Risk factors for invasive pneumococcal infections on shipyards: A systematic review

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Abbreviations

IPD= Invasive Pneumococcal Diseases

JBI= Joanna Briggs institute

CAP = Community-Acquired Pneumonia

SPD = Serious Pneumococcal Disease

RSV = Respiratory Syncytial virus

PPV= Pneumococcal Polysaccharide Vaccines

PCV =Pneumococcal Conjugate Vaccines

CSF= Cerebrospinal Fluid

NLIA =the Norwegian Labour Inspection Authority

NIPH = the Norwegian Institute of Public Health

COPD = Chronic Obstructive Pulmonary Disease

LEV = Local Exhaust Ventilation

VWS = Ministry of Health, Welfare and Sport

NWO = Netherlands Organisation for Scientific Research

SD= standard deviation

IQR= Interquartile range

Abstract

Introduction

Outbreaks of invasive pneumococcal infections happen, usually when a new *Streptococcus pneumoniae (S. pneumoniae)* strain is introduced in closed settings such as child day-care centres, schools or nursing homes. However, recently outbreaks of invasive pneumococcal disease (IPD) have been reported at shipyards. The aim of this review is to define the occupational risk factors for IPD at shipyards.

Methods

A systematic literature search was performed in the databases PubMed and Google Scholar from inception until the 11th of May 2020. Studies were included if they reported an IPD outbreak related to occupational exposure in shipyards. The quality of the studies was analysed with the Joanna Briggs Institute (JBI) critical appraisal checklist for case series. Primary outcome was the risk factors for IPD in shipyards.

Results

From a total of 1479 studies, five case series were selected. The overall quality score of the studies was considered to be high. The results suggest that shipyard workers have a higher risk for developing IPD due to the working environment on shipyards. Risk factors contributing to the IPD susceptibility in shipyards were: exposure to respiratory irritants, current smoking, viral influenza infections, working and living in crowded environments, poor ventilation in the work environment rooms, poor usage of respiratory protective equipment and invalid vaccination status.

Conclusion

Shipyard workers might have a higher chance for developing IPD mainly due to specific environmental factors present at shipyards. To prevent future IPD outbreaks in shipyards, there is an urgent need to decrease the influence of risk factors in the working environment. Preventive measures may include pneumococcal- and influenza vaccination, improved ventilation in crowded workspaces, occupational hygiene measures, reinforcement of proper use of respiratory protective equipment, improvement of housing conditions and an anti-smoking campaign. Cohort or case-control studies may reveal how work factors increase the risk for IPD and whether particular preventive measures can prevent pneumococcal diseases.

Samenvatting

Introductie

Uitbraken van invasieve pneumokokken ziektes (IPD) vinden meestal plaats wanneer een nieuwe *S. pneumoniae* stam wordt geïntroduceerd op plekken waar veel mensen dicht opeen zijn zoals kinderdagverblijven, scholen of verpleeghuizen. Recent zijn er enkele uitbraken van pneumokokkenziekten geweest op scheepswerven. Het doel van deze review is om de beroepsgebonden risicofactoren van invasieve pneumokokkenziekten op scheepswerven te onderzoeken.

Methoden

In de databases PubMed en Google Scholar is vanaf het begin tot 11 mei 2020 systematisch gezocht naar literatuur. Studies die pneumokokken uitbraken beschreven gerelateerd aan beroepsmatige blootstelling op scheepswerven werden geïncludeerd. De kwaliteit van de geïncludeerde studies werd geanalyseerd met het Joanna Briggs Institute (JBI) critical appraisal checklist voor case studies. In deze review zijn de risicofactoren op scheepswerven voor invasieve pneumokokkenziekten geanalyseerd.

Resultaten

De systematische zoektocht leverde in totaal 1479 studies op waaruit vijf case series werden geselecteerd. De JBI-kwaliteitsscore van de geïncludeerde studies was hoog. De resultaten suggereren dat werknemers op scheepswerven als gevolg van de werkomgeving een hoger risico hebben op het ontwikkelen van invasieve pneumokokkenziekte. Risicofactoren die bijdragen aan de vatbaarheid voor invasieve pneumokokkenziekte op scheepswerven zijn: blootstelling aan irriterende stoffen, actief roken, influenza infecties, werken en leven in een drukke omgeving, slechte ventilatie in de werkruimtes, slecht gebruik van persoonlijke beschermingsmiddelen en niet adequate vaccinatiestatus.

Conclusie

Scheepswerfmedewerkers hebben een grotere kans om IPD te ontwikkelen als gevolg van specifieke omgevingsfactoren die op de scheepswerven aanwezig zijn. Om uitbraken van pneumokokkenziektes op scheepswerven te voorkomen, is het noodzakelijk om de risicofactoren in de werkomgeving te onderzoeken. Preventieve maatregelen kunnen bestaan uit vaccinatie tegen influenza en de pneumokok, verbeterde ventilatie in werkruimten, maatregelen op het gebied van arbeidshygiëne, toezicht op het juiste gebruik van ademhalingsbeschermingsmiddelen, het verbetering van de huisvestingsomstandigheden en een anti rook campagne. Cohort of case-control studies kunnen duidelijk maken hoe

werkfactoren het risico op IPD verhogen en/of bepaalde preventieve maatregelen pneumokokken ziekten kunnen voorkomen.

Introduction

Pneumococcal infections are caused by the Gram-positive bacterium *Streptococcus pneumoniae* (*S. pneumoniae*).[1] This pathogen commonly colonizes the nasopharyngeal tract without causing any symptoms in 70% of the population.[1-2-3-4] Occasionally, pneumococcus may migrate from the nasopharynx to the lungs and cause disease.[5] *S. pneumoniae* is the most common cause of community-acquired pneumonia (CAP). [1]

S. *pneumoniae* gives rise to a wide range of infections.[5] Disease caused by *S. pneumoniae* can largely be divided in two groups, namely non-invasive and invasive (respiratory) diseases. The non-invasive infections cause milder illnesses such as otitis media, sinusitis, and pneumococcal pneumonia. In adults, pneumonia is the most common clinical presentation of pneumococcal infection. Otitis media is especially common in young children and sinusitis is frequently seen in older children and adults.[1]
Invasive disease is rare but may lead to more severe disease such as invasive pneumonia, sepsis, and meningitis.[3] Together described as serious pneumococcal disease (SPD) or invasive pneumococcal disease (IPD).[6]

The most important hosts of the S. *pneumoniae* bacteria are humans. The transmission route is aerogenic or through direct contact.[3] The *S. pneumoniae* spreads itself through respiratory droplets from mostly asymptomatic infected individuals to healthy individuals.[5] Pneumococcal diseases occur more commonly during the winter months (from October to March). This may be because viral respiratory infections, in particular influenza and respiratory syncytial virus (RSV), are more frequent during the winter months. It is known that other respiratory tract infections, especially influenza but also RSV, may lead to secondary pneumococcal pneumonia.[1,7]

Pneumococcal pneumonia can be diagnosed in the presence of clinical signs of pneumonia, a lung infiltrate chest X-ray, and microbiological findings.[1] There are several methods to establish the final diagnosis of pneumococcal pneumonia through microbiological findings. A positive bacterial blood culture is the main tool but Gram's strains and sputum culture are also reliable. A urinary antigen test provides a positive or negative diagnosis within fifteen minutes.[8]

The pathogenic strains of the *S. pneumoniae* are encased in a polysaccharide capsule. Based on the composition of the capsule, more than 90 different serotypes are distinguished. Some serotypes are more invasive than others.[1-2] The human body defends itself against *S.*

pneumoniae through binding of type-specific antibodies to the polysaccharide capsule. The binding changes the structure of the cellular surface of the bacteria in such a way that phagocytosis is stimulated. A functioning antibody response is crucial in this defence mechanism. Defects in the usual defence mechanisms of the human body against colonization, aspiration, or invasion of the bacteria, an infection with S. *Pneumoniae* may contribute to pneumococcal disease.[1]

Polysaccharide vaccines are recommended for prevention of pneumococcal infection in risk groups for IPD.[9] The currently available polysaccharide vaccines protect against 23 pneumococcal serotypes. There are currently two types of vaccines available: pneumococcal polysaccharide vaccines (PPV) and pneumococcal conjugate vaccines (PCV).[10] The pneumococcal polysaccharide vaccine contains pieces of the pneumococcal polysaccharide capsule as antigens to induce an immune response. The polysaccharide capsule of the bacteria in the conjugate pneumococcal vaccines are conjugated to a carrier protein. The duration of protection after vaccination with the conjugate vaccine is longer than vaccination with the polysaccharide vaccine.[3,9] A drawback of the conjugate vaccine is that it only protects against ten to thirteen of the 90 known S. *pneumoniae* serotypes.[1,3]

The most important risk factors for pneumococcal pneumonia are age, male gender, comorbidity and smoking. Pneumococcal infections can lead much faster to invasive pneumococcal infections in the very young and the elderly and patients with underlying conditions. For age, the incidence of IPD is up to fifty times higher in children under 2 years of age and the elderly over 65 years of age.[1,6] Males have a higher risk of pneumococcal pneumonia than females. This higher prevalence among males may be because cigarette smoking and alcoholism are more common in males than females.[1] Other known risk factors are smoking and immunosuppression.[11] Regarding environmental factors, it is known that certain jobs and exposures increase the risk of IPD. The latest research identified exposure to welding fumes and organic solvents as risk factors for IPD.[7,12-13-14] The exact mechanism for these associations is yet unknown.[12-13]

Outbreaks of pneumococcal infections usually occur, when a new *S. pneumoniae* strain is introduced in a closed setting. Examples of these settings are child day-care centres, schools and nursing homes.[1,6] In recent years a couple of large outbreaks of IPD have been reported in shipyards in different countries. This is not completely new. Already in 1943 the United States Maritime Commission reported on the prevalence of pneumococcal pneumonia among shipyard workers. However they found no evidence supporting for higher incidence of IPD

amongst the shipyard workers compared to the general population, nor did they find any indication of varying levels of IPD between the different occupations carried out on shipyards.[15]

Facing the recent outbreaks in shipyards it is nevertheless important to investigate specific factors in the work or environment that increase the risk for IPD among shipyard workers. The reports on outbreaks published thus far describe the outbreaks and the control measures, but do not look in depth into the risk factors for the occurrence of the outbreaks in shipyards.
Therefore, the aim of this systematic review is to explore the occupational risk factors for IPD in shipyards in order to prevent outbreaks in the future.

Methods

Literature search

In a systematic literature search, a PICO is often used, where P stands for population, I for the intervention, C for the control group and O for the outcome. In this occupational health research, the main focus is identifying risk or exposure factors. Then a PECO can be better used instead. P = population; in this study workers at a shipyard. E = occupational risk or exposure factor; in this study risk factors in work and work setting of a shipyard. C = control group; in this study workers not exposed to the risk factors of interest or the general population. O = outcome; in this study, invasive pneumococcal disease.

A systematic literature search was executed in the databases PubMed and Google Scholar with a search string based on the PECO criteria to find studies in which occupational pneumococcal infections on shipyards were clearly described. The search was performed from inception until the 11th of May 2020. In addition to the original Mesh-terms, several other Mesh-terms were used in PubMed to collect more data. The reference lists of the included studies were used to form the base of further research in order to supplement the original search strategy. The complete search strings on PubMed and Google Scholar are shown in Appendix 1.

Only studies reporting on serious pneumococcal outbreaks reports with IPD cases in a shipyard setting were included. Invasive pneumococcal diseases and severe pneumococcal diseases were both defined as IPD which can lead to invasive pneumonia, sepsis and meningitis.

In four outbreaks [2,6,17-18] pneumococcal infected cases were designated either confirmed or probable. Confirmed cases were defined as a shipyard worker presented with clinical IPD AND S. *pneumoniae* was isolated from a sterile site. S. *pneumoniae* isolates could be obtained from blood cultures, cerebrospinal fluid (CSF), joint fluid, peritoneal fluid, pleural fluid, endobronchial samples or pneumococcal antigen or detection in urine samples. Cases were defined as probable if individual shipyard workers had clinical signs compatible with IPD but did not have microbiological confirmation. Most isolation sites were taken from blood cultures and pneumococcal antigen detection in urine in order to identify the *S. pneumoniae* (Table 7).

Study selection

Studies were only included for analysis if they reported IPD cases among shipyard workers related to occupational exposure in a shipyard setting. Studies were excluded if they did not mention specific IPD cases among shipyard workers. Also studies written in a language other

than English were excluded. No studies were excluded based on publication year and study design.

Critical appraisal

After the selection, all the included studies were analysed with the JBI critical appraisal checklist tool for case series. The JBI checklist contains questions meant to measure the quality and validity of each study, according to the study design. The quality of the case series studies were measured with the JBI checklist for case series. The JBI checklist for case series contains ten questions. For an overview of the checklist questions see Appendix 2. Each question has four possible answers: Yes, No, Unclear and Not applicable. The quality of the studies was based on the amount of 'yes' answers the studies received. The studies were considered to be high quality if they scored an eight or higher on the final score.

Data extraction

Study and patients' characteristics were extracted. Study characteristics were determined and incorporated. The following data on study characteristics were selected: title, first author, publication year, study design, country, follow-up time of the study, outbreak period, number of IPD patients, number of IPD patients hospitalized, serotype of the S. *pneumoniae*, sequence type of the S. *pneumoniae* and the number of workers on the shipyard.
In addition to the study characteristics, also data on patients characteristics were recorded. The following data on patients characteristics were selected and tabulated: number of confirmed patients with IPD, number of probable patients with IPD, occupation, work related exposure, gender, age, nationality, comorbidity, smoking status and co-infections.
Information regarding the outbreak control measures were also recorded. The following data on outbreak control were recorded: antibiotics, vaccines, type of confirmation of diagnosis and fatality rate.
Four extra tables were made. The first additional table was created to further elaborate the underlying conditions (Table 5). The second table was created to further elaborate the smoking status of IPD shipyard workers (Table 6). The third table was created to more extensively highlight the used control measures, besides vaccination and antibiotic prophylaxis (Table 8). The last additional table was created to summarize the reported environmental risk factors for IPD in shipyards (Table 9).

Outcome measures

The primary outcomes of this systematic review are the risk factors for IPD in shipyards settings.

Results

Eligible studies

The systematic literature search resulted in a total of 1479 studies. Forty four studies were selected after a quick title and abstract scan based on the inclusion and exclusion criteria. After a full-text scan of the 44 studies only six studies remained. The other studies were excluded because they did not meet the PECO-criteria. One additional study was excluded, because this study was a preliminary report of a more comprehensive study that was already included.[11] For a visual representation of the study selection see the selection flow-diagram in Figure 1. Five case series describing outbreaks of pneumococcal infection on shipyards met the inclusion criteria. These studies reported on an IPD outbreak related to occupational exposure in a shipyard setting.

Quality assessment

The five included studies were critically appraised using the JBI checklist score for case series. The three studies from Lee Eng Kiang, Cassir et al. and Linkevicius et al. scored ten out of ten. Despite being of exceptional quality the publication by Lee Eng Kiang provided the least information. The article reported on a very small number of cases and occupational work exposure on the shipyards was not verified. The two studies from Ewing et al. and Berild et al. scored nine out of ten. Both studies failed to supply complete clinical information of the participants. The critical appraisal outcome of the five case series are summarized in Table 1. The overall score of the five studies was considered to be high.

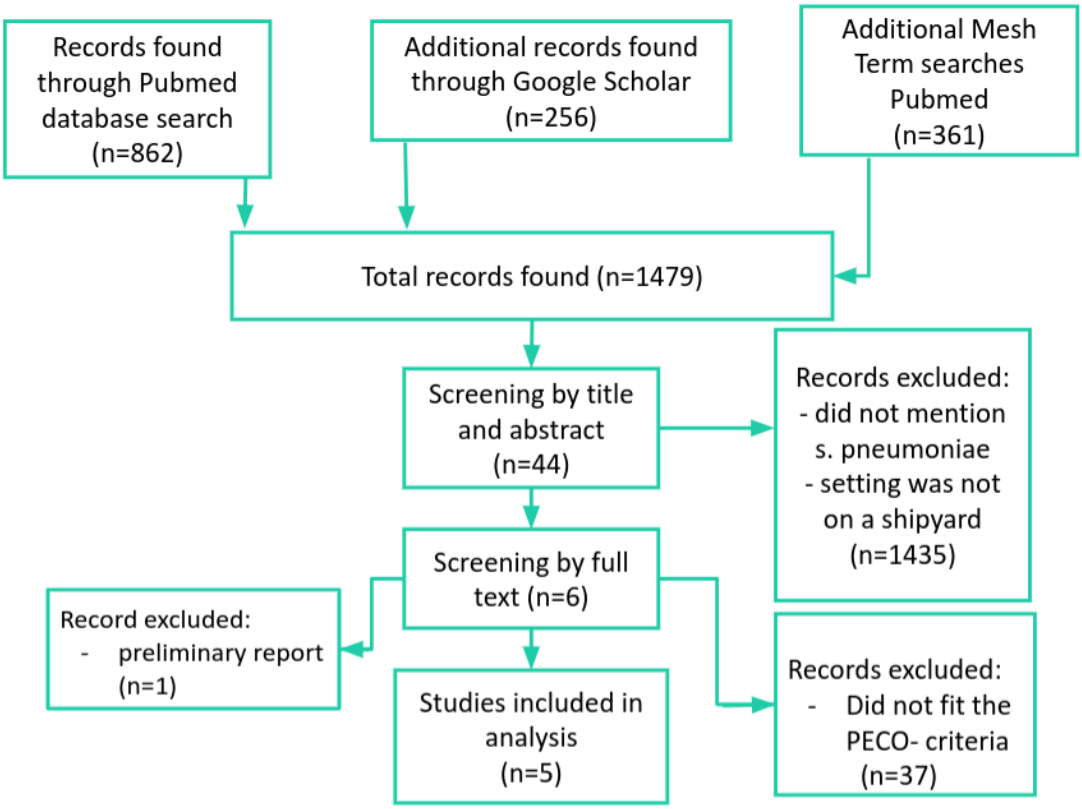

figure 1: Study selection flow-diagram

The five IPD outbreaks took place between April 2015 and February 2020 and the studies were published between 2017 and 2020. The median duration of follow-up was 3 months with a range from 2 to 7 months. Four outbreaks occurred in Europe and one in Asia. The European outbreaks occurred in shipyards in Finland, France, Ireland, and Norway. The outbreak in Asia was reported in a hospital in Singapore. Most outbreaks (n=4) occurred on shipyards and the article of Ewing et al.[6] is specifically on an oil rig that arrived for refurbishment at the Belfast shipyard. The study of Lee Eng Kiang provides information on three IPD cases at the Department of Anaesthesiology of the Ng Teng Fong General Hospital in Singapore. The only common risk factor in these three hospitalized patients was the fact that it involved foreign shipyard workers that might be exposed to the same unknown factor in their work environment.[16]

A total of 106 shipyard workers with IPD were included in this systematic review from the five case series. The number of IPD shipyard workers in the case series varied from 3 to 37, with a median of 20 patients. More than two-third (69%) of the total IPD shipyard workers were hospitalized (Table 2). One shipyard worker died, because of pneumococcal meningitis (Linkevicius et al.[2]).

In four of the five case series serotypes of the pneumococcal bacteria were known. In all the four reported outbreaks, the most prevalent pneumococcal strain was serotype 4. In the

article of Berild et al.[18] serotype 4 was the only serotype seen. The microbiological findings reveal that most outbreaks were instigated by multiple distinct serotypes. Other reported serotypes were 3,8, 9N and 12F (Table 2).

Non-work-related risk factors

Gender and age

In all the five case series, 98% of the shipyard workers with IPD consisted of men. Both studies of Cassir et al.[17] and Linkevicius et al.[2] reported on a female worker among the IPD cases. Between the studies the median age of the shipyard workers varied 24 and 48 years old. Shipyard workers with an age higher than 65 years were reported in one article.[17] The age of the workers with IPD therefore deviates from the usual risk groups in terms of age(Table 3).

Comorbidity

Information on medical history was not provided for all shipyard workers with IPD, so the combined percentages given do not always add up to 100%.

In the article of Cassir et al.[17] medical history and smoking status was collected from 17 of the 37 confirmed and probable IPD shipyard workers. Seven of these 17 (41%) participants reported underlying conditions: 4 workers suffered from chronic respiratory disease, two ischemic heart disease and one diabetes. In the article of Linkevicius et al.[2] 25/37 (68%) shipyard workers with confirmed and probable IPD were interviewed and therefore smoking status and medical history was available. Three of these 25 (12%) workers reported comorbidities: chronic obstructive pulmonary disease (COPD), lung cancer, and asthma. In the article of Berild et al.[18] information on medical history and smoking was available for all 20 patients. One of 20 (5%) shipyard workers had undefined comorbidity. From the article of Lee Eng Kiang information on medical history was provided for all three shipyard workers.[16] One shipyard worker reported a short period of childhood asthma. In the article of Ewing et al.[6] medical history and smoking status was collected for all nine confirmed and probable shipyard workers. One shipyard worker was in a medical risk group for IPD, but no further determination on the type of medical history was given. From the five case series 61/74 (82%) of the shipyard workers reported having no comorbidities or medical history. Besides the expected higher incidence of IPD among individuals with comorbidities[1], the case series reveals that IPD also occurs in previously healthy shipyard workers.

Smoking status

Information on smoking status was not provided for all shipyard workers with IPD, so the combined percentages given do not always add up to 100%.

In the article of Cassir et al.[17] half of the 17 shipyard workers reported current smoking. Seven of 20 shipyard workers reported current smoking in the article of Berild et al.[18]. In the article from Linkevicius et al.[2] 19 of the 25 shipyard workers reported current smoking. In the article of Ewing et al.[6] 5 of the 9 shipyard workers were current smokers and one shipyard worker was an ex- smoker. In the article of Lee Eng Kiang no smoking status from the three foreign shipyard workers was reported.[16]

Even though the majority (56%) of infected shipyard workers were indeed smokers, we see that a large group (44%) of non-smokers was also infected. (Table 4 and 6).

Other potentially relevant factors in work or work setting

Diversity in nationalities

Information on nationalities was not provided for all shipyard workers with IPD, so the combined percentages given don't always add up to 100%.

The shipyards in which the IPD outbreaks took place reported a high turnover of workers from different countries, with most of them hailing from European descent. A small proportion had no European roots however and was employed by either the shipyard itself or numerous subcontractors (Table 3).

The workforce and crew members on the shipyard in the article of Cassir et al.[17] consisted of 5823 workers from 102 different nationalities. The most frequent nationalities were Italian (25%), Romanian(11%), Polish(10%), Filipino(8%) and Ukrainian(5%). The majority of workers were in the employment of foreign organisations involved in the shipyard with only a minority being employed by local contractors or the shipyard of Marseille itself. The shipyard workers and crew members worked and lived in crowded spaces on three ships which were undergoing renovation.[17]

In the article of Linkevicius et al.[2] the nationalities from the 31 IPD cases were Finnish(42%), other European Union/ European Economic Area (52%) non- European Union/ European Economic Area(6%). The workforce was multinational acquired, most of the hull building workers were employed by the shipyard itself and most of the ship outfitting workers were employed by numerous subcontractors.

Approximately 3000 workers in the article of Ewing et al.[6] were employed for the refurbishment of the oil rig. A third of the workers resided in Northern Ireland, another third hailed from other parts of the United Kingdom and the remainder were inhabitants of other

European countries. The workers involved in the project were either employees of the shipyard of Belfast or the oil rig owner or were employed by various contractors. There was a significant turnover of shipyard workers with long- and short -term contracts during the refurbishment of this oil rig. The shipyard workers resided around Belfast in hotels and private accommodation.

In the article of Berild et al.[18] 20% of the confirmed and probable cases came from Norway and the other 80% came from other European countries. This article also reported a high turnover of personnel workers from whom many of them lived in temporary accommodation. A combination of different nationalities and the rapidly changing composition of the labour force could have led to insufficient attention being given to health issues. The outbreaks could have been exacerbated by poor access to health care, the language barrier, variation in vaccination status, poor housing conditions and employment by different contractors.

Type of work - occupation

Information on type of occupation was not provided for all shipyard workers with IPD, so the combined percentages given do not always add up to 100%.

Specification of the type of work and the work related exposure was available in four out of five studies (Table 3).

One third of the nine IPD shipyard workers in the study of Ewing et al.[6] were welders. The other occupations who worked closely alongside welders are reported in Table 3. Not only welders reported to be exposed to metal fumes but also other professions reported being indirectly exposed to these metal fumes.

The twenty IPD shipyard workers in the study of Berild et al.[18] had several occupations mostly including metal welding and interior outfitting. Occupations related to welding and interior outfitting result in direct exposure to fumes while working in small, enclosed spaces.

In 24 of 37 IPD shipyard workers in the study of Cassir et al.[17] the professions were known. The professions from the shipyard workers with IPD that likely facilitated their exposure to respiratory irritants were technicians (7), interior outfitters and installers (6), fire-guards (2), managers (2), painter(1), welder(1) and carpenter (1), crew members (4). Seven of the 24 workers reported being in direct contact with dust, solvents or metal fumes. Not only shipyard workers but also four crew members were infected in this outbreak. The crew members worked on the ships as hotel staff to accommodate the other shipyard workers.

All 25 IPD shipyard workers in the study of Linkevicius et al.[2] had occupations in the final stages of ship outfitting. Obtained occupations were electrician(7), plumber(3), site supervisor(3), shipbuilder(2) and other interior outfitters(10). Interviewed workers reported

spending extended hours of work in either inadequately ventilated or draughty conditions close to one another. Fifteen of the interviewed shipyard workers with IPD reported working indoor and nine reported working both indoor and outdoor.
The interviewed shipyard workers were exposed to inorganic dust, metal fumes, solvents, gases, acids and paint fumes.

Shipyard workers in the four reported IPD outbreaks were predominantly occupied with interior ship outfitting.[2,6,17-18] Interior outfitting deals with the refurbishment of interior spaces in (cruise) ships.[2,17] The work tasks are located inside the ships in small spaces which are difficult to vent due to the absence of windows. Especially in these indoor spaces proper ventilation or extraction systems are needed to minimize the concentration of respiratory hazards.
In summary, these studies reported several work related conditions, which contribute to IPD: many people working indoors in close proximity, exposed to irritants, solvents and welding fumes for hours on end. Furthermore, the work areas were poorly ventilated and draughty. As a result of these work settings workers who did not work with harmful substances themselves can still be exposed in an indirect way.

Use of protective equipment

In the article of Linkevicius et al.[2] 25 of the 37 confirmed and probable shipyard workers with IPD were interviewed. From the 25 participants, 15 shipyard workers indicated that they never used respiratory masks while working and 7 reported that they use respiratory masks occasionally. This shows that only 3 from the 25 infected shipyard workers always used a respiratory mask while working. Most likely this was because wearing a mask was not mandatory for most of their tasks.
The lack of usage of personal protective equipment was also reported in the article of Berild et al.[18] where The Norwegian Labour Inspection Authority (NLIA) inspected a shipyard and observed a polluted work environment with little use of personal protective equipment among the shipyard workers. In contrast, the study of Ewing et al.[6] reported that during the inspection health and safety risks were properly managed. Air handling equipment was used in enclosed workspaces and respiratory protective equipment was distributed among the workers. In general, inadequate use of respiratory protective equipment (RPE) is reported among shipyard workers in the shipyards where these outbreaks occurred.

Treatment and prevention

Vaccine protection

A pneumococcal mass vaccination campaign was applied in four of the five reported outbreaks (Table 7). In the studies of Berild et al.[18] , Cassir et al.[17], Linkevicius et al.[2] and Ewing et al.[6] a vaccine was administered in order to interrupt disease transmission and provide long-term prevention for the non-infected shipyard workers. The 23- valent pneumococcal polysaccharide vaccine (PPV23) was given in three quarters of the outbreaks. One outbreak used the 13- valent conjugate vaccine(PCV13) (Table 7).

Both the PCV13 and PPV23 protect against the pneumococcal serotype 4. According to the article of Berild et al.[18] the PCV13 vaccine is preferred because it may also affect colonization. The use of the PPV23 vaccine over the PCV13 vaccine is preferred in the studies of Linkevicius et al.[2], Ewing et al.[6] and Cassir et al.[17] due to the protection against a wider range of pneumococcal serotypes. In all four outbreaks pneumococcal mass vaccination campaigns were a successful way to control the outbreaks.

Antibiotics

Antibiotic treatments were given in all outbreaks to treat the pneumococcal infection for all symptomatic patients. Several antibiotics were used (Table 7). Antibiotic prophylaxis was offered only in the study of Ewing et al.[6]. Shipyard workers meeting the criteria for antibiotic prophylaxis were orally given 500 mg azithromycin once a day for 3 days in addition to the PPV23 vaccine. Prophylaxis was given for those working on the oil rig exposed to metal fumes. Candidates for prophylaxis were welders and others working closely to welders.

In contrast, the Norwegian Institute of Public Health (NIPH) in the study of Berild et al.[18] did not recommend antibiotic prophylaxis. The shipyard workers were healthy, according to the NIPH, reasoning that they had neither an advanced age nor immunocompromising conditions. Therefore it was considered undesirable to offer antibiotics to 1800 asymptomatic shipyard workers with the risk of antibiotic resistance. In line with the NIPH, the use of antibiotic prophylaxis was not considered desirable in the study of Cassir et al.[17].

In all studies antibiotics were issued in the IPD patients, but only one study thought it necessary to prescribe antibiotic prophylaxis to the asymptomatic workers as well.

Other infection control measures

Four out of five case studies documented the control measures during the outbreak. Infection control measures other than preventive pneumococcal vaccination, antibiotic prophylaxis and antibacterial treatment of four outbreaks are summarized in Table 8. Reinforcing hand and respiratory hygiene as a control measure was described in three quarters of the outbreaks.

Usage of RPE was reported in three out of four case series. Providing information and advice was reported in all the outbreaks. Furthermore, one article reported on offering a seasonal influenza vaccine. Three outbreaks reported difficulties in the implementation of the control measures. [6,17-18] Independently of each other, the shipbuilding companies took their own measures during these outbreaks. Some of these measures are similar. There seems to be little consensus on the appropriate measures to tackle outbreaks on infectious diseases.

Discussion

At the beginning of 2020 an IPD outbreak was reported in a shipyard in France.[17] This marks the third consecutive pneumococcal outbreak in shipyards within the timeframe of one year. The first two occurring in the beginning of 2019 in Finland and Norway.[2,18] In 2015 there was also an IPD outbreak in Northern Ireland and three shipyard workers with IPD were reported in Singapore in 2017.[6,16] We used the data of these five recent IPD outbreaks on shipyards to determine which specific occupational risk factors may have contributed to these outbreaks. Specific risk factors in the work setting which enhance the shipyard workers to acquire IPD found in this review were: exposure to respiratory irritants, current smoking, influenza infections, working and living in crowded environments, poor ventilation in the work environment rooms, poor usage of respiratory protective equipment and no proper vaccination status.

In the five outbreaks, 98% of the infected shipyard workers consisted of men. The male gender is a known risk factor for pneumococcal pneumonia.[1,10] The affected patients in this outbreak were relatively young and therefore do not fit into the age category (<2 and ≥ 65 years) that is known to have higher risk of pneumococcal infections.[1,10] There were also few comorbidities reported among the pneumococcal infected employees. The fact that these workers were relatively young and had virtually no comorbidities argues that other factors must have contributed to cause IPD in these workers.

Seroprevalence

The most prevalent pneumococcal serotype seen in these five outbreaks was serotype 4, notorious for having a high attack rate.[2,20] Attack rate is defined as the number of IPD that occurs per number of individuals that get infected with the S. *pneumoniae*. The capsule of the S. *pneumoniae* serotype is a determining factor for the pneumococcal duration of carriage and the attack rate.[20] Pneumococcal serotypes 1,4,5 and 9A have high attack rates whilst serotypes 9N, 16F, 20 and 38 have low attack rates.[5] When choosing a protective vaccine, it is important to include these common and virulent serotypes.[10]

Influenza co infection

Respiratory infections, including those caused by the influenza virus, were seen in the study of Cassir et al.[17]. Respiratory infection with the influenza virus is a known risk factor for IPD.[1,17] Moreover, according to the literature, the influenza vaccine is an effective tool to decrease the risk for all pneumonia.[1] Recent research also emphasizes the importance of vaccinating staff members who are in close contact with at-risk employees.[10] In this review, at-risk occupations are those occupations on the shipyard in which workers get in contact with the risk factors for IPD. Therefore, the enforcement of seasonal influenza vaccination may reduce the incidence of IPD among the people working in at-risk occupations and those working in close proximity to them.

Smoking status

Smoking is a recognized independent risk factor for IPD.[1] Smoking and alcohol abuse are prevalent in young males and are the most preventable risk factors in these two groups.[21] Accordingly, prevalence of cigarette smoking was high among the infected shipyard workers in these five reported outbreaks. An anti-smoking campaign would therefore be a recommendation as a large proportion of employees still smoke. Nevertheless, also a significant group of workers without a smoking history became infected and developed IPD.

Nationality

The shipyards in which the outbreaks took place reported a high turnover of workers from various countries. A combination of different nationalities and the rapidly changing composition of the labour force could have led to insufficient attention being given to health measures. This could have been exacerbated by poor access to health care, the language barrier, variation in vaccination status, poor housing conditions and employment by different contractors.

Because the shipyard workers in these five IPD outbreaks came from many different countries as temporary workers, it was unclear what their vaccination status was and whether these workers have been vaccinated with the pneumococcal vaccine in the last five years.[18]

Vaccination and antibiotics

In all four outbreaks pneumococcal mass vaccination campaigns were a successful way to control the outbreaks and may be given to the employees to prevent future pneumococcal outbreaks. In only one outbreak report antibiotic prophylaxis was offered as a protective measure to workers exposed to metal fumes.[6]Treatment with antibiotic prophylaxis on its own provides only short-term protection. Vaccination with one of the pneumococcal vaccines is the best method to ensure long-term protection.[10] It is useful to vaccinate these temporary workers preventatively against the most prevalent pneumococcal serotypes, especially since the distribution of serotypes varies between countries depending on national vaccination policy.[2,6]It is important to protect these employees for an extended period of time with vaccination campaigns, because they have an ongoing work-related risk for invasive pneumococcal infections.[6] This should then be clearly kept in a medical record so that the shipyards can see if the workers have been properly vaccinated.

Type of work and exposure

Several work related conditions found in the shipyard outbreaks could contribute to IPD susceptibility: too many people working indoors in close proximity as well as exposure to irritants, solvents and welding fumes. Furthermore, the work areas were poorly ventilated and draughty and there was little use of protective equipment. As a result of these cramped and poorly ventilated spaces, we see that occupations that do not come into direct contact with harmful substances themselves are also indirectly exposed by those who do.

Because of their direct exposure to polluted fumes welders have higher risk for obtaining invasive pneumococcal infections.[4,7,12-13] Several theories exist that might explain how welding smoke could increase susceptibility to respiratory infections.[7,13]
In the four reported outbreaks in this review[2,6,17-18] employees working in close proximity of welders also got infected. Shipyard workers who were interviewed told spending extended hours of work in either inadequately ventilated or draughty conditions close to one another.[2]
Research indicates that shipyard workers are exposed to various respiratory hazards.[22-23]
Occupational tasks that require arc welding involving metals such as steel, aluminium, copper, and nickel are custom place performed on shipyards.[22] Besides exposure to metal fumes shipyard workers may also be exposed to other hazardous substances such as asbestos, lead, cadmium, arsenic, silica dust, benzene and formaldehyde which are currently known to be harmful to the lungs.[22-23]
The outbreaks in this review substantiate these data and state that shipyard workers are indeed exposed to various hazardous substances and chemicals. Respiratory irritants

reported in these outbreaks were metal fumes, inorganic dust, acids, paint fumes and solvents in the shipyard area.[2,6,17]

A case control-study in 2015 showed that shipyard workers exposed to respiratory hazards had significantly more respiratory signs and symptoms along with abnormal spirometry patterns in comparison to office workers at the same shipyard.[22] It may be that invasive pneumococcal diseases arise more often in individuals with already compromised lung function secondary to work-related exposure to hazardous substances and gases.

Apart from high exposure levels, most of the work tasks were conducted in confined spaces with suboptimal ventilation.[2,6,18,] A study on the effectiveness of ventilation systems on shipyards revealed that mechanical ventilation is a successful way to reduce exposure levels. The study highlights that despite the proven advantages of ventilation systems such as local exhaust ventilation (LEV) to reduce exposure to harmful substances, these systems were only sparsely on the work floor during observations. Mixing of air in the workspace is an effective alternative option to reduce the contaminated air in the breathing zone of the workers, even when the hazardous substances are not directly removed from the workspace.[24] Advanced fine dust meters can also be used to measure the degree of exposure to harmful substances in the workspaces.

One study in this review reported that health and safety risks were properly managed, but this does not indicate that the management is always properly done.[6] The outbreak report in Finland found that respiratory masks are often not properly used by shipment crew. It is remarkable that a high percentage of the pneumococcal infected workers in this outbreak reported never wearing respiratory masks during their work tasks.[2] The same was reported by the NLIA which held a shipyard inspection and observed an infected work environment with little to no usage of personal protective equipment.[18] Proper use of protective personal equipment can reduce the incidence of IPD. But wearing RPE can be uncomfortable and should be implemented with care. Multi-language communication and information about proper use of RPE and its importance is necessary in order to enhance using RPE among shipyard workers from diverse countries. It is recommendable to check the shipyard employees' lung functions on a regular basis.[22]

Furthermore, a lot of workers were present at any time and various amenities were shared among these workers.[6] The workforce of the involved shipyards varied between 1800 and 7000 employees.[2,6,17-18] The high number of employees may very well be an additional factor for dissemination. In large working force populations from various countries it may be hard to ensure adherence to hygiene protocols.[17] It may be useful to create up-to-date and easily applicable European control measure directives, so that public health measures can be implemented quickly to prevent rapid spread of IPD.

It is still unclear whether the outbreaks result from the spread between shipyard workers or whether the commensal bacteria may have become pathogenic as a result of the working conditions.[17] It may be speculated that the immune status of the shipyard workers is compromised and allows the strains to become more invasive.[22] Although we know that people with underlying disorders such as COPD are more vulnerable to pneumococcal disease[1], it is remarkable that among the infected workers only a few have underlying conditions. This suggests that environmental factors on the shipyards may have contributed to the outbreaks.

Strengths

This systematic review contributes to the knowledge about currently unknown risk factors in shipyards which can lead to IPD. This is the first time that relevant data on IPD outbreaks have been gathered and that risk factors mentioned in working environments on shipyards are determined and summarised. Identifying the shipyard work conditions that promote IPD is important to further protect these workers.

Furthermore, the search strategy of this systematic review was very extensive, in which all relevant literature has been well searched to find the studies that fit the inclusion criteria. Although only five studies were included, the overall score of the five case series was considered to be high according to the JBI critical appraisal checklists.

Limitations

One of the main limitations of this systematic review is the limited amount of included studies. Only five relevant case series of IPD outbreaks were available. This may be due to the fact that this is a fairly new occupational health risk and no systematic studies have been performed yet. As with many other systematic reviews, there may be limitations in this review through publication bias. Bias may also have occurred in the way working conditions at shipyards have been obtained. Because the included studies did not focus on the risk factors in the working environment of shipyards, certain exhibition factors may not have been taken into account. Not all variables of the employees with IPD are known. For example, the type of work, nationality, medical history and smoking status is not known for all IPD shipyard workers.

Furthermore, the validity of case series is generally considered as low compared to other study designs because of the absence of a control group. Methods of microbiological testing during the outbreaks varied between studies each using distinct combinations of sampling from blood cultures to urinary antigen tests and isolations from sterile sites.

Conclusion

The results suggest that shipyard workers have a higher risk for developing IPD and that this may be due to the working environment on shipyards. Risk factors contributing to the IPD susceptibility on shipyards found in this review were: exposure to respiratory irritants, current smoking, influenza infections, working and living in crowded environments, poor ventilation in the work environment rooms, poor usage of respiratory protective equipment and vaccination status. Measures that can be taken to limit the influence of these risk factors are pneumococcal and influenza vaccines, ventilation measures in crowded workspaces, reinforcement of proper use of respiratory protective equipment, anti-smoking campaigns, occupational hygiene measures, and improving housing conditions. These comparable outbreaks also highlight that shipyards and public health organizations need to pool the information from these outbreaks to make adequate responses to future outbreaks possible. Further studies are needed to validate the influence of different work factors on the risk of developing IPD and on the best way to prevent outbreaks. This may require case-control or cohort studies with a longer follow-up. It may be also important to see whether these shipyard workers have an additional higher risk of developing other pulmonary diseases such as COPD and lung cancer.

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Tables

Table 1. Critical appraisal score of the five included studies

	Cassir *et al.*[17]	**Linkevicius et al.[2]**	**Berild *et al.*[18]**	**Lee Eng Kiang[16]**	**Ewing *et al.* [6]**
1.Were there clear criteria for inclusion in the case series?	+	+	+	+	+
2.Was the condition measured in a standard, reliable way for all participants included in the case series?	+	+	+	+	+
3.Were valid methods used for identification of the condition for all participants included in the case series?	+	+	+	+	+
4.Did the case series have consecutive inclusion of participants?	+	+	+	+	+
5.Did the case series have complete inclusion of participants?	+	+	+	+	+
6.Was there clear reporting of the demographics of the participants in the study?	+	+	+	+	+
7.Was there clear reporting of clinical information of the participants?	+	+	+/-	+	+/-
8.Were the outcomes or follow up results of cases clearly reported?	+	+	+	+	+
9.Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	+	+	+	+	+
10.Was statistical analysis appropriate?	+	+	+	+	+
Total score:	10	10	9	10	9

Table 2. Study characteristics of the IPD outbreaks between 2015-2020

In total	Lee Eng Kiang[16]	Berild et al. [18]	Ewing et al. [6]	Linkevicius et al.[2]	Cassir et al. [17]	**First author**
	2018	2019	2017	2019	2020	**Publication year**
	case series	case series	case series	case series	case series	**Study design**
	Singapore	Norway	Ireland	Finland	France	**Country**
	3 months	3 months	3 months	7 months	2 months	**Follow- up time**
	April - June 2017	28 January - 3 April 2019	14 April - 8 June 2015	3 May - 28 November	3 January - 7 February	**Outbreak period**
106	3	20	9	37	37	**N of IPD patients**
73	3	15	7		18	**N of IPD patients hospitalized**
	N/A	4	4 3	12F 4 8	3 4 8 9N	**Serotype**
	N/A	4(ST801) 4(ST15063)	4(ST801) 4(ST205)	12F(ST6202) 4(ST801) 8(ST1480)	N/A	**sequence type**
17.623	N/A	1800	3000	7000	5823	**N of workers on Shipyard**

N= number
N/A= not available
† = deceased

Table 3. Patients characteristics part 1

Lee Eng Kiang[16]	Berild et al. [18]	Ewing et al. [6]	Linkevicius et al. [2]	Cassir et al. [17]	**First author**
3	10	4	31	19	**N of confirmed IPD patients**
0	10	5	6	18	**N of probable IPD patients**
Shipyard workers* (n=3)	interior outfitting welders	welders (n=3) heat treatment technician metal fitter cleaner supervisor	electrician (n=7) plumber (n=3) site supervisor (n=3) ship builder (n=2) interior outfitters (n=10)	interior outfitting and installers (n=6) crew members (n=4) technicians (n=7) fire guards (n=2) managers (n=2) painter(n=1) welder(n=1) carpenter(n=1)	**Occupation**
N/A	N/A	metal fume	Inorganic dust, metal fumes solvents, gases,	fumes, dust and solvents	**work related exposure**
men (n=3)	men (n=20)	men (n=9)	men (n=36), women (n=1)	men (n=36), women (n=1)	**Gender**
median 24 (range	mean 47 (range 20-	median 43 (range	median 48 (range 19-64)	median 39 (range 22-66)	**Age**
Bangladesh (n=1), Indian (n=2)	Norway(n=4) other EC (n=16)	NI(n=3),UK (n=3), other EC (n=3)	Finland (n=13), EU/EEA (n=16), Non- EU/EEA (n=2)	Italian (n=1456), Romanian(n=641), Polish (n=582), Filipino(n=466), Ukrainian(n=292)	**Nationality**
N/A	N/A	N/A	N/A	17 (6 with Influenza)	**N of patients with co-infection**

*= no further specification EU/EEA= European Union/ European Economic Area
UK= United Kingdom
EC= European countries
NI= Northern Ireland

Table 4. Patients characteristics part 2

First author	Medical history	Type of medical history	N of Smokers
Cassir et al.[17]	7 of 17	Chronic respiratory disease (n=4), heart disease (n=2) and diabetic (n=1)	9 of 17
Linkevicius et al.[2]	3 of 25	Chronic obstructive pulmonary disease (COPD) (n=1), lung cancer (n=1) and asthma (n=1)	19 of 25
Ewing et al.[6]	1 of 9	N/A	5 of 9, 1 ex-smoker
Berild et al.[18]	1 of 20	N/A	7 of 20
Lee Eng Kiang. [16]	1 of 3	Childhood asthma (n=1)	N/A

Table 5. Further elaboration underlying conditions of IPD shipyard workers

	Ewing et al.[6]	Lee Eng Kiang[16]	Berild et al.[18]	Linkevicius et al.[2]	Cassir et al.[17]	Total
No comorbidity	8	2	19	22	10	61
Comorbidity	1	1 (childhood asthma)	1	3 (COPD, lung cancer, asthma)	7 (COPD (4), Heart disease (2), Diabetes (1))	13
Total	9	3	20	25	17	74

Table 6. Further elaboration smoking status of IPD shipyard workers

	Ewing et al.[6]	Lee Eng Kiang[16]	Berild et al.[18]	Linkevicius et al.[2]	Cassir et al.[17]	Total:
Current smokers	5	N/A	7	19	9	40
No smoking or stopped smoking	4	N/A	13	6	8	31
Total:	9	N/A	20	25	17	71

Table 7. Outbreak control measures

	Treatment of infection	Name of antibiotic	Prevention vaccine	Type of confirmation	Fatality rate
Cassir et al.[17]	antibiotics	amoxicillin	V(PPV23)	UAT (n=9), isolation [a] (n=4) both (n=6)	0
Linkevicius et al.[2]	antibiotics	N/A	V(PPV23) + SIV	blood cultures (n=25)	2,7% (1/37)
Ewing et al.[6]	antibiotics	azithromycin	V(PPV23)	blood cultures (n=2) UAT (n=1), both (n=1)	0
Berild et al.[18]	antibiotics	penicillin	V(PCV13)	isolated from sterile site (n=10)	0
Lee Eng Kiang[16]	antibiotics	amoxicillin- clavulanate, ceftazidime and azithromycin	N/A	blood cultures (n=2), UAT (n=1)	0

[a] isolation from blood or endobronchial samples

V= vaccination

UAT= urinary antigen test

SIV= seasonal pneumococcal vaccine

Table 8. outbreak control measures other than preventive vaccination, antibiotic prophylaxis and antibacterial treatment in four outbreaks

	Used control measures other than vaccination/ antibiotic prophylaxis and antibacterial treatment
Linkevicius et al.[2]	Hygiene measures were maintained. A press announcement regarding IPD and vaccinations in three languages; Finnish, English and Russian. RPE for all workers exposed to metal fumes and inorganic substances. Seasonal influenza co-vaccination.
Cassir et al.[17]	Emphasizing of hand hygiene, utilization of face masks and a medical consultation for workers with respiratory symptoms. Consent forms and flyers with information in six different languages. Co- vaccination with the seasonal influenza vaccine could for some reasons not be conducted. The control measures were difficult to carry out as workers had various contractors, spoke different languages and had different national vaccination programmes.
Berild et al.[18]	Information and advice regarding IPD written in several languages to raise symptom awareness. Hygiene measures were held at the shipyard and accommodations. Local medical clinics and hospitals were notified about the outbreak and were encouraged to be proactive in treating possible pneumococcal infected cases. It was still difficult to target a specific group of workers for vaccination since various work tasks were carried out in parallel activities and in confined and poorly ventilated spaces. Therefore, all shipyard workers were targeted for vaccination during a four-day period.
Ewing et al.[6]	Information and advice regarding IPD to raise symptom awareness. Respiratory equipment (RPE) was distributed amongst employees. The setting on the oil rig made it difficult to identify a target group for control measures. The workforce/staff on the yard was large and they shared many amenities.

Table 9. Summary of the founded risk factors for pneumococcal infections on shipyards

Risk factors
Age > 65 years old The men gender Cigarette smoking Viral respiratory infection (e.g. influenza) Working and living in a crowded space Poor ventilation Poor usage of respiratory protective equipment (RPE) Exposure to respiratory irritants (e.g. metal fumes, solvents, paint fumes) Chronic diseases (e.g. chronic heart and lung disease) No proper vaccination status Type of occupation

Appendices

Appendix 1: Complete search terms

1. Main search term on PubMed:

‘Pneumonia, Pneumococcal [Mesh] OR Pneumococcal Infections [Mesh] OR Invasive Pneumococcal Disease [Mesh] AND Welding/adverse effects [Mesh]) OR Ships [Mesh]) AND Maintenance [Mesh] OR shipyard’.

2. Additional Mesh- term search links:

’(("Oxidative Stress"[Mesh]) AND "Pneumonia, Pneumococcal"[Mesh]) AND "Pneumococcal Infections"[Mesh])’
AND
‘(("Risk Factors"[Mesh]) AND "Pneumonia, Pneumococcal"[Mesh])’.

3. Keywords in Google scholar:

‘invasive pneumococcal disease "shipyard workers"

Appendix 2: JBI Critical Appraisal checklist

JBI Critical Appraisal Checklist for Case Series

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
3. Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
4. Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
5. Did the case series have complete inclusion of participants?	☐	☐	☐	☐
6. Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
7. Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
8. Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
10. Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Source: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewers Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org

Appendix 3: A visual presentation of a sample questionnaire

Sample questionnaire

Risk factor Age

Question 1: What is your Age?

<20 years - 20-30 years - 30-40 years - 40-50 years - <60 years

Risk factor Gender

Question 2: What is your Gender?

male - female - other

Risk factor exposition harmful substances

Question 3: Is there a daily exhibition of smoke/lash-smoke/organic substances/ toxic substances/fine dust?

never- regular- often- always

Question 4: What kind of work do you mainly do?

inside work- outside work - both

Question 5: How many years have you been working on the site?

0-5 years - 5-10 years - 10-20 years - 20-30 years - >30 years

Question 6: How many months do you work per year?

3 months - 6 months - 6-9 months - 9-12 months

Risk factor vaccination

Question 7: Have you been vaccinated with the pneumococcal vaccine less than 5 years ago?

yes - no - I don't know

Question 8: Have you received an influenza vaccination?

yes - no - I don't know

Risk factor smoking

Question 9: Do you smoke?

no - yes - stopped

Question 10: How many packages do you some per day?

<0,5 packages - 0,5 to 1 packages - 1 to 2 packages (s) - >2 packages

Question 11: How many years do you smoke?

<5 years - 5-10 years - 10-15 years - >20 years

Risk factor respiratory protective equipment

Question 12: When exposed to harmful substances do you use RPE?

I'm using it... never - regular - often - always

Question 13: Do you suffer from coughing?

never - regular - often - always

Risk factor comorbidities

Question 14: Do you suffer from mucus production?

never - regular - often - always

Question 15: Do you suffer from mucus production?

never - regular - often - always

Question 16: Do you have a history of asthma, bronchitis or other respiratory problems?

yes - no - I don't know

Question 17: Have you had a pneumococcal infection?

yes - no - I don't know

Question 18: You have had a pneumococcal infection, how long in advance did your symptoms start?

Longer than a week - longer than a month

Risk factors housing conditions

Question 19: Do you share your house with others during your work on the site?

No, I'm living alone - Yes I'm living with others

Question 20: With how many people are you living together?

1-4 people - 5-10 people - >10 people

In-depth assignment: Follow-up Research Proposal

Title

Individual and occupational risk factors for Invasive Pneumococcal Diseases in Shipyard workers: a study protocol for a case-control study

Acronym

SHIPD stands for Shipyard workers Health and Invasive Pneumococcal Disease.

Subsidy provider

I am writing this research proposal for the subsidizer ZonMw.

Objective of the grantor

ZonMw is an organization which finances health research in order to improve the quality and availability of healthcare. The principal clients of ZonMw are the Ministry of Health, Welfare and Sport (VWS) and the Netherlands Organisation for Scientific Research (NWO). ZonMw is an advocate for development of new medical knowledge, which can actually be used in a clinical setting. By developing medical knowledge, healthcare can improve resulting in a better treatment. Innovation stays an important theme in research for amelioration of the quality of care.[1-2]

Summary

Dear shipyard employee,

There have been several outbreaks of severe pneumonia on major European shipyards. This raises the question whether there are factors on shipyards which may increase the risk for this serious disease. In this light researchers from the University of Amsterdam are conducting a study to understand which individual and work-related factors influence the risk of contracting pneumonia. It is therefore essential that we ask shipyard employees about their working environment. That is why you, being a shipyard employee, are invited to share your knowledge about your work with us through this online questionnaire.

By completing this one-off 10 minutes survey you are enabling our team to identify possible work-related risk factors for contracting pneumonia in shipyards. If we can identify these risk factors, measures can be taken on the shipyards to protect shipyard employees from pneumococcal diseases in the future. We ask you to answer a number of work-related questions. We realize that filling in the questionnaire will take your time and effort, but with your cooperation we believe we can protect future employees from these invasive pneumococcal diseases.

We realise privacy is an incredibly important factor for you, and therefore this questionnaire is completely anonymous and confidential. Although we ask about your personal situation, we do not collect your name, address or birth date, thus guaranteeing that your answers cannot be traced back to you.

If you have any questions about this research, please contact Mrs. Zoë Zwiers

Email: c.z.zwiers@amsterdamumc.nl

Abstract

Background: Invasive pneumococcal disease (IPD) outbreaks recently occurred in shipyards. Although these outbreaks have been documented in the literature there is not much insight in the occupational risk factors on shipyards regarding IPD. In my bachelor's thesis I used previous published literature to identify risk factors for IPD among shipyard employees. I hypothesized that the higher risk for obtaining IPD for workers at the shipyard is caused by the occupational factors.

Aim: The main objective of the research is to find out what are the work-related environmental factors at shipyards that can lead to IPD among shipyard employees.
Study design: This research is an observational epidemiological case-control study.

Material and methods: The cases are European shipyard employees with IPD and the controls are a matched group of shipyard employees without IPD. We ask an estimated sample size of 400 cases and an equal number of controls to complete an one-off digital questionnaire. The questions in this questionnaire are based upon the risk factors for IPD found in my bachelor thesis. The outcome measures are statistical analysed and evaluated.

Safety and privacy: A questionnaire has a low load-bearing capacity for the test subjects since the questionnaire only has to be taken once and there are no specific risks related to filling out the questionnaire. A disadvantage of conducting questionnaires is that it is against the privacy of the subjects. In order to guarantee privacy, data is processed anonymously in a secure database server. We also indicate that the test subjects can always give up the research in the second instance.

Research team

Expertise	Role in the project
Senior researcher	Formulate research questions, design study, oversee data collection, analysis and report writing.
Junior researcher	Elaborate research design, recruitment of participants with medical doctors, data collection, analysis with statistician, draft writing of report.
Occupational Health Physician	identify pneumococcal infections in patients and recruit subjects
Pulmonary specialist	identify pneumococcal infections in patients and recruit subjects
General practitioner	identify pneumococcal infections in patients and recruit subjects
IT- specialist	Create online platform for digital questionnaire
Statistician	Data analysis

Background

IPD is caused by a gram positive bacterium *Streptococcus pneumoniae* (S. *pneumoniae*) which is asymptomatically carried by humans in the nasopharyngeal tract in 70% of the population. Almost five out of every 1000 people a year get pneumococcal pneumonia, with an incidence fifty times higher in children under 2 years of age and the elderly over 65 years of age.[3] Invasive pneumococcal infections lead to serious medical problems and reduced quality of life among shipyard workers. As a consequence these workers are not able to work anymore, resulting in a reduced workforce at shipyards. Invasive pneumococcal infections have a high disease burden and can even lead to mortality.[5]

IPD outbreaks usually occur in confined spaces such as schools, prisons and/or nursing homes.[3] One place where we increasingly see these IPD outbreaks is in shipyards. Several case series have already explicitly described IPD outbreaks in shipyards. From these described outbreaks a number of work-related risk factors have emerged that can contribute to the development of IPD among shipyard employees. [5-6-7-8-9] Nevertheless, a lot of information is still lacking about these risk factors and it is important that these risk factors are more extensively investigated in order to prevent further invasive diseases among shipyard employees. In my bachelor's thesis I used previous literature to identify risk factors for IPD

among shipyard employees. The following risk factors in shipyards for IPD have emerged: exposure to respiratory irritants, current smoking, viral influenza infections, working and living in crowded environments, poor ventilation in the work environment, poor usage of respiratory protective equipment and poor vaccination status. However, my bachelor thesis was a small literature review and a more extensive case control study needs to be conducted in which we can clearly demonstrate that these are the actual risk factors contributing to IPD.

I hypothesize that the higher risk for obtaining IPD for workers at the shipyard is caused by the aforementioned factors. From this research I particularly expect to see a significant difference in the risk factor exposure to harmful substances and no proper vaccination status. But there might be more previously unidentified work factors. That is why I am drawing up a plan for a retrospective case-control study to investigate the individual and work-related risk factors of shipyard employees for IPD in practice. I will collect data by questionnaire from both the shipyard employees with IPD and the shipyard employees who are matched but do not have IPD. By anonymity, I expect to gather answers reflecting the true circumstances of working on a shipyard.

Research objective

The main objective of the research is to find what the work-related environmental risk factors in shipyards are that can lead to IPD among shipyard employees.

Research Proposal

Material and methods

Recruitment and inclusion criteria of cases and controls

Through a large group of physicians (general practitioners, lung physicians and occupational health and safety doctors), we want to recruit participants. The inclusion criteria for this study are European shipyard employees with IPD (a) and an equal group of shipyard employees without IPD (b). Exclusion criteria are employees who do not work at shipyards.

Material and method

The participant has to sign a consent form before participation. We ask the participants to complete an one-off digital questionnaire. The questionnaire contains questions that can be translated into different languages. By translating the questionnaires, we aim to reduce the influence of the language barrier on the results. For every IPD patient (cases) we have a matched control patient who has no IPD (controls). By matching a control patient we can limit the influence of a number of non-work related disruptive variables such as age, gender and smoking. As a result, the risk of distortion of the outcomes due to these disruptive variables is smaller and the validity is higher. Both cases and controls complete the questionnaire.

Because we give both groups the same standard digital questionnaire, we can guarantee a good reliability of the research. Certain factors in exposure can be missed by means of a questionnaire. Recall bias may occur since this questionnaire is a retrospective study.

The questions in the questionnaire are based on the risk factors for IPD. The survey contains questions about: exposure to respiratory irritants, smoking status, influenza infections, working and living situation, ventilation in the work environment, usage of respiratory protective equipment and vaccination status. For the sample questionnaire, see Appendix 3.

Sample size

The five outbreaks in the included studies had a total of 106 patients with IPD. Due to the wide range of influencing factors it is important to obtain a large group of test subjects. I estimate that 300 cases and 300 controls are needed in order to achieve significant results.

Safety and privacy

A questionnaire has a low load-bearing capacity for the test subjects since the questionnaire only has to be taken once and there are no specific risks related to the questionnaire. A disadvantage of conducting questionnaires is that it is against the privacy of the subjects. In order to guarantee privacy, data is processed anonymously in a secure database server. We also indicate that the test subjects can always give up the research in the second instance.

Data collection, processing and analysis

The predictor variables are two conditions, namely the experimental (cases) and the control. The outcome variable is the score the subjects can score on the questions. Points can be scored for each multiple choice answer. These scores can then be compared with each other. The null hypothesis is that there is no difference between the scores of the two conditions and the alternative hypothesis is that there is a difference between the scores of the two conditions. By comparing this with all the questions you can find out what the risk factors are for IPD.

The survey results are to be analysed in R studio.[10] First we check whether the assumptions are violated or not. We investigate this using the Shapiro-Wilk Test to test normality and the Levene's Test for equal variances. When the assumptions are met we can test parametrically with the independent T-test/independent T-test. Here we look at the mean and the standard deviation. When the assumptions are violated, you have to test non-parametrically with the Mann-Whitney test. Here, the median and the IQR are looked at.

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In dept-assignment: Peer review report

Title: The Long-term Effects of Infantile Colic: A Systematic Review

Student Number: 12194204

Thesis received:15-06-2020

Review sent:21-06-2020

Summary:

This very clear described systematic review distributes the long term effects of infantile colic which is normally seen as a benign, often self -limiting disease.

An infant can be defined, according to the Wessel's 'criteria of three', as an infant who cries three or more hours a day, for three or more days a week and at the minimum of three weeks. Infantile colic can be very stressful for the parents and parental support, in which the parents get informed, can reduce their anxiety. The pathogenesis of infantile colic is not yet well known, so the treatment of infantile colic is still quite limited. The aim of this study is to investigate the long term effects of infantile colics so that prevention can be taken in the long run. The following long term effects are detected among individuals with a history of infantile colic; gastrointestinal problems, allergies and atopic disease, behaviour issues, behaviour issues, development problems, migraine, ear infections and family problems.

Major comments:

Introduction:

1. There are certain aspects in the systematic review that could be communicated better. In my opinion, the introduction could be worked out a little further. A little more background knowledge can be given on certain points the author mentions in the introduction. The author writes the following: 'There are various pathogenesis for infantile colic, most often it is referred to as a functional gastrointestinal disorder[6] or cow milk allergy.[7-8]'. Then no further description is given, making it unclear to the reader what the author wanted to make clear. The author also describes: 'The main type of therapy is parental support[9]'. Furthermore, no clear content of parental support is given.

Methods

2. It may be useful to also describe whether the inclusion and exclusion of articles also took into account a specific time period in which the articles were published. The study characteristics describe the following: 'All of the studies were carried out from 1990 until 2018, or which 33% was performed before the year 2000'. Has the aforementioned publication years also been a reason to include or exclude certain studies because of perhaps outdated information?

Discussion

3. Certain parts of the systematic review can be elaborated further. For example, the strengths and limitations are not finished yet. The author can still mention a number of points. So far, only limitations are described that look at the information in the included articles. The author can also look at the limitations of the systematic review itself. Such as limitations by not investigating certain aspects of the subject. In the strengths the author only describes strengths in the field of literature search and quality of research. I would mention further strengths such as the fact that many articles were included and processed and that a lot of information was obtained for this research. Also, the method has been described very clearly and systematically so that everyone could repeat this study.

4. In my opinion, the clinical relevance of the research is not yet clearly reflected in the discussion of the study. The clinical relevance can be described in this systematic review as a point at the strengths because very structured research has been done in which a lot of insight is given on a subject about which very little is known yet, namely: the long-term effects of infantile colics.

5. No recommendations for further research have yet been described in the discussion. However, this is indicated under the heading 'discussion' in the Prisma criteria.

Minor comments

General

1. In general, the review is written in correct scientific language. There are a number of language errors that I have corrected as comments in the Word file. These corrections were some language errors where the structure of the sentences was incorrect or the words were misspelled.
2. The tables at the end of the thesis are clearly legible and have a good contributing addition to the text. Only not all tables are yet properly labelled. Some tables still need a clear description of what is shown in the tables.

Results

3. At the very bottom of the tables the different definition criteria for infantry colics are given. In the results, the author always mentions these criteria but does not refer to the place where the actual description of the criteria is mentioned. Without further explanation it is not clear what these criteria mean by reading it in the first place. In my opinion it is either useful to explain the criteria immediately after they are mentioned in the results, or to refer directly behind the criteria to the place where this is further explained.

Methods:

4. The author writes the following in the method: 'All checklists are added in Appendix 2. I wouldn't write this down as not all completed checklists are actually displayed in the results. I would describe more clearly what is shown in Appendix 2, namely: empty checklists have been added to give the reader an idea of what the checklists look like.

In dept-assignment: Rebuttal of peer review

Title: Risk factors for invasive pneumococcal infections on shipyards: A systematic review

Thesis sent: 15-06-2020

Review received: 19-06-2020

Major comments:

Introduction

1. *Reviewer:* 'The introduction has a nice funnel form and gives a lot of information. It starts broad and as you read further it gets narrowed. The only comment that I have is that it starts too broad. Especially the part of the pathogenic of *S. pneumoniae* is very broad. Maybe you can shorten/summarize that a little.'

   Comment: I agree with the reviewer that the introduction may start too broad. Therefore I've deleted a few sentences in the first two paragraphs.

Methods

2. Reviewer: 'In the paragraph study selection it is not clear if you have mentioned all your inclusion criteria (I see only one), or just some of the inclusion criteria.'

   Comment: I've put all the inclusion criteria in one sentence, namely: 'Studies were included for further analysis if they reported a pneumococcal infection outbreak related to occupational exposure in shipyards.' I can imagine that the words 'all the inclusion criteria' in the following sentence made it confusing whether there were more inclusion criteria: 'Studies that did not meet all the inclusion criteria were excluded.' Therefore, I've changed the sentence to: 'Studies that did not meet the inclusion criteria were excluded.'

3. *Reviewer:* 'In the paragraph critical appraisal you mention that 6 articles were included. But then further in the paragraph it is mentioned that six articles were case-series and one article was a cross-sectional study. In figure 2 (the critical appraisal) I only see five articles. It is not clear how many articles you included.'

   Comment: The reviewer is here completely in it's right, the data in the critical appraisal (methods) and results is not consequent with figure 2 of the paragraph. I changed the number of articles in the method and results from 6 to 5, exactly as is shown in figure 2.

Results

4. *Reviewer:* 'A lot of good information is being given in the results. It will help to also make some tables so that the reader can have a nice overview of all the information.

   Comment: I agree with the reviewer that tables can give a nice overview of the results. At the time tables were not yet included because lay out measures still had to be taken in Excel and it wasn't clear to me where I had to place the tables. Therefore I've added the tables later on in the process.'

   In the results section, I think you should give clear and specific numbers. I see the words *'a lot'* and '*most*'. When reading this section I have no idea what 'a lot' or 'most' means. So maybe you can put percentages or total numbers?
   Comment: I agree with the reviewer that the described word as 'a lot' and 'most' can be ambiguous if no further amounts are given. I've deleted the words 'a lot' and 'most'. On the spot where these words were written down, I have written down other words that more clearly indicate an amount. Like: "one-third" of the... '

5. *Reviewer:* 'Is there a cut off score made for the critical appraisal? You have now defined the articles as high quality because almost all the answers were 'yes'. But what if a study had 'yes' just 5 out of 10 times?'

   Comment: At the time no described cut off score was made in the critical appraisal. I immediately agree that it is confusing to the reader if no marks on outcome scales are given. I hereby made a cut off score and added it in the methods under the heading 'Critical Appraisal'.

Discussion

1. *Reviewer:* 'I think the section which gives a summary of the evidence and a comparison with other studies, is very broad. Maybe you can summarize this a little bit more. Otherwise it feels as if I am reading your results section again.'
   Comment: I agree. I've reread the discussion and several pieces of information can indeed be deleted. I've shortened the section which gives a summary of the evidence because this was already described in the results.

Minor comments:

Methods

1. *Reviewer:* 'In the paragraph critical appraisal you make reference to figure 2. But I can't find a figure 2, only a table 1. I think you need to change the name of the figure.'

Comment: Agreed. At the time of the review lots of tables and figures were still not included nor properly labelled. I've added the missing tables and figures later on and labelled them.

2. *Reviewer: '*Can we find the google spreadsheet table somewhere?'
    - "The selected data … google spreadsheet table." (paragraph; outcome measures)
    - "Information based on … google spreadsheet table" (paragraph; data extraction)

    Comment: I agree with the reviewer that the tables were still missing. I've added the google spreadsheet tables in Excel and inserted them later on in this review.

3. *Reviewer: '*In the flow diagram (figure 1) you can maybe add why certain studies were excluded after full text analysis.'

    Comment: Agreed. The flow diagram was still missing information why certain studies were excluded after the analysis. I've added the exclusion reasons to the flow diagram.

Results

1. *Reviewer:* 'I think you should leave the words *'it was interesting'* out of your results section. It is an opinion and it is better in place in the discussion, I think.'
    - "***It was interesting*** … (range 3-10 days)" (paragraph; serotypes)
    - **"It is interesting** to see that only 3 from the 25 infected shipyard workers always used a respiratory mask while working." (paragraph: use of protective equipment

    Comment: I agree with the opinion of the reviewer that opinions should not be given in the results. Therefore, I've deleted the words 'it was interesting..' and replaced the words 'it is interesting..' to 'This shows..'.

2. *Reviewer:* 'The paragraph 'results of critical appraisal' should be mentioned earlier in the results.'

    Comment: Agreed. This section was set in the wrong place. I've added the section 'results of critical appraisal' to the methods under the heading 'critical appraisal'.

3. *Reviewer:* 'There are figures/tables in the results section without any description. It would be good to add a description and the studies so that the reader knows what the figure/table is about.'

Comment: I agree with the reviewer that several tables and figures still need to be labelled. I've labelled all tables and figures later on and placed them in on the right spot.

In dept-assignment: Peer support

Wat waren de voornaamste kritiekpunten die ik kreeg?

Ik kreeg de volgende kritiekpunten van mijn medestudenten tijdens de presentatie:

1. Heel vaak ‘uhmmm’ gezegd, dit komt een beetje slordig over.
2. Vaker oefenen dan weet je sneller wat en hoe je iets gaat zeggen.
3. Lange zinnen in de dia’s wel laten staan maar de belangrijke woorden wel onderstrepen zodat het duidelijk is waar de luisteraar op moet letten.
4. Rijen op de dia’s naast elkaar zetten en niet onder elkaar. (staat overzichtelijker)

Was ik het eens met die kritiek?

Ik ben het eens met de vier kritiekpunten die ik heb gekregen van mijn medestudenten.
Ik heb al vaker gehoord dat ik tijdens het presenteren erg in mijn hoofd kan zitten. Ik moet dan lang nadenken voordat ik iets ga zeggen. Dit resulteert bij mij in het zeggen van ‘uhmmm’ wat als storend gezien kan worden door luisteraars. Ik ga proberen dit minder vaak te zeggen door mijn presentatie vaker te oefenen. Ik zie in dat ik de eerste twee feedbackpunten kan verbeteren door meer te oefenen. De laatste twee feedbackpunten heb ik aangepast in mijn presentatie slides.

Hoe heb ik dit kunnen gebruiken in de daadwerkelijke voordracht?

Op advies van mijn medestudenten heb ik de presentatie vaker geoefend. Doordat ik dit had gedaan ben ik zelfverzekerder mijn voordracht in gegaan. Ik wist sneller wat ik wilde zeggen en ook hoe ik dingen wilde verwoorden.

Was je tevreden met je feedback op je medestudent?

Ik heb mijn beste gedaan om mijn medestudenten zo goed als mogelijk van feedback te voorzien.
Ik heb gemerkt dat mijn medestudenten veel hadden aan mijn feedback. Het hulpschema op canvas heeft zeker ook goed geholpen bij het geven van feedback aan mijn medestudenten.
Door elkaar feedback te geven hielpen we elkaar verder met het voorbereiden van de daadwerkelijke voordracht. Ik vond dit een erg prettige manier van voorbereiden.