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Pneumococcal Pneumonia in Disguise: contribution of *Streptococcus pneumoniae* infections to morbidity and mortality during times of pandemics

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ABSTRACT

Streptococcus pneumoniae is the major cause of community acquired pneumonia. The clinical picture of other respiratory infections such as influenza or SARS-CoV-2 may resemble that of pneumonia. During pandemics, such as the 1918 influenza pandemic and COVID-19, *S. pneumoniae* could come in disguise and contribute to overall morbidity and mortality. It is estimated that during the 1918 influenza pandemic up to 50% of deaths were due to *S. pneumoniae* co- or super-infections. A century later, during COVID-19 estimates are that pneumococcal pneumonia contributed to up to 10% of morbidity. Adequate diagnostic procedures and treatment, as well as optimalization of pneumococcal vaccination programs could reduce the burden of pneumococcal disease, also in times of pandemics.

Introduction

Streptococcus pneumoniae is an encapsulated bacterium and the major cause of community acquired pneumonia in children, in elderly, and patients with underlying conditions[1]. The highest burden of pneumococcal pneumonia is in children, elderly, and patients with underlying conditions[2,3]. Analysis of the global distribution of pneumonia shows the highest incidence rates and mortality in the Indian subcontinent, South East Asia and Africa[3]. Pneumococcal conjugate vaccines have been implemented widely, but because of discrepancies between the composition of the vaccine and prevailing serotypes in a given region, efficacy of vaccination can be suboptimal[4].

Pneumococcal pneumonia has a clear seasonal pattern, partly overlapping with the influenza season[5]. Not only is there an epidemiological association between *S. pneumoniae* and influenza virus infections, but there are also pathophysiological interactions, including viral induced damage to respiratory epithelia and augmentation of cytokine responses[6,7]. The close association between *S. pneumoniae* and influenza during a regular influenza season could have an even higher impact during times of pandemics. The aim of this paper is to analyse and compare the contribution of *S. pneumoniae* to overall morbidity and mortality during the last two major pandemics, the influenza pandemic which started in 1918, and COVID-19.

Influenza pandemic 1918

The 1918-1919 influenza pandemic, also referred to as the Spanish influenza, was one of the deadliest outbreaks of an infectious disease in history, reaching even the most remote places on Earth[8]. Probably more than 500 million people were infected, amounting for about one-third of the global population at the time[8,9]. It is estimated that the global mortality ranges from 50-100 million in the first year of the pandemic[10]. The pandemic was caused by an H1N1 influenza A virus[8]. The H1N1 influenza virus marked the beginning of an era of recurring influenza pandemics, as subsequent influenza A viruses, including those responsible for later (smaller) pandemics in 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Swine flu (H1N1) all are genetically descended from the 1918 strain[8,11,12].

The influenza pandemic of 1918 was marked by its extreme severity, with high mortality rates and young adults being the prime risk group. Several lines of evidence indicate that the primary cause of death in the 1918 pandemic was likely due to complications of a secondary bacterial pneumonia, and thus not the influenza virus itself[8,13,14]. Autopsies and bacteriological studies from that time consistently pointed to bacterial infections, mainly *S. pneumoniae*, but also *S. pyogenes*, and *Staphylococcus aureus,* as the main contributors to the fatalities[8,13].

Postmortem studies and military data revealed that influenza cases in the deathly second wave (fall 1918) were 25 times more likely to develop severe bacterial pneumonia compared to the first wave (spring 1918)[15]. This suggests that a mutant of the original viral strain, circulating in the second wave, increased susceptibility to secondary bacterial infections by increasing viral damage to the respiratory tract, weakening the lung's defence mechanisms[15].

Evidence from lung tissues, antemortem blood cultures, and historical analyses - including postmortem bacterial and pathological studies - suggests the critical role of secondary pneumonia as the leading cause of death[13,16,17]. Klugman et al. compared the time from illness onset to death in influenza-related pneumonia cases from 1918 with untreated pneumococcal pneumonia cases from the pre-antimicrobial era of the 1920s and 1930s, finding similar time-to-death distributions[18,19,20]. These findings, along with reports of pneumococcal bacteraemia in up to 50% of pneumonia deaths during the 1918 pandemic, provides further evidence that most fatalities were actually due to pneumococcal bacterial infection.

Influenza virus increases susceptibility to pneumococcal bacterial infection, by destroying the epithelial lining of the respiratory tract, thus exposing bacterial attachment sites, leading to enhanced bacterial colonization of the lungs[21,22]. Alternatively, but not mutually exclusive, it has also been suggested that a loss of lung repair processes following the viral infection also contributes to the high mortality rates caused by secondary bacterial infection[14,21]. Experimental evidence from mouse models also mirror findings from the autopsies[8]. Co-infection with the 1918 influenza virus and *S. pneumoniae* demonstrated enhanced neutrophil activity, increased bacterial replication, and widespread vascular thrombosis, leading to severe lung damage and a shortened survival period[8,23].

During the 1918 influenza pandemic, experts believed that deaths were primarily caused by secondary bacterial pneumonia rather than the influenza virus itself, which was not yet fully identified[24]. While the exact bacterium responsible for the fatal pneumonia could not be pinpointed at that time, mixed bacterial vaccines were developed using strains of bacteria that were found in high concentrations in patients, later known as pneumococci, streptococci, and staphylococci[24]. Although the methods used to create these vaccines did not meet modern Good Laboratory Practice standards, they demonstrated a reasonable level of efficacy in reducing mortality during the pandemic as trials from Australia, Canada and Britain have shown[24,25].

Pathological and bacteriological data from later pandemics, such as those in 1957 and 1968, revealed that the influenza virus responsible for these outbreaks evolved from the 1918 strain[13]. Although 1957 influenza had lower mortality rates than the 1918 pandemic, most deaths were still attributed to secondary bacterial pneumonia, with *Staphylococcus aureus* emerging as the predominant cause, unlike in 1918, where *S. pneumoniae* was the predominant cause[13,16]. Negative lung cultures were more common, likely due to widespread antibiotics use. The 1968-1969 pandemic has also shown similar characteristics as its precedent influenza pandemics earlier in the century[13].

As a rule of thumb in epidemiology, but not based on firm evidence, it has often been stated that a major pandemic occurs once every hundred years. Whether or not that is true, it was exactly 100 years after the end of the 1918-1919 influenza pandemic that the first reports of an outbreak of a novel virus in Wuhan were published[26].

Coronavirus Disease 2019 Pandemic

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19), has led to approximately 777 million cases and more than 7 million deaths globally[27]. Early reports indicated that bacterial co-infections in COVID-19 were uncommon and had minimal impact on severity and mortality. However, more recent evidence suggests that bacterial co-infections might affect mortality rates[28]. In children with SARS-CoV-2 the carriage rate of *S. pneumoniae* is higher than patients that are not infected with SARS-CoV-2[29]. This could be harmful because the immune system of COVID-19 patients is often compromised. A study conducted by Stahlfeld et al. from March to August 2020 in 148 patients with a median age of 65 years showed that 11.0% of individuals tested positive in a pneumococcal serotype-specific urine antigen detection assay[30]. Severe COVID-19 patients tested more often positive than moderate COVID-19 patients[30]. A meta-analysis of studies from 2020 showed that bacterial co-infections were present in 7% of hospitalised patients with SARS-CoV-2, with this percentage rising to 14% in studies focusing specifically on patients with severe disease admitted to the intensive care unit[31].

In general, secondary bacterial coinfections or bacterial coinfections are frequent complications of respiratory viral diseases. These infections can exacerbate the severity of the illness and lead to

worse clinical outcomes, ultimately raising the risk of morbidity and mortality. In SARS and MERS patients, coinfection has been reported, similarly in COVID-19 patients a common complication are bacterial coinfections. Studies suggest that SARS-CoV-2 may promote the colonization of bacteria and enhance their ability to attach to host tissues. This can lead to severe tissue damage that is irreversible and worsen pathophysiology. Moreover, research indicates that the rate of COVID-19 patients experiencing secondary or co-infections can reach up to 45%, with bacterial infections contributing to half of all COVID-19 related deaths[32]. Additionally, individuals with both a bacterial infection and COVID-19 faced a 5.82 times higher risk of death compared to those without such coinfections[32].

High risk groups (mainly based on age) are already offered both the (seasonal) influenza vaccine and a pneumococcal vaccine. A critical preventative measure therefore is optimization of pneumococcal vaccination, particularly during the COVID-19 pandemic[32]. Risk factors for COVID-19 and pneumococcal disease are similar, such as smoking, asthma, cancer, old age, diabetes mellitus, as well as underlying liver-, chronic heart- and kidney-diseases. The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) have stated that severe pneumonia, resulting from acute respiratory infection, is the most frequent diagnosis in COVID-19 cases[32]. In older adults vaccinated with PCV13, a 35% reduced risk of contracting COVID-19 was observed, as compared to those who were not vaccinated[33]. Additionally, a randomized controlled trial involving both children and adults showed that PCVs provided 23 to 49% protection against respiratory viruses, including circulating coronaviruses, also supporting the idea that pneumococci play a role in virus-related respiratory illnesses[34]. These studies were performed during the period when COVID-19 vaccines were not available yet. While pneumococcal vaccines cannot directly prevent COVID-19, the data suggest that PCV can lower COVID-19 mortality among high-risk adults.

During times of COVID-19, any patient admitted to the hospital with respiratory symptoms, was tested for SARS-CoV-2, as well as other respiratory viruses. Testing for bacterial infections, notably *S. pneumoniae*, has not always been done, which may have led to an underestimation of pneumococcal co-/superinfections during COVID-19. For future use, it would be beneficial to combine molecular viral testing with *S. pneumoniae* testing in a single multiplex PCR assay, targeting lytA and/or SP2020[35].

Conclusions

It can be concluded that the contribution of *S. pneumoniae* to overall morbidity and mortality during the 1918-1919 influenza pandemic may have been as high as 50%. During COVID-19 most estimates of involvement of *S. pneumoniae* are lower, around 10%[36]. This difference could be due to many factors, including the differences between the viruses, the appropriate use of antibiotics, the vaccination of elderly with pneumococcal vaccines, and 100 years of improvement of medical care systems. *S. pneumoniae* can be considered a true opportunistic pathogen. The moment an opportunity arises; it can cause severe morbidity and mortality in vulnerable populations. During times of pandemics, pneumococcal pneumonia can come in disguise. Awareness and appropriate diagnostics and treatment can limit the consequences of pneumococcal co-morbidities.

Conflict of Interest:

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