumonia

Main described risk factors for invasive disease are immunosuppression, chronic disease, respiratory tract abnormalities, age, heavy alcohol or drug use, and splenectomy.[5]

Hypothesis:

The following hypothesis was set:

- Serotypes of S. pneumonia that aren't covered by the available vaccines are becoming more prevalent in Latvian patients suffering from invasive disease caused by Streptococcus pneumonia.

Literature Review:

Streptococcus pneumonia as Invasive Disease

In population studies it is shown that there is an age-dependent pattern seen present in the incidences of invasive pneumococcal disease, whereas the highest rate is in infants. The pattern then decreases until the age of 5, and later increases again in the population aged over 60, before it peaks again in seniors above the age of 65[6].

As S. pneumonia is residing in the oropharynx and colonizing there, both local and systemic factors are needed to promote its progression from colonization to disease. The pathway from colonization to disease can be described as follows:

Pneumococcal neuraminidases can facilitate exposure of receptors on epithelial cells, further causing them to bind to pneumococcal surface-associated proteins. In case of local inflammation caused for instance by a viral etiology, systemic cytokines such as TNF-α and IL-1 will be activated, facilitating further binding of pneumococci and eliciting their uptake and migration across the epithelium and endothelium. The host IgA that aids in protection against pneumococci by binding to its capsule can be cleaved by bacterial IgA1 protease. Complement factors, antibodies to the bacteria and the activity of phagocytes are also crucial in preventing S. pneumonia to go from the stage of colonization to disease. Failure to produce antibodies in immunocompromised patients predisposes to disease progression. Antibodies will bind to Fab regions of the bacterial surface components, engaging Fc receptors on phagocytotic cells (neutrophils and macrophages), providing them a bridge to the organism to be phagocytized. Complement activation via any of the three pathways; classical, lectin or alternative, can occur both by antibody-dependent and antibody-independent mechanisms, and is effective in uptaking and killing the bacteria. In advanced HIV disease there might be decreased amounts of B cells, leading to a poorer IgM response to the vaccine, predisposing to disease. As for people who have undergone splenectomy, the increased risk of pneumococcal septicemia is thought to be due to the spleen being the major organ that clears unopsonized pneumocci from the body. The route of infection for S. pneumonia to result in bacteremia is not always so easy to determine. If

bacteremia occurs without any clear source or focus of infection, it is named as primary bacteremia.[7]

In a population-based study of pneumococcal bacteremia, 71% of patients had recognizable pneumonia by plain chest radiograph without computerized tomography. Meningitis was present in 8% and otitis media or sinusitis in 4%; bacteremia was regarded as primary in 18%. Primary bacteremia is more common in children than adults.[8]

Connection Between Serotypes and Colonization, Disease and Mortality

The different serotypes of S. pneumonia that can cause disease may vary by age, geography and outcome of the infection, and may give information about whether colonization, disease and higher mortality is more likely.[9] Studies analyzing this came up with the following results:

- Strains with serotypes 6A, 6B, 9N, 19F, and 23F are more likely to remain as colonizers.
- Strains with serotypes 14, 5, 1, 7F, 18C, 8, 38, and 33F are more likely to cause invasive disease.
- Strains with serotypes likely to remain as colonizers (6A, 6B, 9N, 19F, and 23F) have however a higher mortality than the strains that are usually causing disease. [10] [11] [12] [13] [14] [15]

What Is the Mortality Rate of Patients With S. pneumonia In Their Blood

For young adults, the mortality rate of pneumococcemia is from 10% - 20%.

- Much higher in elderly and immunocompromised patients[16].

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) states that there are increased incidences of sepsis, most likely due to the aging populations suffering from more comorbidities. It is the number one cause of death from infection, especially if it isn't recognized early, and treated from an early stage. The syndrome with characteristics of both pathological and physiological abnormalities is different from an infection by a dysregulated host response and the presence of organ dysfunction.

To determine the severity of organ failure, different scoring systems are being used to quantify the organ abnormalities. The most common scoring system being used today is the Sequential Organ Failure Assessment, abbreviated SOFA. It is a scoring system that takes into account measurements of different organ systems. The higher the SOFA-score, the higher the probability of mortality is present. The parameters used are as follows:

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

If the SOFA-score is ≥2 points it can be viewed as an acute change of organ dysfunction. It also reflects an increase in mortality rate by 10% in patients with a suspected infection.

In addition to the SOFA scoring system, the term Quick-SOFA (qSOFA) is being used, with the purpose of having rapid and simple criteria to identify patients with suspected infection. These criteria are as follows:

- Respiratory rate ≥22/min
- Altered mentation (Glasgow Coma Scale score less than 13)
- Systolic blood pressure ≤100 mmHg

Having two or more of these criteria fulfilled from the Quick-SOFA offers predictive validity similar to that of a full SOFA score outside of the ICU[17].

Meningitis Caused by Streptococcus pneumonia

In the United States, Streptococcus pneumonia is the leading cause of bacterial meningitis, with an incidence of 0.3 per 100 000 people (data from 2010)[18].

Prevention of Invasive Disease Caused by Streptococcus pneumonia

Invasive pneumococcal disease is carrying a high morbidity and mortality, and prevention of the disease is of high importance. The first vaccine available was a 23-valent polysaccharide vaccine, but now there are available so-called conjugate vaccines against S. pneumonia. Hausdorff et al. reported in a study on Streptococcus pneumonia serotypes causing the most invasive diseases, that seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) were responsible for about 80% of invasive pneumococcal disease in children less than 6 years of age in the USA[19]. These made part of the foundation of the first conjugate vaccine against Streptococcus pneumonia launched in the year 2000, and it was a 7-valent vaccine. Today the newest conjugate vaccine is 13-valent.

Studies performed after the launch in 2000 to evaluate the efficacy showed that there was a decrease of 69% of invasive pneumococcal disease in children 2 years old or less within 21 months of the launch. The rate of disease also declined in the adults in 2001, showing a decrease

of 32% in adults 20 to 39 years of age, 8% decrease in those 40 to 64 years of age, and 18% decrease in patients aged 65 years or more[20].

Effect of the 7-valent conjugate vaccine on invasive pneumococcal disease

A study that analyzed incidents of invasive disease caused by S. pneumonia serotypes covered by the first conjugate vaccine (7-valent conjugate) showed a decrease during a 7 year period after introduction of the vaccine, while incidence of disease caused serotypes not covered by the vaccine increased at the same time. The study concluded however that the overall rate of invasive pneumococcal disease was reduced by 50-60% compared to the period before introduction of the vaccine[21].

Effect of the 13-Valent Vaccine

A study from Sweden that was published in 2014 to analyze the clinical manifestations of invasive pneumococcal disease by vaccine and non-vaccine serotypes showed that 23% (484 out of 2096) of the patients were infected with serotypes that aren't covered by the 13-valent vaccine. All of the included patients were did not have any of the pneumococcal vaccines from before.

The study concluded that the 13-valent conjugate vaccine does indeed give protection against invasive pneumococcal disease, but that the vaccine will most promote more non-vaccine strains eventually[22].

Methods and Materials:

The Hospital Microbiology Database and Medical Records were used to extract the necessary information.

Serotyping was performed in National reference laboratory, Riga Eastern University Hospital.

Statistical analysis of data was done by using SPSS, Microsoft Excel and Microsoft Word.

Analysis and Results:

In total there were 33 patients suffering from invasive pneumococcal disease, and that were part of our study. The patient data was collected from January 2016 until sixth of April 2018. Below is a barchart showing the frequency distribution across the years of our study illustrated in amount of cases and percentage.

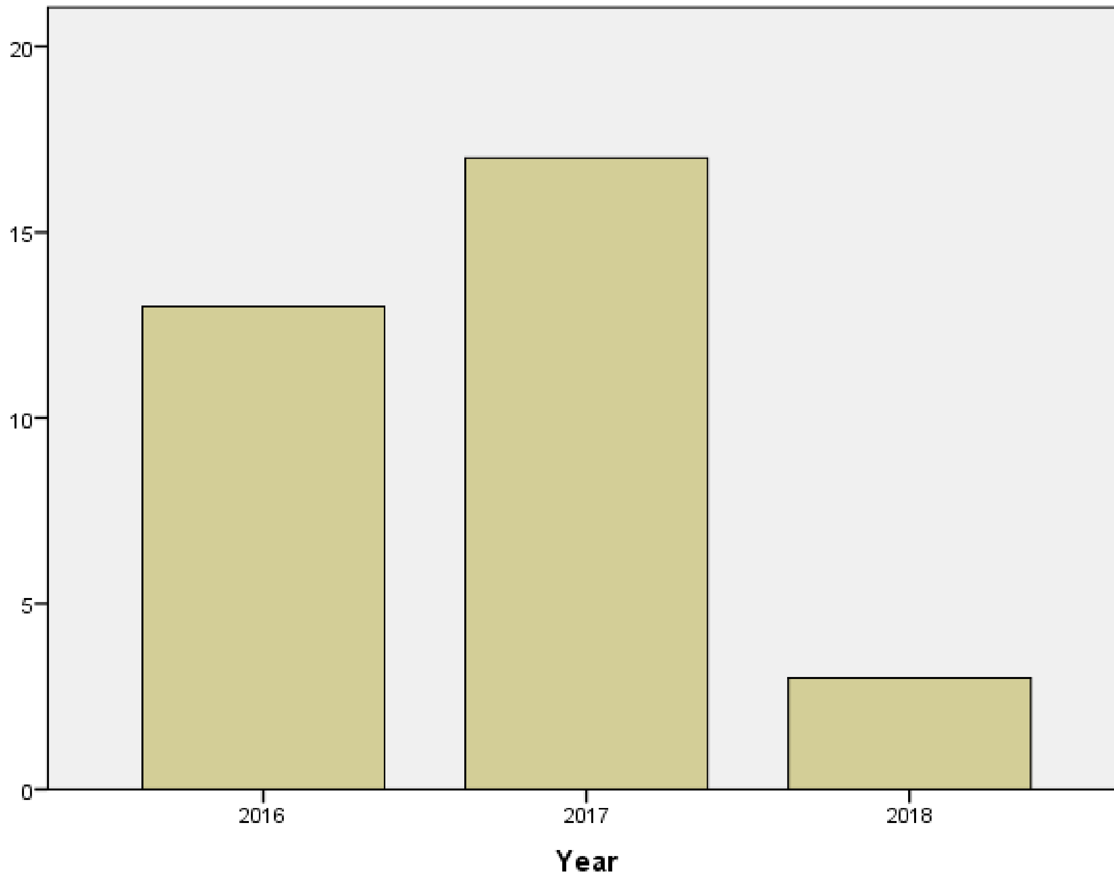


Figure 1: Number of Cases of Invasive Pneumococcal Disease

In our study 24 patients suffered from sepsis, five from meningitis, and four suffering from both at the same time. Below is a barchart illustrating the amount of cases and their distribution.

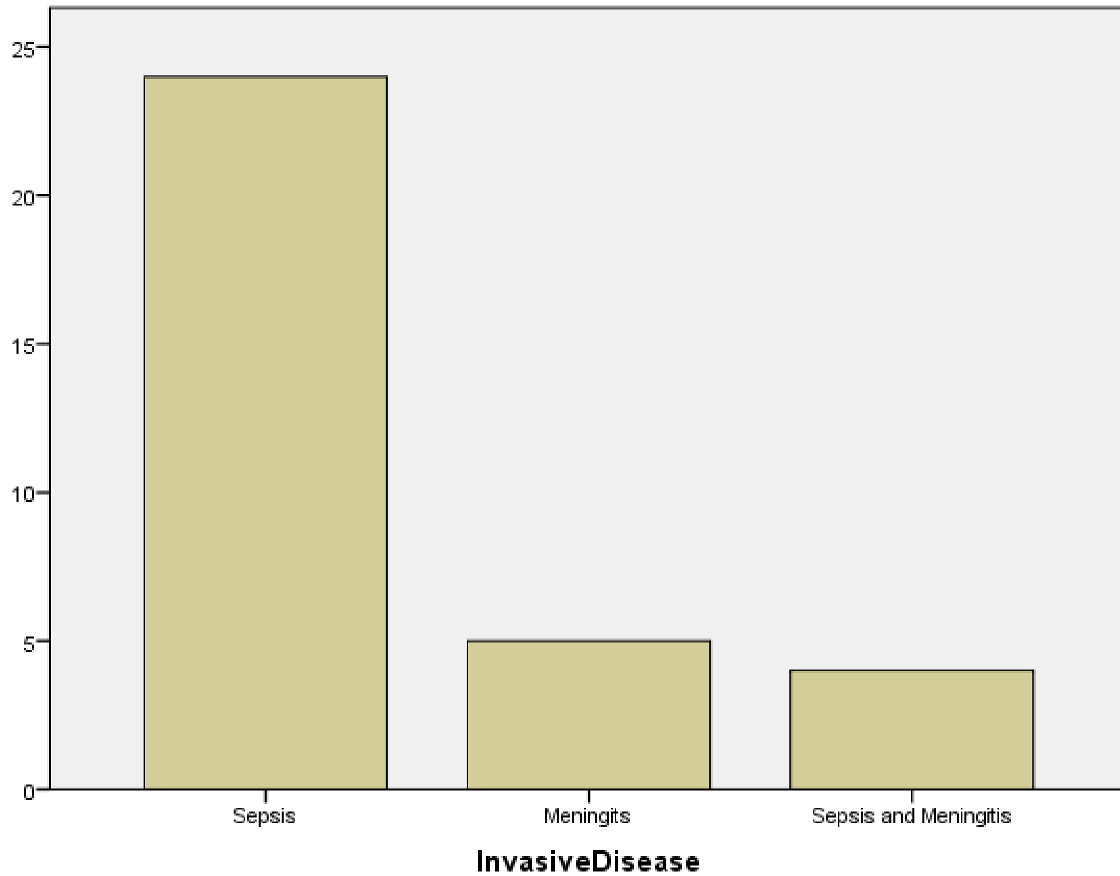


Figure 2: Frequency Distribution of Defined Invasive Pneumococcal Disease

Data on 33 patients hospitalized from January 2016 until April 2018 were included in the study. 60% of the patients were females, and 40% were men.
The mean age of the women was 60 years and 65.5 years for the men.

We analyzed the association between gender and final outcome of invasive pneumococcal disease, and the result was a P-value = 0.346, calculated by using the Pearson Chi-Square test, showing no statistical significance in the final outcome between males and females in our study.

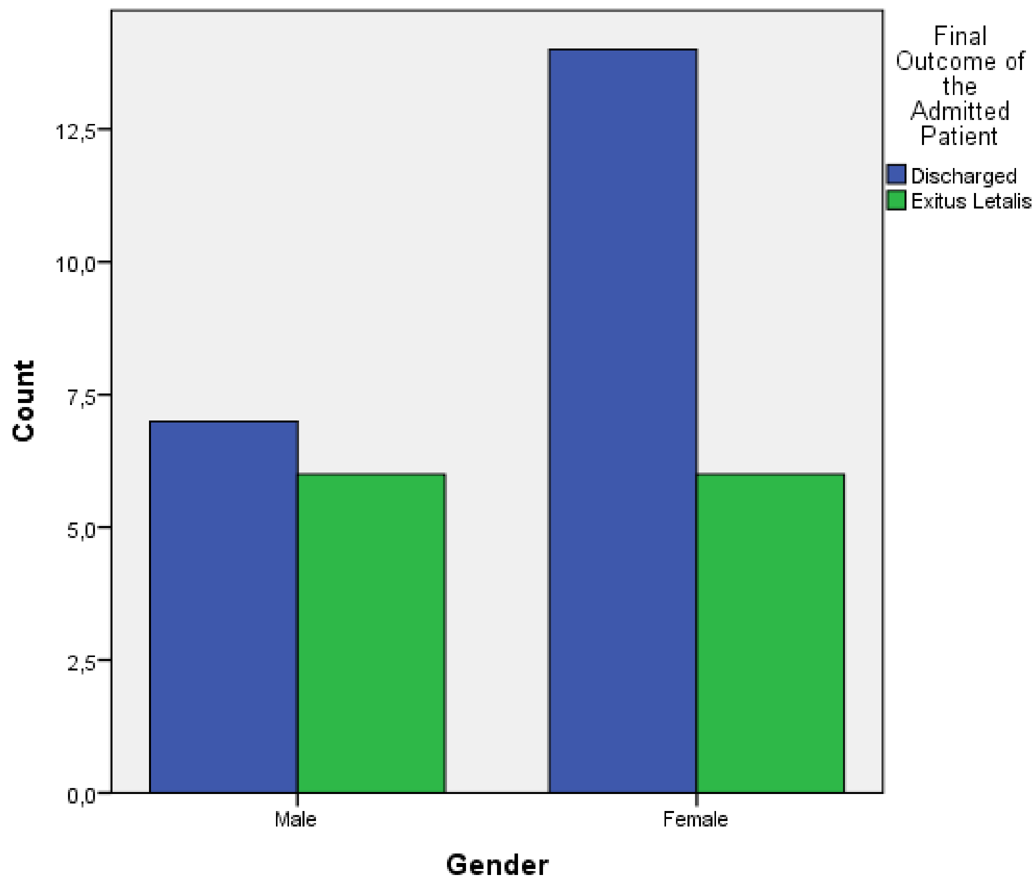


Figure 3: Relationship Between Gender and Final Outcome of Patients

A total of 63.6% (n=21) of the patients were discharged home and 36.4% (n=12) died. The Pearson Chi-Square test gave us a P-value = 0.230 and no statistical significance in deaths occurring in the different years of our study. This barchart is illustrating these results.

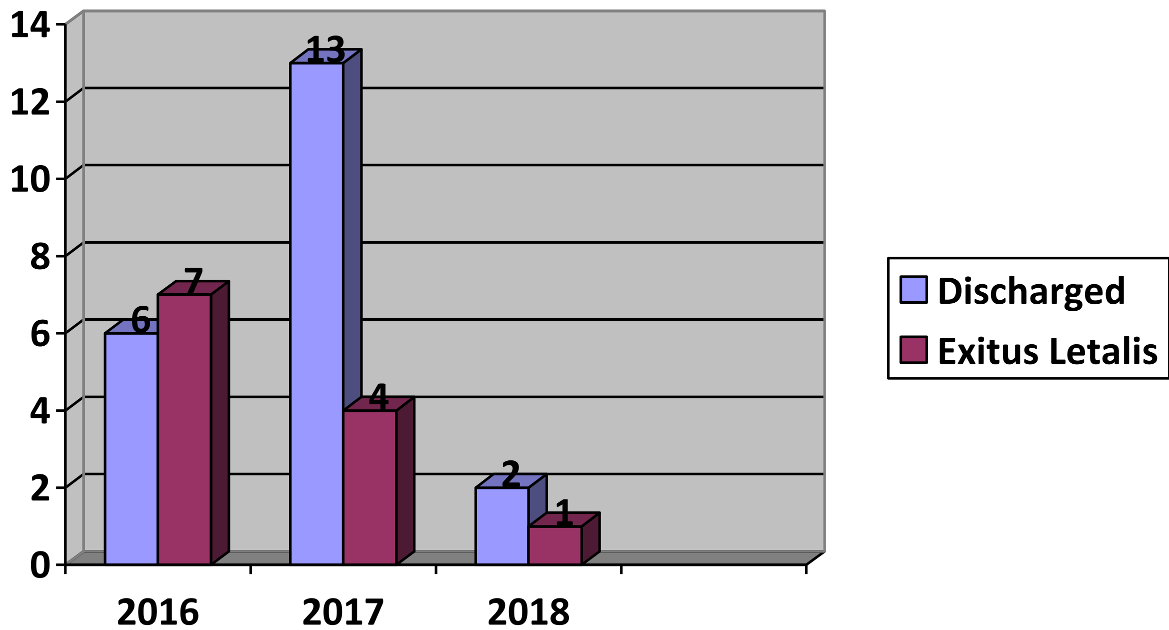


Figure 4: Distribution of Discharged and Dead Patients

66.7% (n=16) of all the patients that had sepsis as their defined invasive pneumococcal disease survived, while 33.3% (n=8) died. 80% (n=4) of all the patients that had meningitis as their defined invasive pneumococcal disease survived, while 20% (n=1) died. Of all the patients that had sepsis and meningitis as their defined invasive pneumococcal disease, 25% (n=1) survived, while 75% (n=3) died. The Pearson Chi-Square test calculated a P-value = 0.197 for this association, showing no statistical significance.

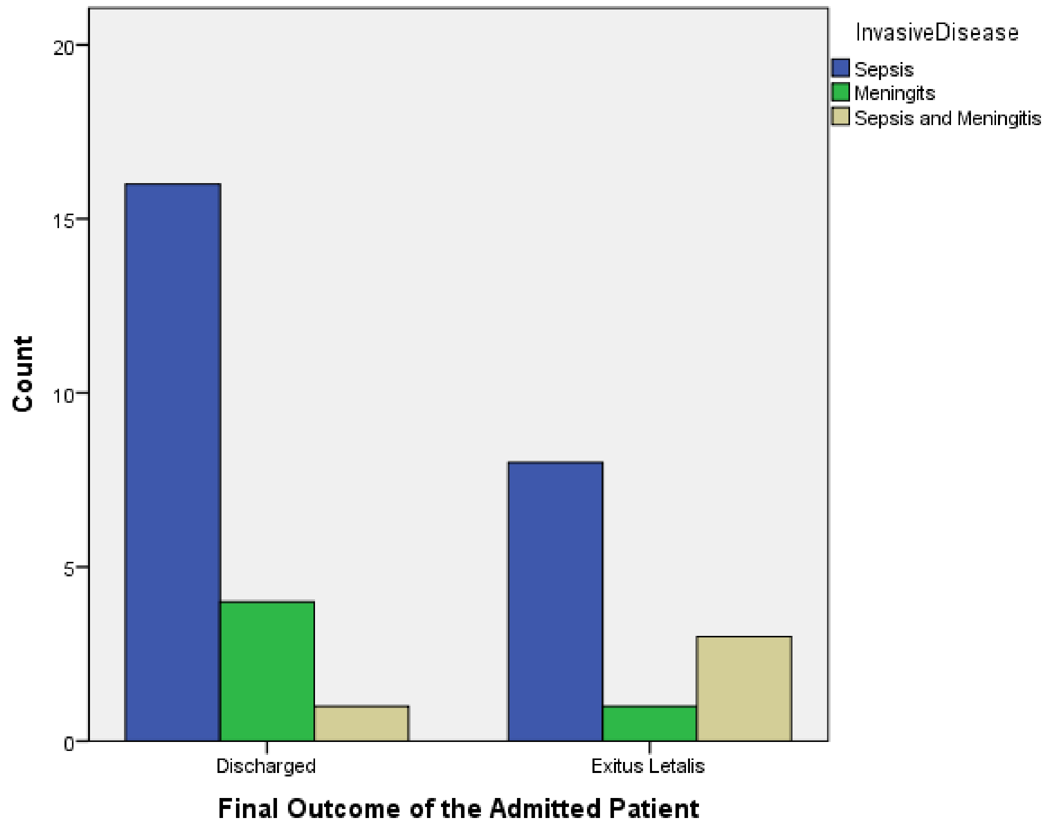


Figure 4: Relationship Between Defined Invasive Pneumococcal Disease and Final Outcome of Patients

Despite that there is no statistical significance between the defined invasive pneumococcal disease and their final outcome, one can discuss whether there would be in case of a bigger amount of patients being included in the study. As 75% of the patients with sepsis and meningitis died, it can be said with a degree of certainty that they have a higher chance of mortality compared to those suffering only from either sepsis or meningitis.

Below are the results of which departments the patients were admitted to. As the first graph is illustrating, the pulmonology ICU department had the highest amount of admittances, covering almost 30% of all the patients.

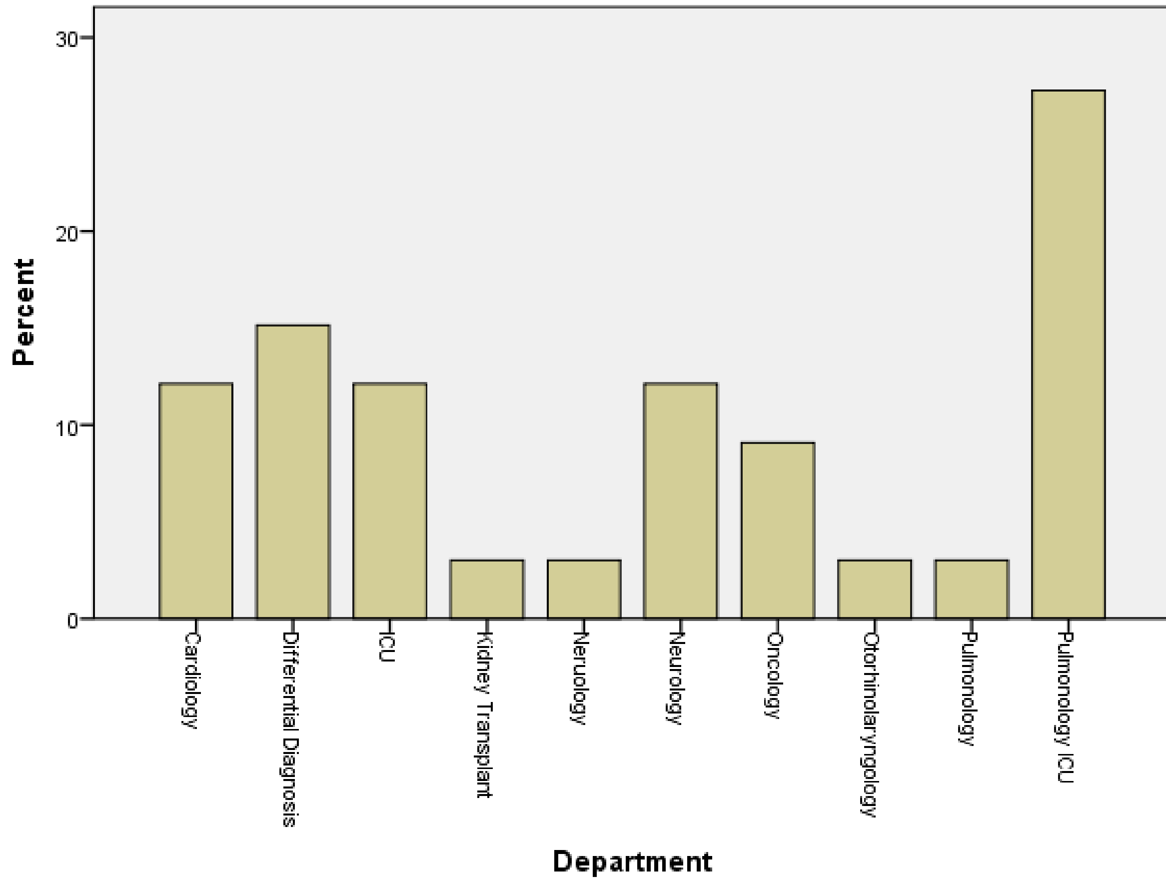


Figure 6: Overview of Department Admittance

The length of stay is shown in the bar chart below, where the average stay was 15.88 days. The shortest stay was 1 day (patient died), and the longest stay 62 days.

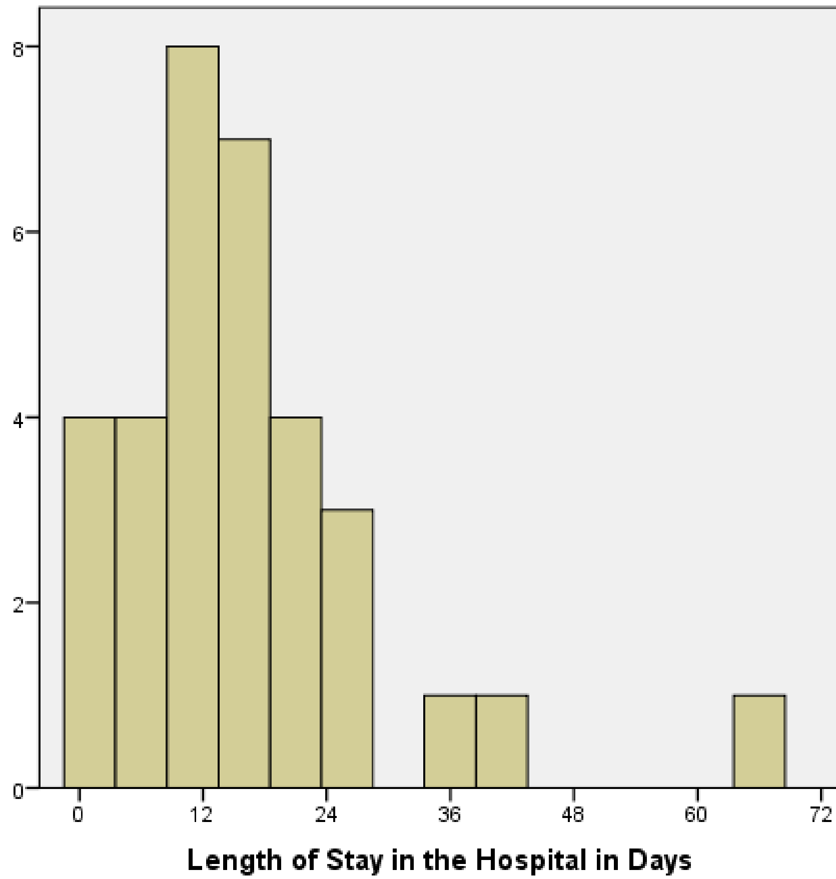


Figure 7: Mean Distribution of Hospital Stay in Days

The correlation between the final outcome of the patients and in which departments they were admitted to, is illustrated in the barchart below. The Pearson Chi-Square test calculated P-value = 0.104 and no statistical significance in between the different departments. The pulmonology department, having the most admitted patients, shows an almost equal distribution of final outcome, where 56% were discharged home and 44% died.

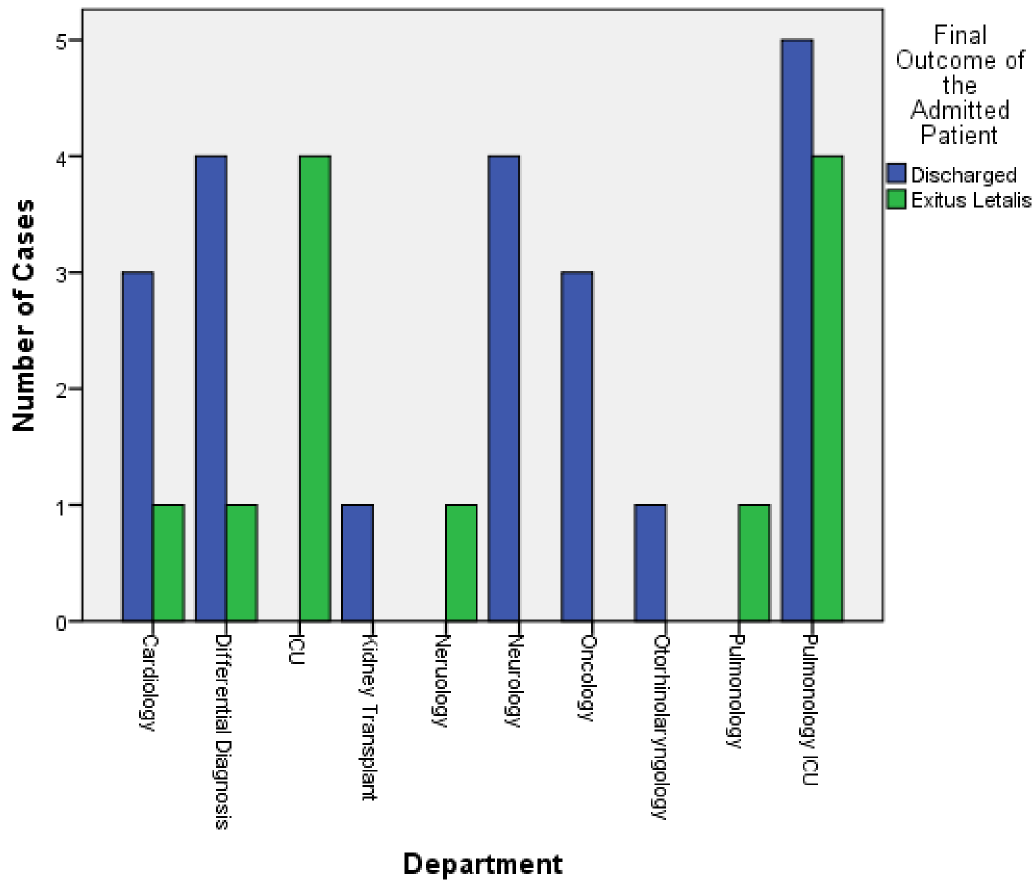


Figure 8: Relationship Between Departments and Final Outcome of Patients

We analyzed how many of the participants had risk factors present upon admission and the final outcome of the patients. In the analysis we didn't compare every single risk factor towards the final outcome. We marked the patients having one or more risk factor for invasive pneumococcal disease, and those who didn't have any risk factors present at all.

A total of 21 patients had one or more risk factors for invasive pneumococcal disease, and 12 did not.

The table is telling us that the risk factors are causing more cases of invasive pneumococcal disease, but not increased mortality rate. The Pearson Chi-Square test calculated a P-value = 0.825 for this association, showing no statistical significance.

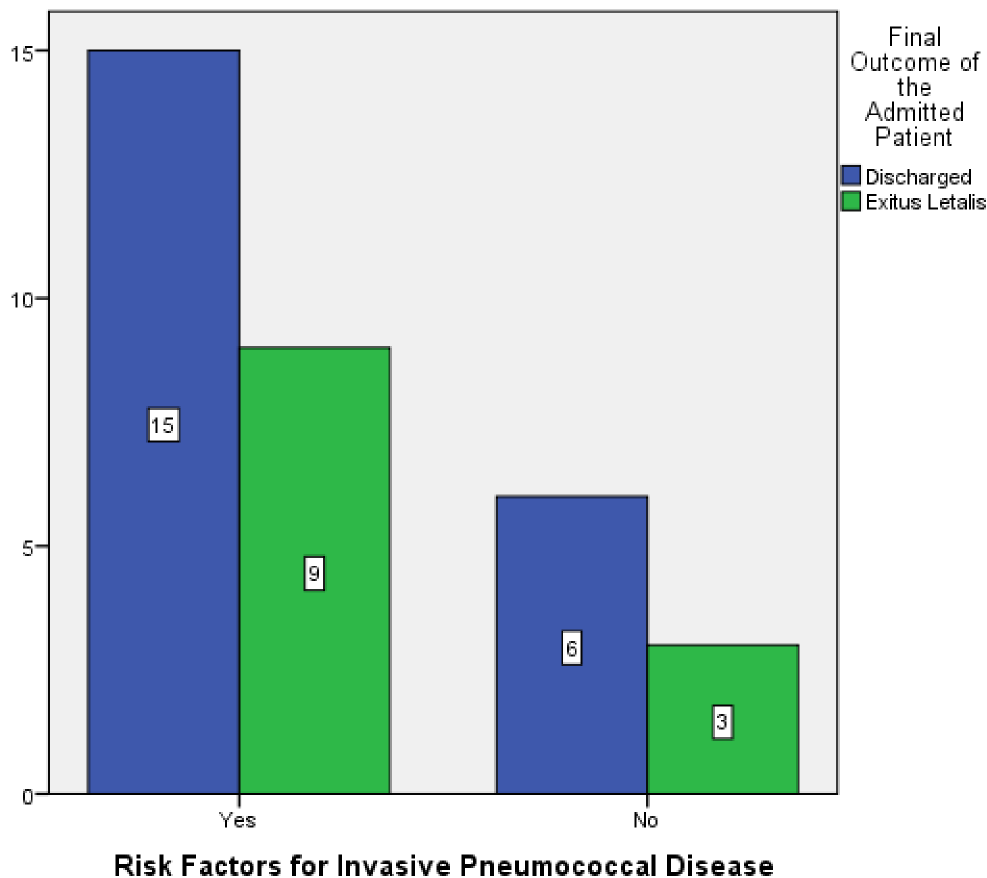


Figure 9: Relationship Between Risk Factors and Final Outcome of Patients

Serotypes:

Serotyping was available for 25 out of 33 patients in the study analysis.

The most common serotypes encountered in the isolates were:

11A: 2 patients that were both discharged.

19A: 3 patients, whereas 2 were discharged home and 1 died.

23B: 2 patients that were both discharged.

4: 2 patients that were both discharged.

9N: 2 patients that were both discharged.

6C: 2 patients, whereas 1 was discharged and 1 died.

Below is a barchart illustrating these findings, and showing also all the different serotypes that were found in the isolates of our patient group.

We analyzed the association between the different serotypes and the final outcome, and a P-value = 0.341 was calculated by using the Pearson Chi-Square test, showing no statistical significance.

Here there are probabilities that our low amount of patients included is giving us a P-value that isn't really representative, and that the association would be different if we would have had more patients included.

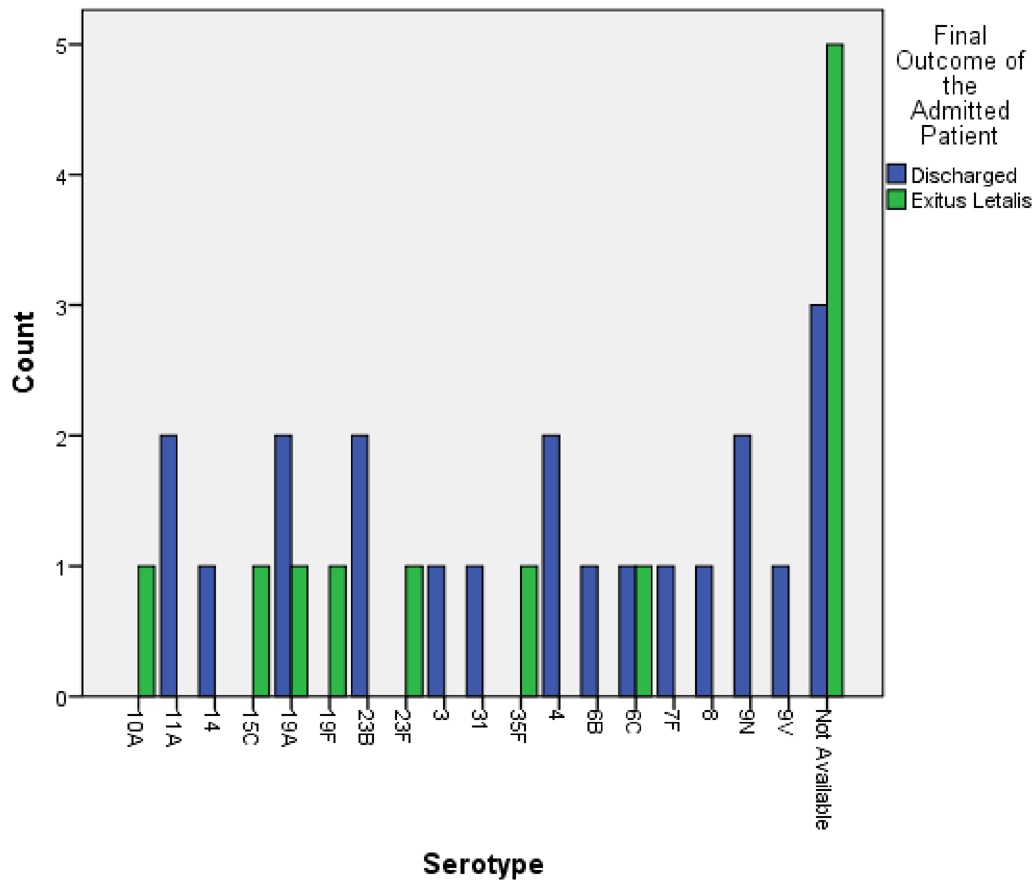


Figure 10: Relationship Between Serotypes and Final Outcome of Patients

We analyzed the serotypes from the patients to see whether they are covered by the available vaccines or not. Below are two barcharts showing the distribution of serotypes covered by the 10-valent vaccine and 13-valent vaccine, respectively.

A total of 8 patients had serotypes covered by the 10-valent vaccine.

A total of 12 patients had serotypes covered by the 13-valent vaccine.

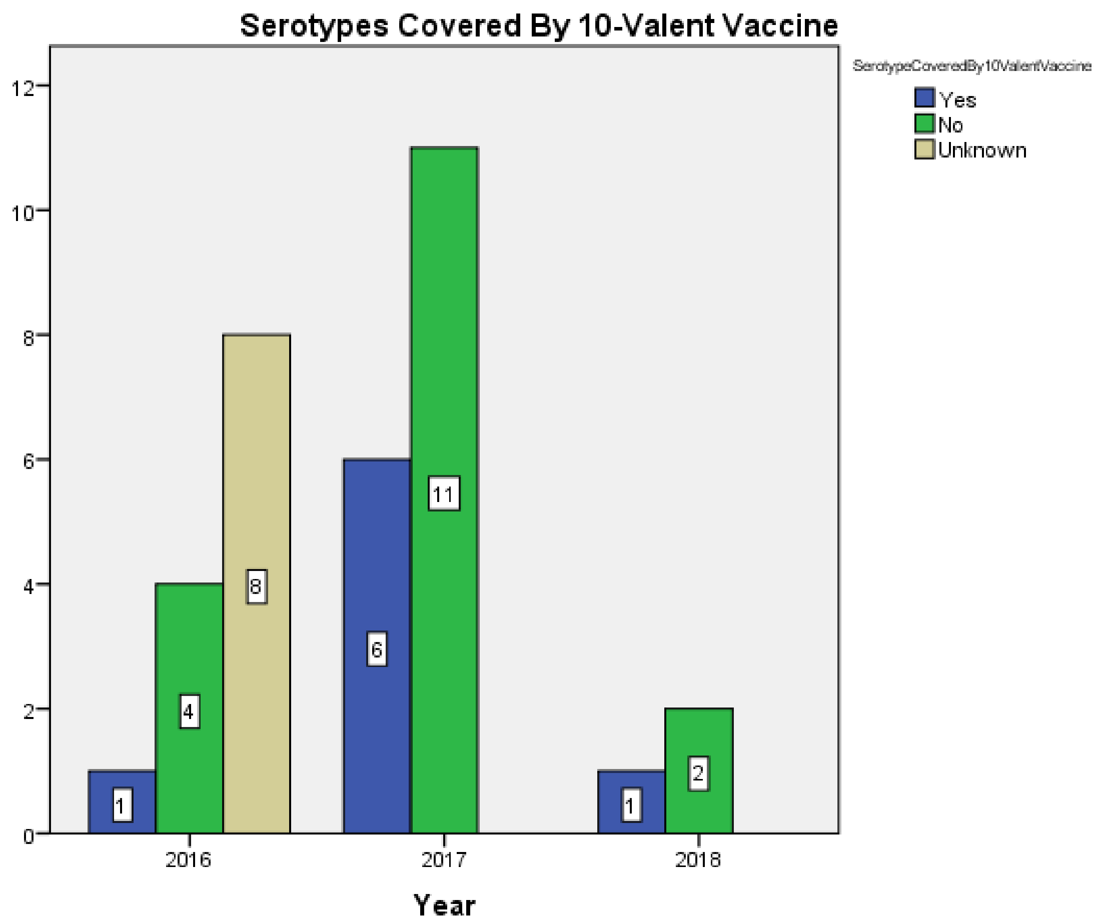


Figure 11: Distribution of the Number of Patients With Serotypes Covered by 10-Valent Vaccine Over the Studied Period of Time

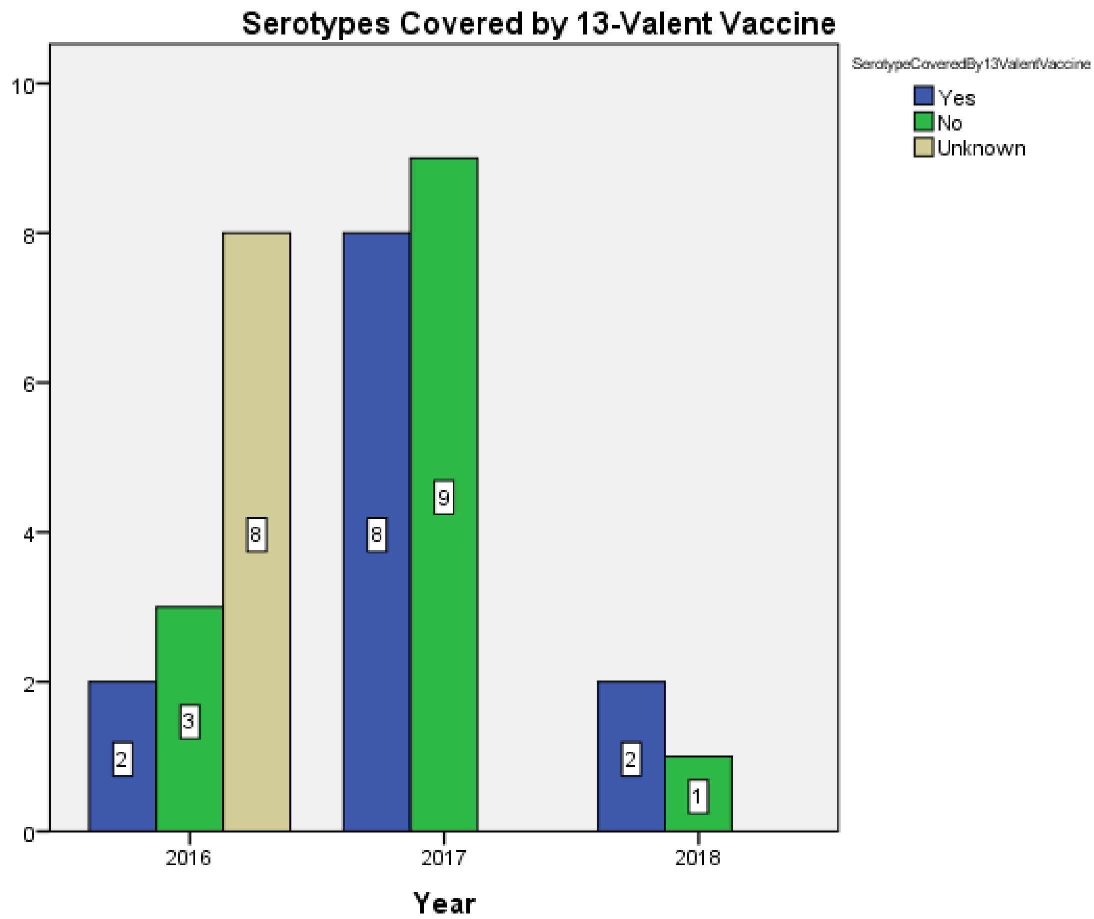


Figure 12: Distribution of the Number of Patients With Serotypes Covered by 13-Valent Vaccine Over the Studied Period of Time

Serotypes Covered By 10-Valent Vaccine Compared to Serotypes Covered By 13-Valent Vaccine

			Number of Patients With Serotypes Covered By 13-Valent Vaccine	
			Yes	No
Number of Patients With Serotypes Covered By 10-Valent Vaccine	Yes	Count	8	0
	No	Count	4	13
Total		Count	12	13

Table 1: Cross-Table Comparison Between the Number of Patients With Serotypes Covered by 10- and 13-Valent Vaccine

From these results we can see that all the 8 patients that had serotypes covered by the 10-valent vaccine, also had full coverage of the 13-valent vaccine. In addition, 4 patients had serotypes covered only by the 13-valent vaccine, as the table nr. 1 above indicates. As a total of 12 patients having serotypes covered by the vaccines, the 10-valent vaccine would protect 32% of the patients, and the 13-valent vaccine would protect 48%. From this we can say that there is a better coverage of the 13-valent vaccine compared to the 10-valent vaccine.

A total of 13 patients had serotypes not covered by any of the available vaccines.

In total, 48% of the patients are covered by the available vaccines, and 52% are not covered by the available vaccines. When we analyzed the association between these two groups using the Pearson Chi-Square test the P-value was = 0.0001, and thereby showing statistical significance between the patients with serotypes covered by vaccines and those not.

We analyzed the serotypes that have a higher chance of causing invasive disease and a higher mortality rate from literature review, and compared them to our results from our isolates.

Serotypes With Higher Probability of Causing Invasive Disease:

Out of the 25 patients with available serotypes, 3 patients had serotypes connected with a higher chance of causing invasive disease. Out of these three, all the patients were discharged home.

P-value for this association was calculated to be 0.250 and statistically insignificant.

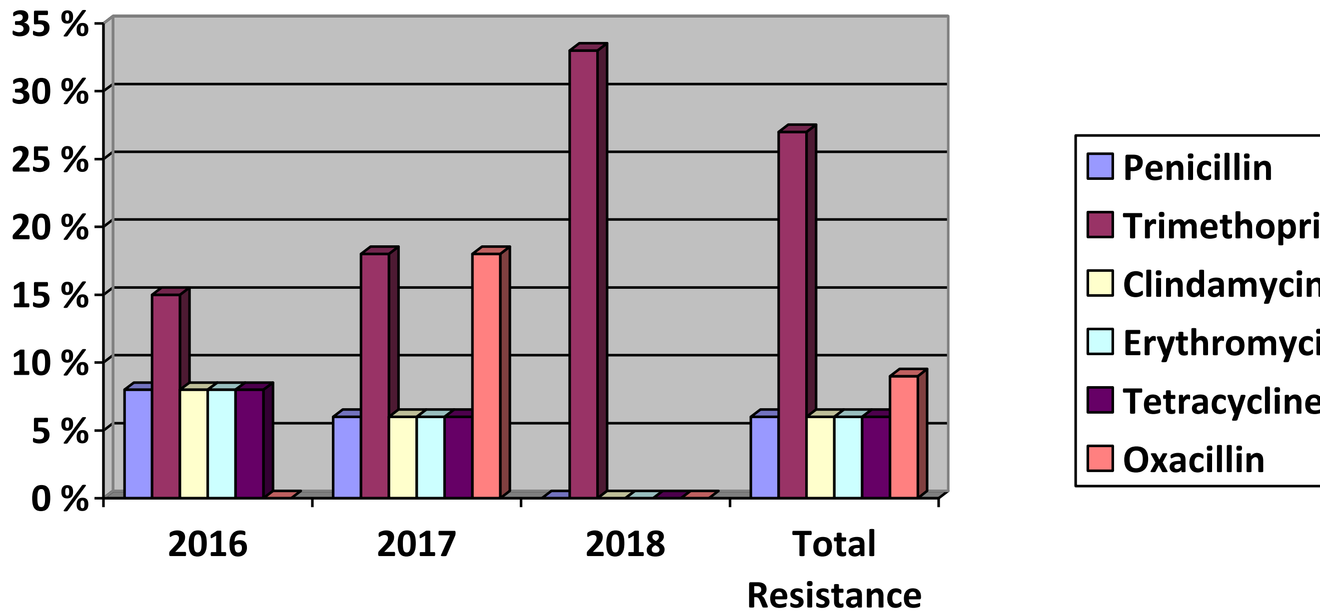
Serotypes With a Higher Mortality Rate:

Out of the 25 patients with available serotypes, 5 patients had serotypes that are connected with higher mortality rate if they cause invasive disease, even though they are more likely to remain as colonizers. 60% (n=3) of these patients were discharged home, while 40% (n=2) died.

P-value for this association was calculated to be 0.504 and statistically insignificant.

Antibiotic Resistance:

We analyzed the antibiotic resistance of the patients in our study. All 33 patients were treated with antibiotics, and all of them had testing of antibiotic resistance available. Below there are listed charts illustrating the antibiotic resistance in our study.



Discussion:

This study is the first one of its kind that has been conducted in this University Hospital. The baseline of the study was to get a better insight of the disease, its behavior, its characteristics and its management. Analysis of the serotypes was set as the main focus of our study, as thorough and deeper understanding of S. pneumonia's serotypes will help us to better manage the disease in a preventive way, as well as to manage it once it is already established.

Our study included 33 patients over a studied period of two years and three months, indicating that the disease is not very common, yet it is very serious. With an overall mortality rate of 36.7%, an average hospital stay of 16 days for each patient, and with 39% of the patients being admitted to the main ICU and Pulmonology ICU, the disease clearly manifests itself as a serious matter. The pattern of incidents of the disease seems to be stable over the studied time period, but needs however to be continued for further years in order to see whether there is a trend towards a steady increase in the number of invasive pneumococcal disease or not. Despite not being the most common disease, it proves itself to be quite a big load on the healthcare system, considering the effort and cost of treating patients in the ICU.

18 different serotypes were found among the 25 patients that had serotyping available for their isolates, and from these 8 patients are covered by the 10-valent vaccine and 12 patients are covered by the available 13-valent vaccine. In total, 48% of the patients would be protected from disease if they would have the 13-valent vaccine, but 52% would still get infected regardless of having the vaccine or not. This association was statistically significant, and important for us in regards to evaluate optimization of disease prevention and control. As more than half of the serotypes in the isolates aren't covered by any of the available vaccines, the question is how this has occurred, and how to manage it further. One can assume that there seems to be a trend going towards a selection of non-vaccine serotypes. In Latvia, the pneumococcal vaccine was introduced into the children's vaccination program in 2010, and there are reasons to believe that the trend has started some time after this. As our study didn't include data from children, it's hard to say whether the results are unique towards the adult population, or if they are similar in the pediatric population. There is also uncertainty whether this could be an incidental finding to this

specific University Hospital, as our data doesn't contain any information about the other hospitals in the country. For a better and more precise statement about whether there is an actual general trend towards a selection of non-vaccine serotypes in the country, more studies are needed from all the major hospitals.

We had great interest in seeing whether there are certain serotypes that can be linked to a higher mortality rate, and whether these correspond to the serotypes from other studies. As our study didn't include that many patients, it is hard to see any clear connection between the serotypes and mortality. However, compared to data from the literature review there is a connection between our serotypes that has higher mortality rate when causing invasive disease, but without statistical significance (P-value = 504). This finding is likely due to the low number of patients available in our study. If the study will be prolonged we should be able to see whether this association is truly significant or not. In addition, a prolongation would help to better map which serotypes should be monitored more closely, and could further help research in this field to decide which ones to take into consideration as potential candidates for future planned vaccines.

The antibiotic resistance was checked for all patients, and shows very little resistance against penicillin, which is the first line choice against invasive pneumococcal disease. This is providing us with evidence that the recommended therapy of the disease remains safe and effective. In our study we didn't check whether there were any connection between serotypes and resistance towards antibiotics, but it could be useful for further studies in this field to better understand how the different serotypes are behaving.

As this is the only study on this topic in this University Hospital so far, we are not yet able to set up general conclusions about the characteristics of invasive pneumococcal disease. We know that it comes with a high mortality rate and a demanding way of treatment. The study is currently pointing us in the direction that it needs to be furthered in order to evaluate more precisely whether there is an actual trend going on in regards to the incidents of the disease, the behavior of the serotypes and the level of antibiotic resistance, or if these are all coincidental findings of our studied period of time. A comparison with other university hospitals as well as smaller local hospitals would provide us with a great deal of information to see whether the findings are limited to certain hospitals only, or if they are present on a national scale. As far as management

goes, it seems that prevention of the disease is still a good option, and efforts should be kept on recommending the vaccine, especially to the people with risk factors for the disease. Even though less than half of the patients would benefit from the vaccine, these people would still be protected. The remaining ones seem to be dependent on how the future vaccines will be designed.

As the antibiotic resistance levels are low, the current treatment options remains safe, but are very demanding on the healthcare resources, as many of the patients require treatment in the ICU. Antibiotics resistance should be monitored further for any potential changes in order to avoid future problems with optimization of administered medication.

Conclusion:

Invasive pneumococcal disease remains as a deadly disease, with a mortality rate of 36.4%, and it requires prompt diagnosis and treatment. Present risk factors and the number of cases with the disease are seen to correspond, but present risk factors are not shown to increase mortality rate.

From our study we're able to conclude that the vaccines would have covered only 48% of the cases by looking solely on the serotypes. There are reasons to believe that this is due to the development of non-vaccine serotypes after the introduction of the pneumococcal vaccine in the children's vaccination program in 2010.

More extended studies from other hospitals and also from the pediatric population is needed to say whether there is a trend growing towards a selection of non-vaccine serotypes.

The antibiotic resistance levels are low, and penicillin remains as a safe option for treatment of patients suffering from invasive pneumococcal disease.

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Bibliography and References:

[1] Warren Levinsion, Review of Medical Microbiology 12th Edition, Publisher: McGraw-Hill Medical, 2012, ISBN: 10: 0071774343 ISBN 13: 9780071774345, Chapter 15, Pages 116 – 126

[2] Warren Levinsion, Review of Medical Microbiology 12th Edition, Publisher: McGraw-Hill Medical, 2012, ISBN: 10: 0071774343 ISBN 13: 9780071774345, Chapter 15, Pages 116 – 126

[3] Mervyn Singer,MD, FRCP; Clifford S. Deutschman, MD, MS; ChristopherWarren Seymour,MD, MSc; Manu Shankar-Hari, MSc,MD, FFICM;
Djillali Annane,MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche,MD, PhD;
Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc;
StevenM. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tomvan der Poll, MD, PhD; Jean-Louis Vincent,MD, PhD; Derek C. Angus, MD, MPH, JAMA. 2016; 315(8), 02/22/2016, Pages 762-774: The Third International Consensus Definitions
for Sepsis and Septic Shock (Sepsis-3)

[4] Warren Levinsion, Review of Medical Microbiology 12th Edition, Publisher: McGraw-Hill Medical, 2012, ISBN: 10: 0071774343 ISBN 13: 9780071774345, Chapter 15, Pages 116 – 126

[5] Warren Levinsion, Review of Medical Microbiology 12th Edition, Publisher: McGraw-Hill Medical, 2012, ISBN: 10: 0071774343 ISBN 13: 9780071774345, Chapter 15, Pages 116 - 126

[6] C. Myers and Alain Gervaix, International Journal of Antimicrobial Agents, 2007-11-01,

Volume 30, Pages 24-28, Copyright © 2007 Elsevier B.V. and the International Society of

Chemotherapy. Streptococcus pneumoniae bacteraemia in children

[7] Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition, Eighth Edition, Copyright © 2015 by Saunders, an imprint of Elsevier Inc. Chapter 201: Streptococcus pneumonia, Edward N. Janoff and Daniel M. Musher, page 2310-2327.

[8] Raz R, Elhanan G, Shimoni Z, et al: Pneumococcal bacteremia in hospitalized Israeli adults: epidemiology and resistance to penicillin. Clinical Infectious Diseases 24(6), June 1997; 24: pp. 1164-1168:

[9] Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition, Eighth Edition, Copyright © 2015 by Saunders, an imprint of Elsevier Inc.
Chapter 201: Streptococcus pneumonia, Edward N. Janoff and Daniel M. Musher, page 2310-2327.

[10] Bogaert, D et al. The Lancet Infectious Diseases, Volume 4, Issue 3, March 2004, 144 - 154 Streptococcus pneumoniae colonisation: the key to pneumococcal disease

[11] Angela B Brueggemann, David T Griffiths, Emma Meats, Timothy Peto, Derrick W Crook, Brian G Spratt, The Journal of Infectious Diseases, Volume 187, Issue 9, 1 May 2003, Pages 1424–1432: Clonal Relationships between Invasive and Carriage Streptococcus pneumoniae and Serotype- and Clone-Specific Differences in Invasive Disease Potential

[12] William P. Hausdorff, John Bryant, Peter R. Paradiso, George R. Siber, Clinical Infectious Diseases, Volume 30, Issue 1, 1 January 2000, Pages 100–121, Which Pneumococcal Serogroups Cause the Most Invasive Disease: Implications for Conjugate Vaccine Formulation and Use, Part I

[13] Bhutta, Zulfiqar A et al. The Lancet, Volume 381, Issue 9875, 12 April 2013, pages 1417 – 1429: Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost?

[14] Daniel M. Weinberger, Zitta B. Harboe, Elisabeth A. M. Sanders, Moses Ndiritu, Keith P. Klugman, Simon Rückinger, Ron Dagan, Richard Adegbola, Felicity Cutts, Hope L. Johnson, Katherine L. O'Brien, J. Anthony Scott, Marc Lipsitch, Clinical Infectious Diseases, Volume 51, Issue 6, 15 September 2010, Pages 692–699, Association of Serotype with Risk of Death Due to Pneumococcal Pneumonia: A Meta-Analysis

[15] S. R. J. Alanee, L. McGee, D. Jackson, C. C. Chiou, C. Feldman, A. J. Morris, A. Ortqvist, J. Rello, C. M. Luna, L. M. Baddour, M. Ip, V. L. Yu, K. P. Klugman, the International Pneumococcal Study Group, Clinical Infectious Diseases, Volume 45, Issue 1, 1 July 2007, Pages 46–51, Association of Serotypes of Streptococcus pneumoniae with Disease Severity and Outcome in Adults: An International Study

[16] Rosen's Emergency Medicine: Concepts and Clinical Practice
Ninth Edition, Copyright © 2018 by Elsevier, Inc. Chapter 121: Bacteria, Madonna Fernández-Frackelton, Pages 1587 – 1589.

[17] Mervyn Singer,MD, FRCP; Clifford S. Deutschman, MD, MS; ChristopherWarren Seymour,MD, MSc; Manu Shankar-Hari, MSc,MD, FFICM;
Djillali Annane,MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche,MD, PhD;
Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc;
StevenM. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tomvan der Poll, MD, PhD; Jean-Louis Vincent,MD, PhD; Derek C. Angus, MD, MPH, JAMA. 2016; 315(8), 02/22/2016, Pages 762-774: The Third International Consensus Definitions
for Sepsis and Septic Shock (Sepsis-3), Assessment of clinical criteria for sepsis

[18] Rodrigo Lopez Castelblanco, MD, MinJae Lee, PhD, Dr Rodrigo Hasbun, MD, The Lancet Infectious Diseases, Volume 14, Issue 9, 4 August 2014, pages 813 – 819, Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study

[19] William P. Hausdorff, John Bryant, Peter R. Paradiso, George R. Siber, Clinical Infectious Diseases, Volume 30, Issue 1, 1 January 2000, Pages 100–121, Which Pneumococcal Serogroups Cause the Most Invasive Disease: Implications for Conjugate Vaccine Formulation and Use, Part I

[20] Cynthia G. Whitney, M.D., M.P.H., Monica M. Farley, M.D., James Hadler, M.D., M.P.H., Lee H. Harrison, M.D., Nancy M. Bennett, M.D., Ruth Lynfield, M.D., Arthur Reingold, M.D., Paul R. Cieslak, M.D., Tamara Pilishvili, M.P.H., Delois Jackson, M.S.A., Richard R. Facklam, Ph.D., James H. Jorgensen, Ph.D., et al.,for the Active Bacterial Core Surveillance of the Emerging Infections Program Network, May 1, 2003, N Engl J Med 2003; 348: Pages 1737-1746, Decline in Invasive Pneumococcal Disease after the Introduction of Protein–Polysaccharide Conjugate Vaccine

[21] Daniel R. Feikin ,Eunice W. Kagucia, Jennifer D. Loo, Ruth Link-Gelles, Milo A. Puhan, Thomas Cherian, Orin S. Levine, Cynthia G. Whitney, Katherine L. O'Brien, Matthew R. Moore, the Serotype Replacement Study Group, September 24, 2013, Serotype-Specific Changes in Invasive Pneumococcal Disease after Pneumococcal Conjugate Vaccine Introduction: A Pooled Analysis of Multiple Surveillance Sites

[22] Daniel R. Feikin ,Eunice W. Kagucia, Jennifer D. Loo, Ruth Link-Gelles, Milo A. Puhan, Thomas Cherian, Orin S. Levine, Cynthia G. Whitney, Katherine L. O'Brien, Matthew R. Moore, the Serotype Replacement Study Group, September 24, 2013, Serotype-Specific Changes in Invasive Pneumococcal Disease after Pneumococcal Conjugate Vaccine Introduction: A Pooled Analysis of Multiple Surveillance Sites

Appendix:

DOCUMENTATION PAGE

This Diploma Thesis

„INVASIVE PNEUMOCOCCAL DISEASE IN LATVIAN UNIVERSITY HOSPITAL"

was developed at the Faculty of Medicine of the University of Latvia.

With my signature, I attest, that this research has been carried out without aid or assistance. Used information was obtained only from indicated sources and the electronically submitted copy of this diploma work complies with printout.

Author: Haakon Vevatne Øverland ______________

(name, surname) *(signature)*

I recommend the work for presentation.

Supervisor: Professor Uga Dumpis, PhD ______________ 11.05

(position, name, surname, degree) *(signature)* *(date)*

Reviewer: Asoc. Professor Alvils Krams, PhD ______________ ______________

(position, name, surname, degree) *(signature)* *(date)*

The diploma thesis was submitted to the Faculty of Medicine on: ______________

(date)

International students' coordinator, Inese Vēvere ______________

(signature)

The diploma thesis is presented at the meeting of the State Examination Commission of Higher Professional Study Program „Medicine"____________2018. Protocol No. ______________

Secretary of Commission: ______________ ______________

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