Faculté de santé publique

Understanding the value of vaccination for improving health equity in older adults: the role of the social determinants of health for vaccine preventable diseases.

Mémoire réalisé par
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Le plagiat

Je déclare sur l'honneur que ce mémoire a été écrit de ma plume, sans avoir sollicité d'aide extérieure illicite, qu'il n'est pas la reprise d'un travail présenté dans une autre institution pour évaluation, et qu'il n'a jamais été publié, en tout ou en partie.

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Table of Contents

1. Introduction

1.1. Objectives

The aim of this work is to understand the value of vaccination beyond cost-effectiveness, in terms of social equity in older adults in North-Western, high-income countries. Health disparities may be observed at disease incidence, access to vaccination or in the outcome of vaccination. This work explores health disparities in the susceptibility to respiratory infectious disease in older adults.

The role of social determinants of health in susceptibility to infectious diseases will be investigated in order to identify the social inequities that vaccination might reduce or erase. This will support ongoing reflection on the suitable health equity criteria to be used for decision making in Health Technology Assessment (HTA) on vaccines.

The population of interest is the older adult population, aged of 50 years old and above. Older adult population has been extended to include the "pre-aging period" (from 50 to 64 years) as there is a high heterogeneity when assessing progression and consequences of infection problems with age.

The focus is a non-pandemic crisis context and concerns vaccine-preventable respiratory diseases with a high burden in older adult population, this includes infections caused by Influenza virus, Streptococcus Pneumoniae, and RSV.

This introduction will provide some background on current knowledge on equity assessment in context of HTA, on the specificities of older adults population and on respiratory infectious diseases preventable by vaccination in older adults to contextualize the research question.

1.2. Health technology assessment and the value of vaccination

Numerous factors drive increases of public health costs. A few examples are the progress in research and development and the subsequent growing number of health technologies available, the increase in life expectancy, the aging of the population with increased prevalence of chronic diseases, etc. As public health resources remains limited, decision-makers have to set priorities and make choices in terms of re-imbursement and access to new therapies(1). They inform their choices through health technology assessment (HTA) relying mainly on economic evaluations using cost-effectiveness analysis (CEA)(2, 3).

Pathway for vaccines market access leading to recommendation and reimbursement of national immunization programs is complex and can take time(4). In Europe, vaccine market access is led nationally, with each member state's individually deciding on the inclusion of a vaccine within their national immunization programs. A common step involves a recommendation by the National Immunization Technical Advisory Groups (NITAG) in each country. NITAG is usually the entity conducting HTA-like process including CEA in the context of vaccines, in complement or replacing HTA bodies. NITAG usually contribute to horizon scanning and early advise when applicable. They recommend inclusion of a vaccine in the national immunization program and make recommendations on fundings(4).

The CEA aims to evaluate jointly health and costs impacts when considering the adoption and use of healthcare technologies. CEAs always evaluate alternative choices in comparison to the standard of care and focus on incremental costs and incremental benefits. Benefits in health are usually expressed in quality-adjusted life year (QALY) gains. QALY can be defined as "*the fraction of perfectly healthy life-year that remains after accounting for the damaging effects of an illness and condition*"(3). QALY can be used to measure the benefit of any health technology across different health conditions and for various health technologies(3, 5).

The ISPOR (International Society for Pharmacoeconomics and Outcomes Research) special taskforce has highlighted the complexity of assessing the value of health and has identified a series of elements that warrant consideration in the value assessment of medical technologies beyond costs and QALYs: workplace productivity, adherence improving factors, reducing uncertainty due to a new diagnostic, fear of contagion, insurance value, severity of the disease, hope, real option value, equity and scientific spillovers(3). The importance of these elements may vary and weight differently depending on the perspective of the evaluation: e.g., traditional payer's perspective, patient or societal perspective(3).

Broadening the view over and above QALYs and costs is particularly relevant to capture the value of vaccination. Recent experience with covid-19 pandemic has highlighted that vaccination programs can provide significant health gains to individuals and society(6). However, despite such benefits of vaccination against infectious diseases are well recognized(7), benefits of vaccination are partly or inconsistently considered in current HTA, with differences between countries(8). Such failure to identify, measure and value wider benefits of vaccination bring a risk of underinvestment in vaccines and a lost opportunity to gain from their societal benefits. Therefore, active research is ongoing to identify and increase knowledge on the elements of the value of vaccination to be consider in HTA in order to better capture the broader spillovers of vaccination(8-11). Based on a literature review and experts' consultation, Beck et al. have proposed a new framework to better capture the value of vaccination with a goal to identify concepts of value that could be used in economic evaluation in a near to mid-term future in HTA(8).

This new framework is organized across 3 dimensions(8) (see figure 1):

> <u>Dimension 1</u>: Conventional concepts and elements included in the HTA/CEA of vaccines from a payer perspective i.e., health gains to vaccinated people, healthcare costs savings (direct savings in medical costs), societal health gains beyond vaccinated individuals like herd immunity.
>
> <u>Dimension 2</u>: Conventional concepts and elements included in the HTA/CEA of vaccines with a societal perspective i.e., health related productivity gains for vaccinated individuals, indirect health and economic gains for caregivers and family/household, societal health gains beyond vaccinated individuals like disease eradication.
>
> <u>Dimension 3:</u> Novel concepts and elements from a wider and extended societal perspective i.e., other productivity gains, community and health systems benefits, macro-economic benefits (vaccine-attributable financial risk protection, decrease antimicrobial resistance, peace of mind, scientific spillovers…)

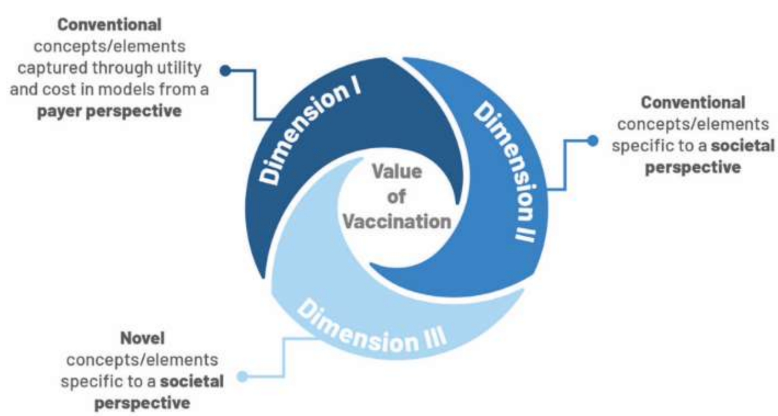
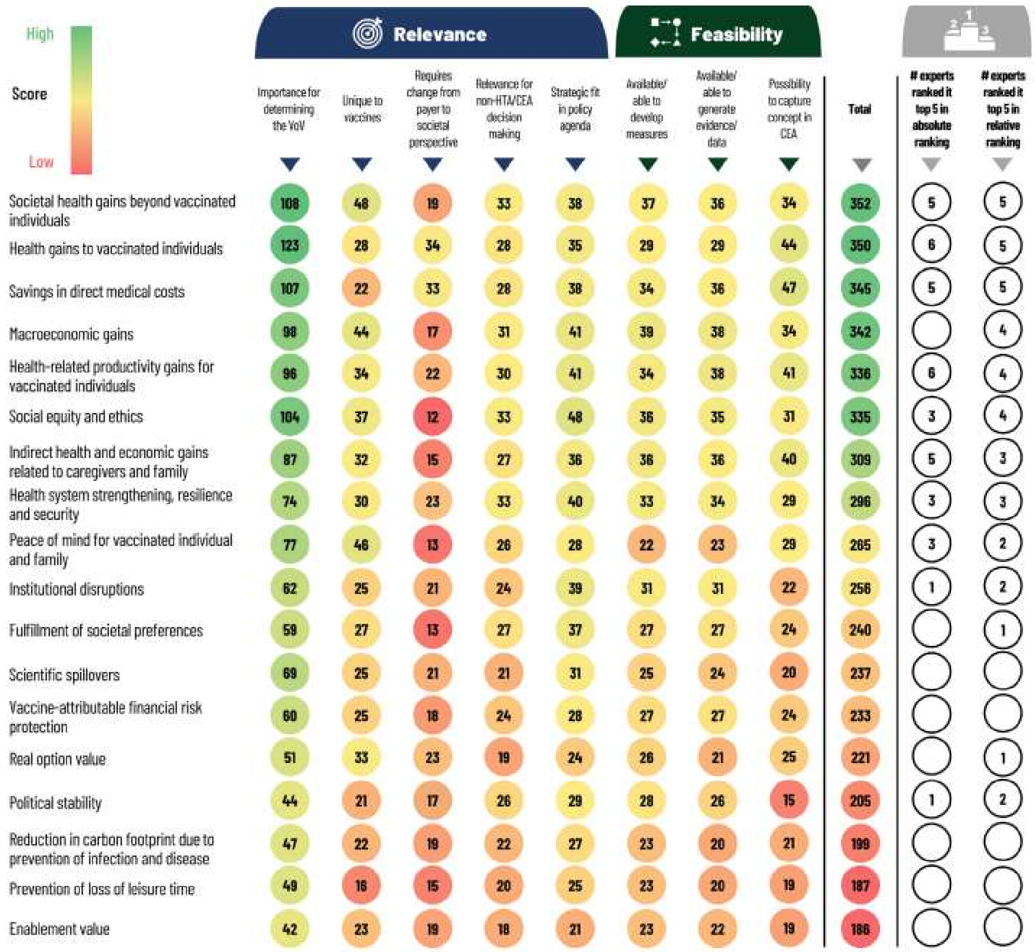


Figure 1: "*Framework to capture the value of vaccination relevant to HTA/CEA*" proposed by Beck et al. (from Beck et al., 2022)(8)

The analysis of the value concepts included in the three dimensions has been pursued by Postma et al. to determine if and how these concepts are used in high income countries with well-established HTA systems(9). The authors have reviewed current guidelines for HTA or health economic assessment of vaccines in Australia, France, Germany, Netherlands, Spain, the United Kingdom (UK) and the United States of America (USA), and they have validated their mapping with experts from the represented countries. Figure 2 shows the list of concepts proposed for value of vaccination assessment in the three dimensions mentioned above and their inclusion across countries.

Figure 2*: "Inclusion of concepts of the value of vaccination in HTA/CEA across countries.* ***a****:* ***e.g***.*, herd immunity;* ***b: e.g***.*, disease eradication****; c: e.g.,*** *decrease in AMR****; ACIP:*** *Advisory Committee on Immunization Practices****; AMR:*** *antimicrobial resistance;* ***CEA:*** *cost-effectiveness analysis;* ***HTA:*** *health technology assessment;* ***VoV:*** *value of vaccination"* (from Postma et al., 2022)(9).

The experts that the authors consulted have highlighted the need for a pragmatic stepwise approach to include broader value-elements into HTA/CEA in the near to mid-term future. The concepts have therefore been prioritized using their relevance for decision-making and their feasibility as criteria for classification as shown in figure 3(9).



	Relevance					Feasibility					
	Importance for determining the VoV	Unique to vaccines	Requires change from payer to societal perspective	Relevance for non-HTA/CEA decision making	Strategic fit in policy agenda	Available/ able to develop measures	Available/ able to generate evidence/ data	Possibility to capture concept in CEA	Total	# experts ranked it top 5 in absolute ranking	# experts ranked it top 5 in relative ranking
Societal health gains beyond vaccinated individuals	108	48	19	33	38	37	36	34	352	5	5
Health gains to vaccinated individuals	123	28	34	28	35	29	29	44	350	6	5
Savings in direct medical costs	107	22	33	28	38	34	36	47	345	5	5
Macroeconomic gains	98	44	17	31	41	39	38	34	342		4
Health-related productivity gains for vaccinated individuals	96	34	22	30	41	34	38	41	336	6	4
Social equity and ethics	104	37	12	33	48	36	35	31	335	3	4
Indirect health and economic gains related to caregivers and family	87	32	15	27	36	36	36	40	309	5	3
Health system strengthening, resilience and security	74	30	23	33	40	33	34	29	296	3	3
Peace of mind for vaccinated individual and family	77	46	13	26	28	22	23	29	265	3	2
Institutional disruptions	62	25	21	24	39	31	31	22	256	1	2
Fulfillment of societal preferences	59	27	13	27	37	27	27	24	240		1
Scientific spillovers	69	25	21	21	31	25	24	20	237		
Vaccine-attributable financial risk protection	60	25	18	24	28	27	27	24	233		
Real option value	51	33	23	19	24	26	21	25	221		1
Political stability	44	21	17	26	29	28	26	15	205	1	2
Reduction in carbon footprint due to prevention of infection and disease	47	22	19	22	27	23	20	21	199		
Prevention of loss of leisure time	49	16	15	20	25	23	20	19	187		
Enablement value	42	23	19	18	21	23	22	19	186		

Figure 3: "*Concepts of value of vaccination in HTA/CEA ranked based on "relevance for decision-making" and "feasibility of measurement" criteria scores and concepts most frequently in top-five absolute and relative ranking.* ***CEA****: cost effectiveness analysis****; HTA:*** *health technology assessment;* ***VoV****: value of vaccination* ***Absolute ranking:*** *concepts ranked in order of importance;* ***Relative ranking:*** *concepts ranked after scoring each concept against the eight weighted criteria.*" (from Postma et al., 2022)(9).

Regarding outcomes, Postma et al. proposed three concepts to be considered for inclusion in HTA namely 1) macroeconomic gains (e.g. benefits to the economy and/or society), 2) social equity and ethics (e.g. equal distribution of health outcomes, reduced health/financial equity gaps) and 3) health system strengthening, resilience and security (e.g. efficiency gains, reduced disruption, increased capacity)(8, 9).

This master thesis is a continuation of the research work started by Beck et al. and Postma et al. that aimed to better capture the value of vaccination in HTA. Here, the aim is to increase the knowledge on social equity of vaccination with a focus on vaccine-preventable infectious respiratory diseases in the population of older adults in developed countries.

1.3. Equity in health technology assessment for vaccines

Health equity is an important objective of healthcare systems in many countries(12-15). The World Health Organization (WHO) defines health equity as "*the absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g. sex, gender, ethnicity, disability, or sexual orientation). Health is a fundamental human right. Health equity is achieved when everyone can attain their full potential for health and well-being."(16).*

Healthcare systems aim to change systems and policies when they result in health disparities that can be considered as unfair(15). Health disparities are defined by the Center for Disease Control and Prevention in United states (CDC) as "*preventable difference in the burden of disease, injury, violence or opportunities to achieve optimal health that are experienced by populations that have been disadvantaged by their social or economic status, geographical location and environment"(14).*

As health disparities are considered as preventable through societal efforts, there is a growing interest in decision bodies in charge of HTA to better understand who gains and who loses from health programs, in order to better anticipate and address health inequalities. An important body of knowledge is currently under development to help decision makers to assess where to make trade-offs between classical cost-effectiveness analysis (CEA) and equity in the distribution of health-related outcomes(17). It takes into account that any decision in healthcare program or public health policy will potentially affect two groups of patients: those who will benefit directly from the new treatment and those who will bear the opportunity cost due to the benefits/resources (re-)allocation(17).

In conventional CEA framework, assessment of health benefits and costs are made for the general population, using the standard judgement that "a QALY is a QALY". Population-level health gain is the unweighted sum of all individual health gains. Individuals and their health gains are treated equally, following the principle of "horizontal equity"(17-19). As such, it does not address the "vertical equity" principles, i.e., "treating unequal individuals unequally", with a greater focus on those with greater needs.

A potential solution is to include health equity trade-off between cost-effectiveness and an alternative health equity objective when assessing a health technology(17). Such a trade-off can be illustrated through a health equity impact plane as proposed by Cookson et al. (see figure 4, from (17)) where the vertical axis shows the cost-effectiveness of a health program, and the horizontal axis shows the net health equity impact. In this graph, cost-effectiveness is expressed as “net total health impact” i.e., “*the total health benefits of the program minus the forgone health benefits that would have been obtained by spending the same money on other health programs”(17)*. The net health equity impact is the “*net impact of the alternative health equity objective after allowing for program opportunity costs and benefits*”(17). A policy falling in quadrant I improves both health and equity while a policy falling in quadrant III harms both. Policy falling in quadrant II or IV would require a trade-off between cost-effectiveness and equity in the decision making(17).

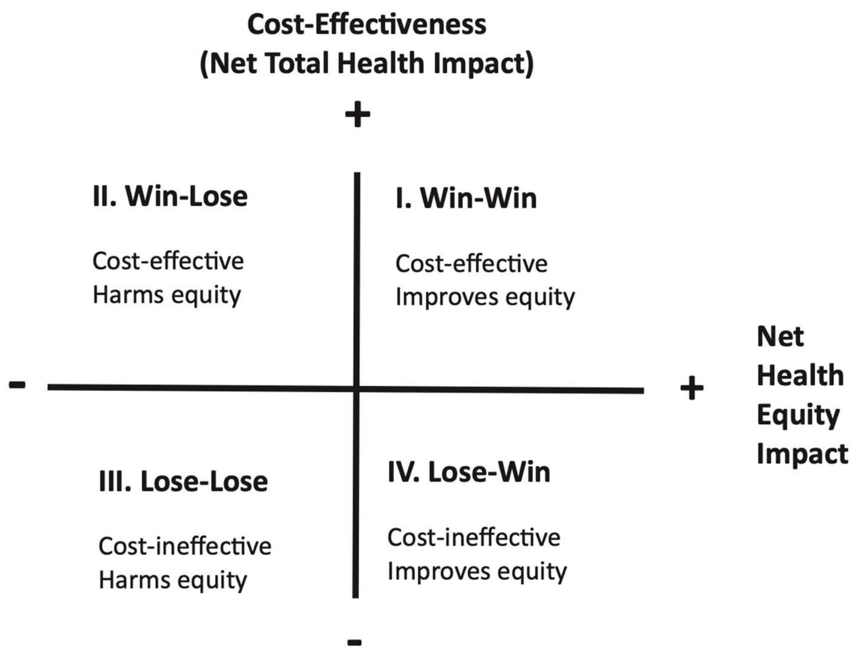


Figure 4: *“Health equity impact plane.”* From Cookson et al., 2017(17).

Conventional CEA does not systematically take into consideration how the health benefits and the opportunity costs are distributed across the different strata within the general population. There are potential health equity implications linked to such distribution as illustrated in figure 5 from Cookson et al.(17). It shows two situations where the opportunity costs are distributed either equally (case 1) or unequally (case 2) in the population. “Gross Health Benefit” measurement (in upper circles) shows only distribution of program benefits, without considering the distribution of opportunity cost. It provides a partial information that may hide the broader social impact of the adoption of the program. With "Net Health Benefit" measurement (in the lower circle), the distribution of health opportunity cost is taken into account in the assessment of benefits of the program. While Gross Health Benefits does not discriminate between case 1 and 2, Net Health Benefits measurement highlight that in case 1, health opportunity costs of the new program are equally distributed and bring social value while in case 2, fundings for new program comes from a program that benefits disproportionately the socially disadvantaged groups resulting in a lower net health benefit for the poorer groups with the new program. The analysis of the efficiency/equity trade-off will therefore ensure a more informed decision in terms of social equity for resource allocation.

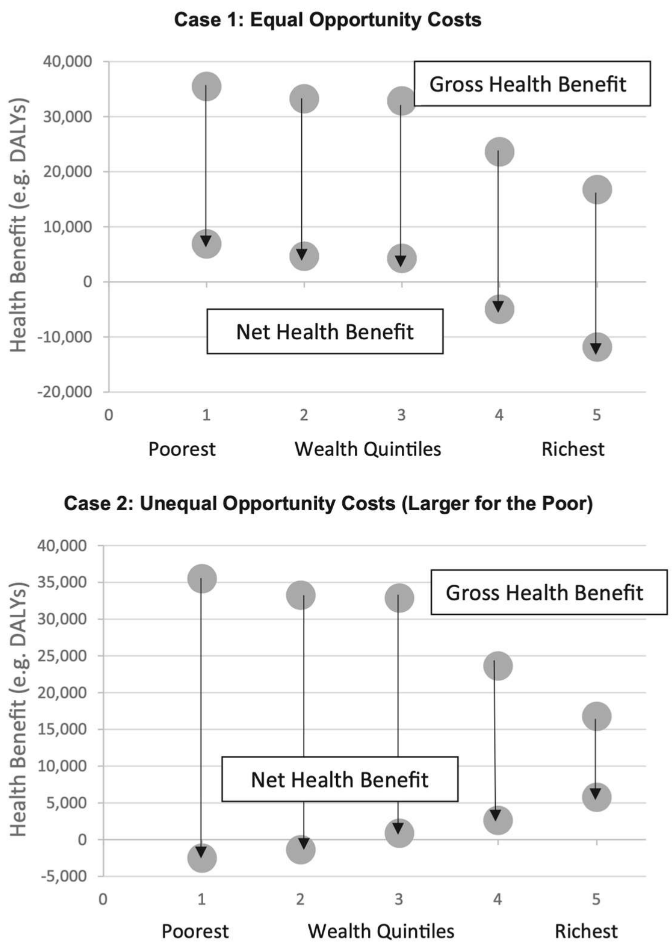


Figure 5: "*Health equity implications of opportunity costs: hidden traps.*" From Cookson et al., 2017(17).

Health conditions and outcomes are known to be influenced by non-medical factors called social determinants of health. WHO refers to them as "*the conditions in which people are born,* *grow, work, live and age and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems."(20)*. The main social determinants of health are the place of residence, race and ethnicity, occupation, gender, religion, education, socio-economic status and social capital.

When speaking about vaccination, disadvantaged groups may experience differences at several stages i.e., in their susceptibility to infectious diseases, in their access to vaccines and in health outcomes as illustrated in "*The staircase of Health Inequality Impact*" by Richard Cookson and James Love-Koh. (see figure 6)(21).

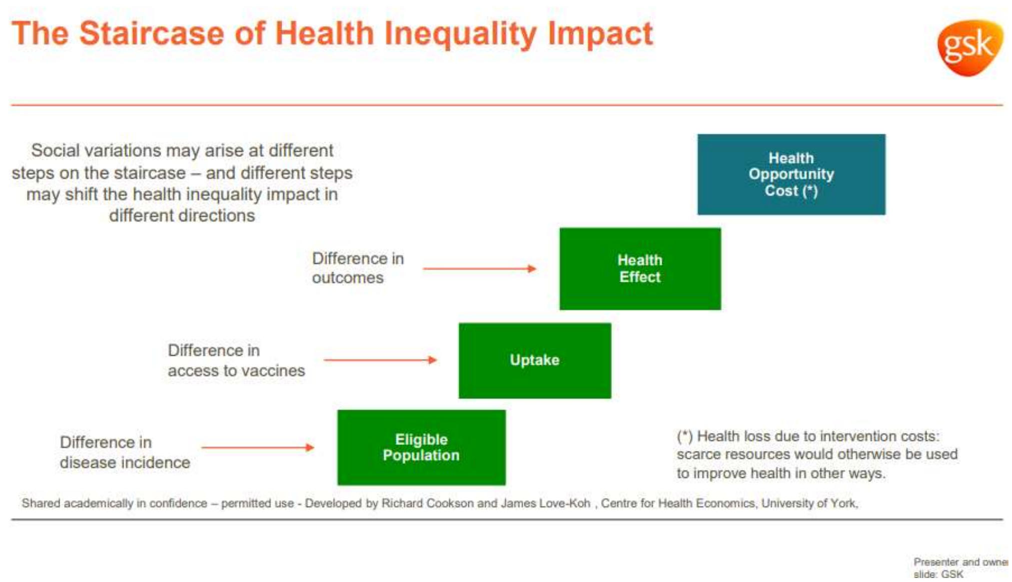


Figure 6: "*The Staircase of Health Inequality Impact*" from Richard Cookson and James Love-Koh, 2022 (21).

The assessment of the impact of vaccination in terms of health equity is currently limited by a lack of knowledge of the relevant equity stratifiers in the case of vaccine preventable diseases(22). In many countries, there is no guidance on which risk factors to consider and this limits evidence generation and decision making.

This master thesis will focus on the first step of "*the Staircase of Health Inequality Impact"* aiming to identify which social determinants of health are relevant in the epidemiology of vaccine-preventable diseases. The population of interest for this research are older adults in developed North-Western countries, with a focus on the identification of risk factors for community acquired respiratory infections.

1.4. Older adult population

The definition of older adult population varies in the literature. It often refers to adults aged 60 or 65 years old and above (23-26). Some studies have further sub-classified the older adults in "youngest-old" (65 to 74 years), "middle-old" (75 to 84 years), and "oldest-old" (85 years and above)(23). When referring to infectious diseases and vaccination topics, older adult population might include the "pre-aging period" defined as the age group from 50 to 64 years to better understand the progression of infection problem with age(27, 28). Rationale is that vaccine preventable disease like influenza or pneumococcal pneumoniae can increase the risk of non-communicable disease and/or exacerbate existing chronic diseases such as chronic obstructive lung disease or cardiovascular disease. Prevalence of such comorbidities starts to increase in adults over age of 50(29). Moreover, generating knowledge on this pre-aging adult group helps to better identify individuals prone to developing immunosenescence (weakened immune system) and those who can mount successful immune response in response to a vaccine or infectious agent(27). Such knowledge is suitable to design and/or adapt vaccination strategies at best for middle-aged and older adults.

1.4.1. Demography

People worldwide are living longer and populations around the world are aging at a faster pace than before. On the opposite, it is expected that the number of newborns will barely increase and even decrease in the near future. These demographic changes are called demographic transition(30). The Northern and Western countries are currently more advanced in the demographic transition as illustrated by median age of the population in figure 7(31). If these richer countries have benefit from the demographic transition in the last decades, they will now face the demographic problems of an increasingly larger share of retired people who are not part of the labor market. This demographic transition will therefore have an impact on several dimensions of society, especially on the health and social systems(32, 33).

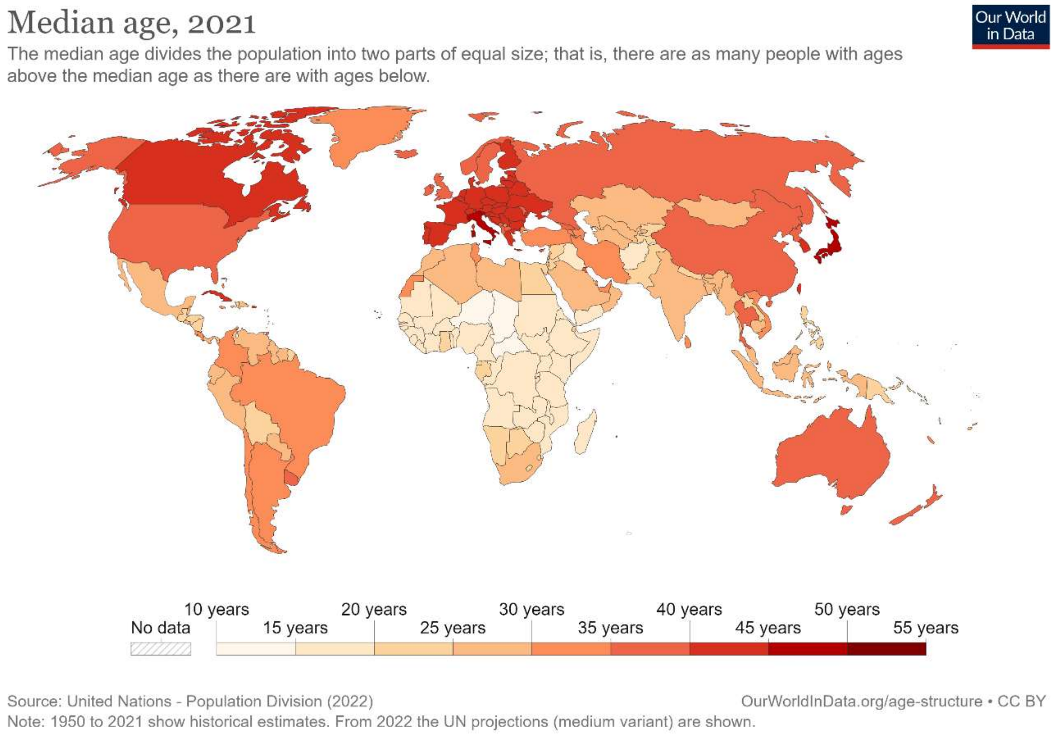


Figure 7: Median age of the population across the world (from Our World in Data, 2022)(31).

Proportion of older adults will increase worldwide in the coming years, but the proportion of older adults will be more important in developed countries. Figure 8 shows the expected evolution of the median age from 1950 to 2100 across a set of representative countries.

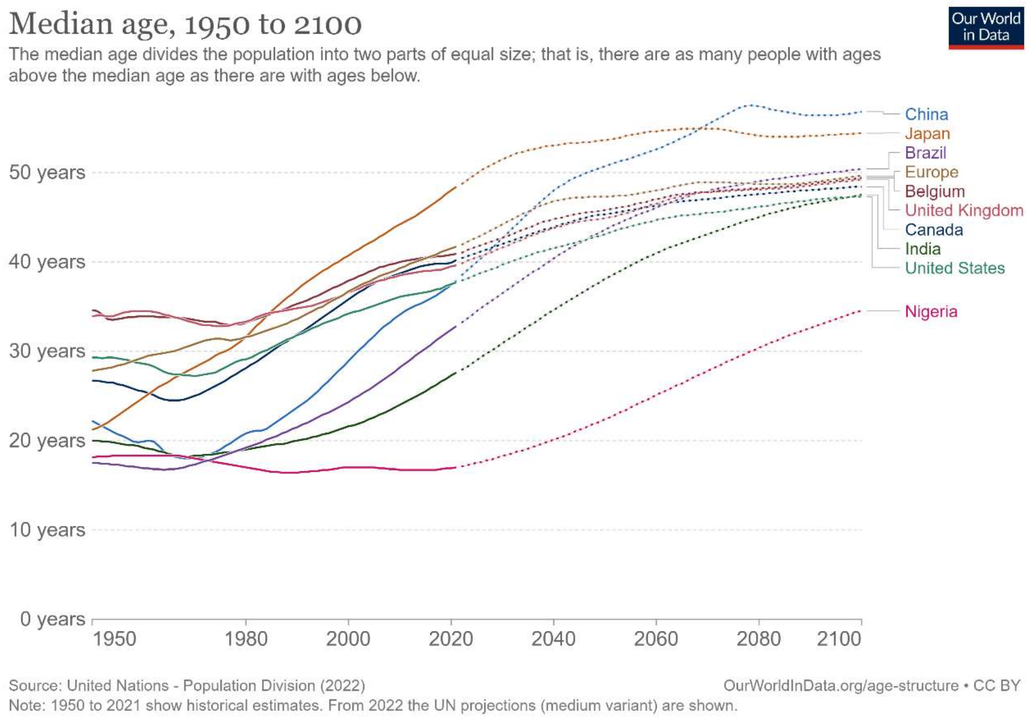


Figure 8: Expected evolution of median age from 1950 to 2100 in China, Brazil, India, Japan, Europe Belgium, the UK, the USA, Canada and Nigeria. (from Our World in Data, 2022)(31).

1.3.2. Aging and overall health status associated with aging

The biological process of aging triggers various functional and anatomical changes resulting in a gradual decrease in physical as well as mental capacity of older adults with a growing risk of disease onset and death(24, 34).

Common health conditions associated with age are sensory changes (hearing loss, decrease of visual acuity, decline of vestibular function), muscle strength and fat changes, immunosenescence and urologic changes.

Common chronic conditions like cardiovascular disease, hypertension, cancer, osteoarthritis, osteoporosis and dementia are more frequent in aged population(24, 35-37). Normal age-related changes and accumulated pathologies contribute to functional changes in older adults who experience declined walking speed, mobility disability, disability in activity of daily living, falls, frailty and urinary incontinence(24, 35, 38).

Vulnerability to infections is higher in older adult population. Incidence and severity of infectious diseases including, among others, skin and soft-tissue, urinary-tract, respiratory-tract and gastrointestinal tract infections increase(39-41). This is driven by functional changes and the weakening of immune system observed with aging due to immunosenescence which leads to a progressive reduction of the ability to mount effective antibody and cellular immune response(42, 43). Management of infectious diseases is complicated by age-related organ system changes, delayed diagnostic, diminished response to therapy or because older adults are often under multiple medications for underlying illnesses(39, 40).

Mental health is also impacted by aging with cognitive symptoms like mild-short term memory loss, word-finding difficulty, and slower processing pace. Normal cognitive aging does not lead to dementia, but rates of dementia increase with age. Not all brain function declines with age: wisdom and knowledge, empathy and altruism may increase with age(35, 44). Changes from normal brain aging can affect driving safety, expose older adults to financial exploitation and reduce their capacity to understand complicated medical information(35). Depression is not a typical consequence of aging but may result from life events that occur with aging (disease, loss of autonomy, loss of a loved one…) and prevalence of depression is high in the older adult population(24, 35). On top of biological and physical evolution, older adults are often exposed to social life transitions such as retirement, loss of income, relocation to more appropriate housing and to the death of friends, family members and/or partners(24).

The main causes of death in older adult population, accounting for 85% of them, are cardiovascular diseases, cancer and respiratory system diseases(26, 27).

The process of aging is not linear and may vary between individuals and with environmental and lifestyle factors (like diet, physical activity, tobacco use…)(24, 28, 45-47). Genetic and social factors (like education and occupation) may be more or less protective(28, 48). For instance, despite a correlation between greater age and increased morbidity, some people live into their 70s, 80s and 90s in good health with active lifestyles and willingness and ability to work(46). This high heterogeneity in the health-related quality of life in the population older than 50 has been nicely illustrated by Lowsky et al. (2014) who showed that the 90th -10th percentile of the EQ-5D[1] range tends to widens with age, with the widest range in the EQ-5D

[1] The EQ-5D is a standardized measure of health-related quality of life developed by EuroQol group. It is composed of 2 elements: a descriptive system of 5 dimensions (mobility, self-care, ability to perform usual activities, pain/discomfort, anxiety/depression) leading to a quality of life score and a visual analogue scale where respondents self-assess their general health status on a scale from 0 to 100.

score among 85+ (see figure 9 extracted from their publication)(46). The authors determined variation in overall health of individuals through a 3-points scale score for each dimension (well-being, mobility, self-care, ability to perform usual activities, pain/discomfort and anxiety/depression)(46).

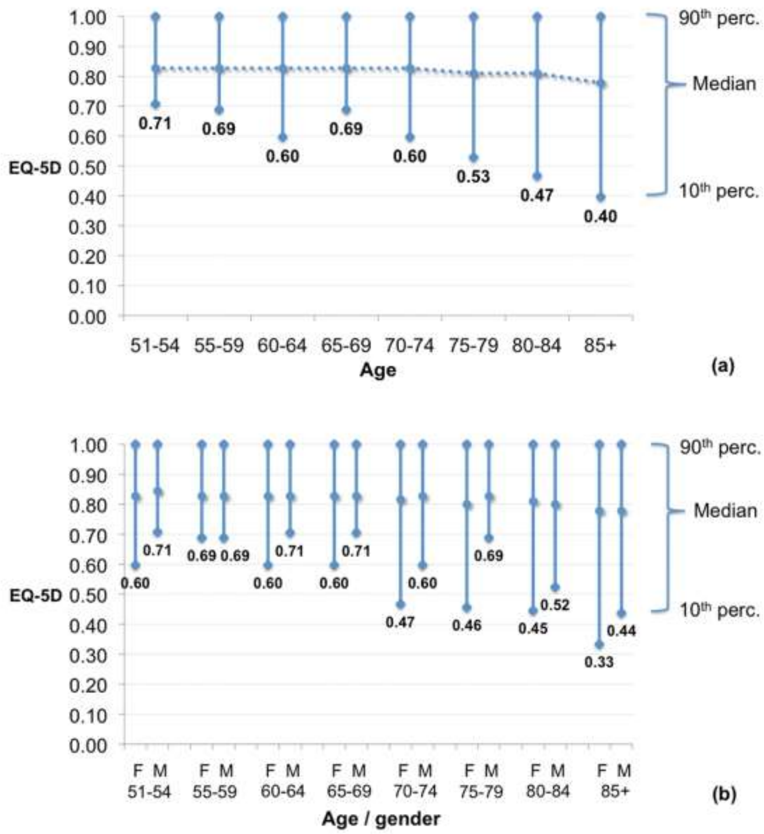


Figure 9: Quality of life score as measured with the EQ-5D by age. *"Upper, middle, and lower points indicate the 90th percentile, median, and 10th percentile EQ-5D within each age group: (a) gender is combined; (b) separate ranges by gender. Source: 2003 Medical Expenditure Panel Survey."* (From Lowsky et al., 2014) (46)

Increased attention is paid in scientific literature to evaluate how strong the link is between chronological age and health decline. The notion of 'biological age' might be a better indicator of health status than chronological age. A variety of biomarkers that are considered as biological age predictors have been identified, including epigenetic clock(28). The knowledge of biological age predictors will contribute to better understand the heterogeneity of the aging process and may provide new tools to monitor the biological aging process, with the ultimate goal to improve individual quality of life and the health span, and to decrease the healthcare burden(28).

Besides the differences in genetic inheritance or lifestyles, the heterogeneity in health status within older adults may also be a consequence of the cumulative disadvantages or advantages over the lifecycle. Physical and social environments where people live may impact their health directly but also indirectly through barriers or incentives that will affect behavior, decisions and opportunities. The relationship with environment varies with sociodemographic characteristics such as family conditions, sex, ethnicity, etc.(49). For example, healthy life expectancy varies with sex, education, and race. Women aged 70 and over experience a higher disability level than men. The observed sex differences in functioning may be due to differences in the likelihood to be institutionalized: older women are more likely to be institutionalized than older men because of the sex difference in mortality and their higher risk to be widowed and not having a caregiving spouse(50). Furthermore, life expectancy and disability-free life expectancy differ with the socio-economic background. Those of higher status are more likely to live in old age with a better physical functioning(49, 50). On the other hand, the less educated live shorter total and active lives. When comparing Black and non-Black in the US older adult population, there is a higher prevalence of disability among Black people with low education due to socio-economic difference impacting disability onset and recovery(50).

Consequently, those with the greatest health needs in older age may have a lower access to the resources they require. To ensure that enjoying a longer and healthier life is not limited to a privileged few, equity is a major objective and is included in public health initiatives to improve the health status of older adults(51, 52). The concept of "*healthy aging*" has been developed by the WHO. It is defined *as "the process of developing and maintaining the functional ability that enables well-being in older age*". Functional ability refers to "*health-related attributes that enable people to be and to do what they have reason to value*"(49). Functional ability is composed of the intrinsic capacity (mental and physical capacity of a person) and environmental characteristics (related to home, community and society). A global long-term strategy and action plan to improve health in older adult population taking into account the wide and various needs of such population has been developed(49, 53, 54).

1.4. Respiratory infectious diseases preventable by vaccination in older adults

As mentioned earlier, older adults are more sensitive to respiratory infections due to changes in their respiratory and immune system with aging(34, 43). Low respiratory tract infections like bronchiolitis and pneumonia represent a high medical burden in the older adult population because it triggers a high number of hospitalizations in the winter period, especially for those living in cluster environment like nursing homes(43). Patients often recover badly and remain weak when leaving healthcare facilities, and their long-term poor overall health condition can lead to a high cost for society(27, 41).

While influenza and pneumococcus are vaccine preventable diseases, they remain a significant cause of morbidity and mortality among the older adult population(55). Respiratory syncytial virus (RSV) is also an important cause of morbidity and mortality in older adults for which a prophylactic vaccine will be soon available(56).

1.4.1. Respiratory infections in older adults

Main respiratory infections in older adults are pneumonia, acute exacerbation of chronic obstructive pulmonary disease (COPD) and non-pneumonic respiratory tract infections. Etiology includes bacteria, respiratory viruses and atypical pathogens, with a significant proportion involving more than one pathogen(57). When global burden of disease was assessed by the WHO before covid-19 pandemic, lower respiratory tract infections including pneumonia and bronchiolitis have been reported as the fifth cause of mortality worldwide in population older than 60, as shown in figure 10 extracted from Beard et al.(54).

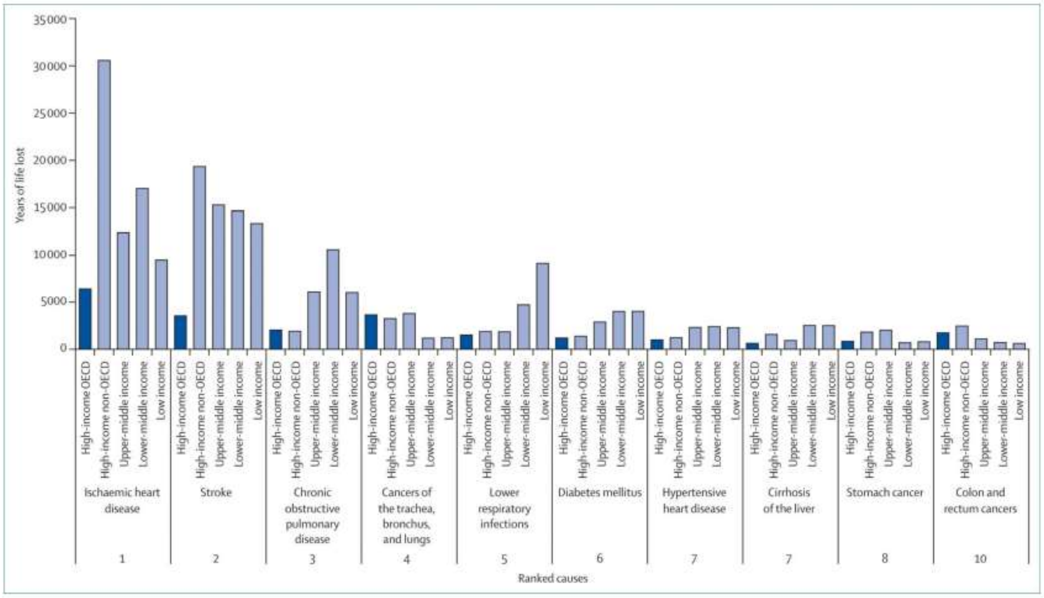


Figure 10: Top ten causes of death resulting in the greatest burden on older people. **"***Years of life lost per 100 000 population, 2012. Top ten causes in people aged 60 years or older from WHO Global Health Estimates. OECD= Organisation for Economic Co-operation and development."* From Beard et al., 2016(54).

Pneumonia is a common acute low respiratory tract infection that affects the alveoli and distal bronchial tree of the lungs. Depending on whether the pneumonia was acquired in the community or in healthcare environment, the disease is characterized as "community-acquired pneumonia" (CAP) or "hospital-acquired pneumonia" (HAP)(55). Both differs by the microorganism causing the infection. Prevalence of microbial aetiologies reported for CAP in Europe and in the USA are summarized in figure 11, extracted from the review of Torres et al. 2021(55). CAP are mainly caused by Streptococcus Pneumoniae, respiratory viruses, Haemophilus Influenza and other bacteria. HAP are caused mainly by Staphylococcus Aureus, Enterobacterales, non-fermenting gram-negative bacilli (for example Pseudomonas Aeruginosa) and Acinetobacter spp(41, 55).

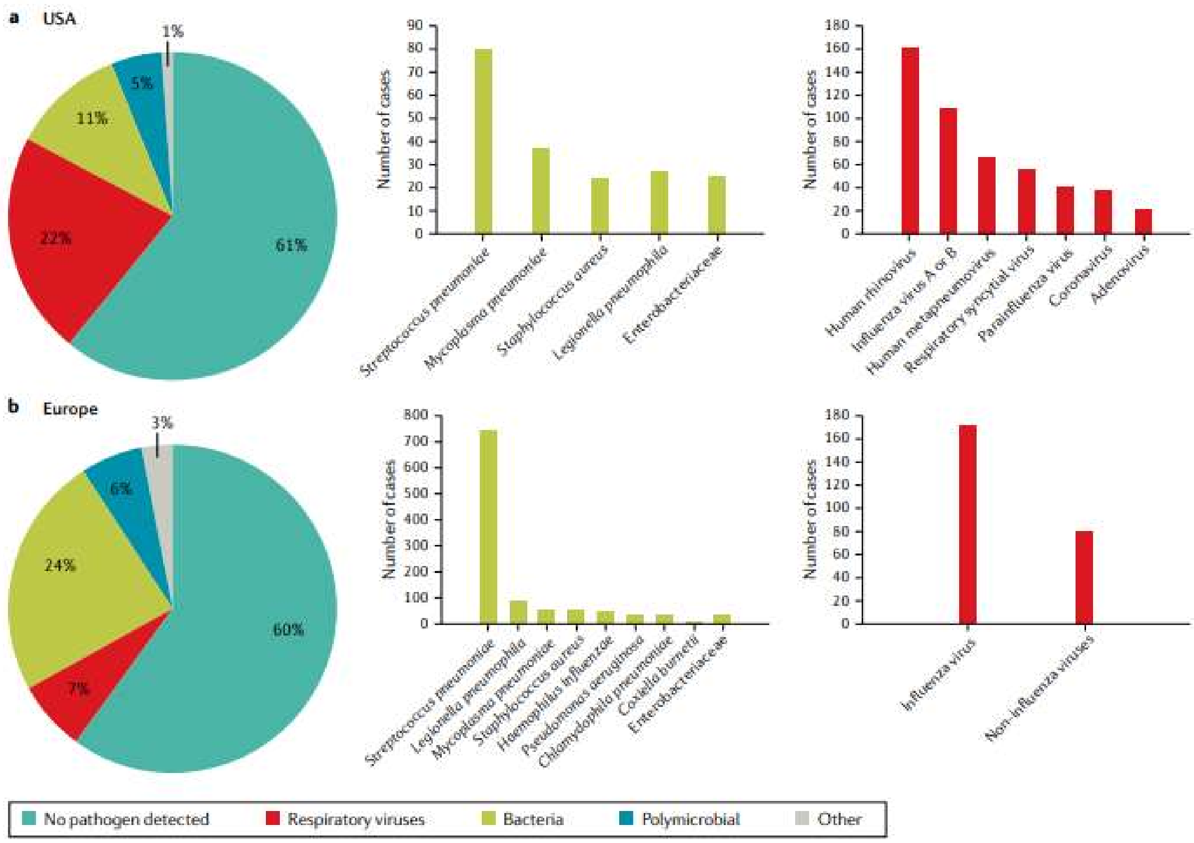


Figure 11: *"Prevalence of microbial aetiologies of CAP in the USA and Europe.* ***a.*** *Aetiology of CAP in the adult population in the USA from 2010 to 2012 (from 2,488 cases).* ***b.*** *Aetiology of CAP in the population of Europe from 2003 to 2014 (from 3,854 cases)*" (from Torres et al., 2021)(55).

In general, mild CAP are treated in outpatient visits, moderately severe CAP are treated in hospital and severe CAP are treated in intensive care units(55). The associated economic burden of CAP is quite important as shown by Campling et al. who estimated the annual cost to the UK National Health Service for adult hospitalized CAP before the covid-19 pandemia equal to £731 million per year(58). The authors also showed that the costs increased with age and were higher with people with either pneumococcal infections or any comorbid conditions(58).

Risk factors for CAP can be classified as host factors (age, presence of COPD or other chronic pulmonary disease, diabetes mellitus, chronic heart failure), unhealthy habits (smoking, excessive alcohol consumption) or medication (immunosuppressive drugs, sedating medication, proton pump inhibitors during the first 3 months of administration, etc.)(55, 59).

There is also a strong association between increased risk of CAP and a higher number of children in the household(60).

Preventive measures to reduce burden of CAP include changes in lifestyles such as smoking or alcohol use cessation, dental hygiene improvements, physical exercise as well as limited contacts with children with respiratory infections. Pneumococcal and influenza vaccination are key in CAP prevention in older adults and are recommended in many countries (42, 55, 57). The 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13 valent pneumococcal conjugate vaccine (PCV13) have demonstrated effectiveness in preventing invasive pneumococcal disease in people aged 65 and over (61, 62). Interestingly, conjugate vaccine programs in children contribute largely to reduce pneumococcal burden in adults through interruption of transmission and herd protection(55, 63, 64). Annual influenza vaccination in "at risks" groups like older adults can reduce the risk of complications of influenza like pneumonia. Influenza vaccination is associated with a decrease in symptoms severity, hospitalizations, ICU admissions and mortality associated with influenza(55, 65, 66).

Respiratory syncytial virus (RSV) is also an important cause of morbidity and mortality in infants and in older adults(56). Some modelling studies suggest that RSV burden in adult older than 65 years might be similar to the burden of seasonal influenza(67). Preliminary economic evaluations have highlighted the potential value of a vaccine for older adults(68). Therefore, significant investments in research and development of an RSV prophylaxis are ongoing(56). There are currently around 33 candidates in clinical development for prevention of RSV. Amongst them, a vaccine specifically designed for older adult is expected to be available on the market as from 2023(56).

The lack of awareness amongst patients, policy makers and healthcare providers about the burden of disease associated with RSV infection might represent a potential challenge for the future implementation of a global vaccine program against RSV. Therefore, more knowledge should be generated on the benefit of RSV prevention products through cost-effectiveness studies(56).

In this work, we will focus the research on vaccine-preventable respiratory infections caused by Streptococcus Pneumoniae, Influenza virus and RSV. Those pathogens are the main responsible of community acquired pneumonia and bronchiolitis in older adults, which can be life-threatening or trigger long-term poor overall health condition. They also represent a significant economic burden for healthcare systems. Amongst initiatives to promote health in older adults, immunization programs are of primary importance to manage the burden of such infectious disease. Infection by RSV is included considering the high probability of having a vaccine on the market for that disease in a near future.

1.4.2. Equity and challenges in disease prevention for older adults

There are several situations that may trigger inequities in the context of vaccine-preventable infectious diseases which may occur in the incidence of the disease (exposure or susceptibility), at the level of access to prevention measures (vaccination) and in the health effects following the vaccination (level of vaccine efficacy).

Despite proven efficacy of vaccines, there are still some gaps in coverage in older adult population. There are significant barriers to the access to vaccination for older adults. There is a global pediatric immunization culture where CEA favor pediatric vaccination to vaccination programs dedicated to older adults. In terms of initial investment, infant vaccination is applicable for one single birth cohort per year and is therefore less costly to initiate than a recommendation for older adults representing a numerous of birth cohorts and a larger initial investment in funding(69). Moreover, the benefits of vaccine accrue in a distant future. Consideration for persistence of immunity and life expectancy therefore favor vaccines used in children comparatively to older adults. Substantial potential improvement in quality of life in older adults are under-evaluated and vaccines for older adults might be less recommended for reimbursement, while unsubsidized vaccines may represent an unaffordable cost for some older adults(69).

Older adults may face constraints like mobility. Limited functional status may decrease the likelihood of vaccine uptake since access might depends on assistance of transportation(69, 70).

Cognitive impairment and/or loss of autonomy could also represent a challenge for older adults. Whilst infants have parent as their advocate, elderly people without advocate may be more vulnerable. They need often to be assisted by their physician for their healthcare decisions(71). It has been shown that some sub-groups of older adults are more at risk of not receiving vaccination like individuals older than 80 or demented frail older person(72).

Some factors are more psychosocial or related to health literacy such as perception of risk and understanding of infectious disease burden. Depending on cultural background, senior population and community in general may not fully appreciate the risk of infectious disease and their potential complications. They may also question efficacy of vaccination and fear potential side-effects(73). There are misconceptions and myths around vaccines that may be more preeminent in certain sub-groups of society(69).

With regards to disparities in the potential outcome of vaccination, there is a need for vaccines industries to improve research on vaccines by considering more the specific needs of the older adult population. It includes conducting randomized controlled trial and cost effectiveness studies in the frail elderly population and to develop specific product to tackle immunosenescence. That would help also to re-inforce confidence of health providers in the effectiveness of vaccination for old and frailty adults(69).

1.5. Research question

The research question is formulated as followed:

"What are the social determinants of health impacting the incidence and/ or prevalence of lower respiratory tract infection caused by the Influenza virus, RSV or Streptococcus Pneumoniae in older adult population (50+ years old)?"

The research question has been established using the PECOS (Population, Exposure, Comparison, Outcome, Study type) method as detailed in Table 1:

Population	Older adult population aged of 50+
Exposure	Lower respiratory tract infection caused by Influenza virus, RSV or Streptococcus Pneumoniae. Focus is made on lower respiratory tract infections as they are critical outcomes against which vaccine efficacy is measured/ assessed.
Comparison	Stratification in sub-groups vs whole population (when applicable)
Outcome	Risk factors linked to social determinants of health or health inequities that might influence the incidence (and/ or prevalence) of the lower respiratory tract infections
Study-type	• Quantitative studies: Epidemiology non-interventional studies: prospective observational cohort studies, retrospective studies, comparative studies, case-control studies, ecological studies, real world evidence database studies • Systematic literature reviews on respiratory infectious diseases of older adult population

Table 1: PECOS for targeted literature review

2. Methods

2.1. Targeted literature review

A research protocol has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and is available in appendix 1. It describes in more details the search queries, eligibility criteria, data extraction process and data management that have been followed for this targeted literature review.

2.1.1. Search strategy

Three targeted literature reviews have been conducted in the Pubmed database for English-languages epidemiology studies identifying and/or describing the role of determinants of health in susceptibility to respiratory infections caused respectively by Influenza virus, Streptococcus Pneunomiae and RSV as these respiratory diseases impose a high burden on older adults. The search strategy considered studies published in the last decade for Streptococcus Pneumoniae and RSV and in the last 5 years for Influenza infections. Period was limited to 5 years for Influenza in order to limit the number of records identified while it was still allowing a good overview of the research question, covering a period before, during and after the covid-19 pandemic.

A fourth targeted literature review has been conducted in EBSCO host database for English-languages epidemiology studies published since 2012 and including these 3 pathogens, in order to explore the topic in a database more specialized in social sciences.

Inclusion and exclusion criteria used to select publications in this targeted literature review have been developed based on PECOS methodology and are listed in table 2 below.

PECOS	Inclusion criteria	Exclusion criteria
Population	o Adult population aged of 50 year or above. It includes older adult population living in the community or in nursing home or other institutions. o Northern Western setting: only studies conducted in populations from high income countries from North America or Northern and Western Europe are selected (USA, Canada, UK, Austria, Belgium, France, Germany, Ireland, Luxembourg, Monaco, Netherland, Switzerland, Andorra, Portugal, Spain, Italy, Denmark, Norway, Sweden, Finland, Iceland) based on geographical location.	o Young population and children, o Healthcare workers younger than 50 years old o Countries not included in inclusion criteria
Exposure	o Studies referring to respiratory tract infectious (pneumonia, bronchiolitis) caused by Influenza, RSV of pneumococcal infections. Focus is made on lower respiratory tract infections as they are critical outcomes against which vaccine efficacy is measured/ assessed.	o Studies focusing (only) on respiratory disease caused by SARS-COV-2 or other infectious agents o Studies on avian flu
Comparator	o As the type of studies are non-interventional, there are no comparator *per se*. Some subgroups with risk factors might be compared to whole population. o Both vaccinated and non-vaccinated population are included in the review. The purpose is to consider potential bias linked to vaccination uptake that might be different in the different social groups and that may impact the incidence of the disease.	
Outcome	o Any social determinants of health as per the WHO Commission on Social Determinants of Health conceptual framework i.e., structural and intermediary determinants of health inequities(74, 75). It includes the place of residence, race & ethnicity, occupation, gender, religion & culture, education, socio-economic status, and social capital but also behaviors and material conditions linked to those determinants.	
Study type	o Epidemiology studies conducted in human population o Quantitative studies: Epidemiology non-interventional studies: prospective observational cohort studies, retrospective studies, comparative studies, case-control studies, cross-sectional design, survey o Systematic literature review. o English-written publications o Studies published in the last 10 years on Streptococcus Pneumoniae and RSV infection, and in the last 5 years for Influenza virus. (Considering the burden of Influenza in older adult population, the number of publications on this topic is much higher. Period will therefore be limited to 5 years to limit the number of records identified while it will still allow a good overview of situations before, during and after the covid-19 pandemic.)	o Randomized controlled trials are excluded as they might be not informative on risk factors distribution in older adult population due to process of randomization that aim to control potential impact of such distribution. o Study focusing only on vaccine uptake, with no information on epidemiology of the disease. o Study on vaccine efficacy and vaccine efficiency. o Model-based estimations o Studies related to Influenza published before 2017 o Studies related to RSV and Streptococcus Pneumoniae published before 2012 o Non-peer-reviewed publications indexed in Medline o Studies focusing on healthcare occupation only, without comparison to the whole population o Publication not written in English

Table 2: Eligibility criteria for publication selection in TLR

Duplicates have been removed from the records identified from the databases. Selection of papers has been first based on titles and abstracts, then full-text articles have been assessed for eligibility. A sample of 5% of titles and abstracts in each targeted literature review has been assessed independently by a second reviewer (Sophie Lucas) to ensure selection of relevant papers. The results were compared by both reviewers and deviations discussed to ensure full alignment in decision process in the selection of publication.

2.1.2. Quality assessment

Quality of the studies has been evaluated based on 2 criteria: the overall quality of the publication and the robustness of the selected study design based on the evidence-based medicine criteria.

Quality of each publication was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools. Specific tools were used as appropriate depending on the type of study. This included checklists for prevalence studies, for case-control studies, for case series, for analytical cross-sectional studies, for systematic reviews and checklist for cohort studies. A subjective qualitative score was attributed to each study based on the outcome of JBI checklist assessment, scaling quality from "Very Low" (0), "Low" (1), "Medium" (2) to "High" (3). The publications scoring "Very Low" were excluded.

To take into consideration the variability of robustness inherent to the study design, the publications were also classified in terms of robustness referring to evidence-based medicine classification. A score has been attributed as per robustness of study type as followed: case series scoring 1, Cross-sectional/database analysis/ecological studies scoring 2, case-control studies scoring 3, cohort studies scoring 4 and meta-analysis/ systematic literature review scoring 4.

A matrix was created based on the 2 criteria to determine final quality score of the study.

2.1.3. Data management

For each search, the list of records identified in Pubmed and EBSCO host was saved for tracking purpose in End-Note. Selection was made in Rayyan. A PDF version of full text was saved for each publication assessed. Lists of publications selected after abstract and full-text reviews were saved in Endnote. Screening to remove duplicates was performed in both systems. JBI quality checklist have been completed and saved in word document for each study included. A data extraction form was created in Excel where data on studies, population description, exposure, information on vaccination, outcomes, main conclusions of the study and quality assessment were recorded. Quality check on the extracted data has been performed and limitations reported for each selected study were captured.

3. Results.

3.1. Results of the targeted literature review

Three literature research have been done independently for each infection (influenza, Streptococcus Pneumoniae and RSV) in Pubmed and one research regrouping the 3 infections was conducted in EBSCO Host. The results of selection process for each research are described in a specific PRISMA flow diagram for each type of infection.

As shown in the PRISMA flow diagram (figure 12), 1148 publications have been retrieved in the database related to influenza. No duplicates were detected. 98 papers were selected for full text assessment after screening based on title and abstract. Out of these, 15 papers could not be retrieved, and 20 publications were finally selected based on eligibility criteria. One publication retrieved from the targeted literature review performed on RSV was meeting eligibility criteria and was added. In total, 21 publications have been included in the review.

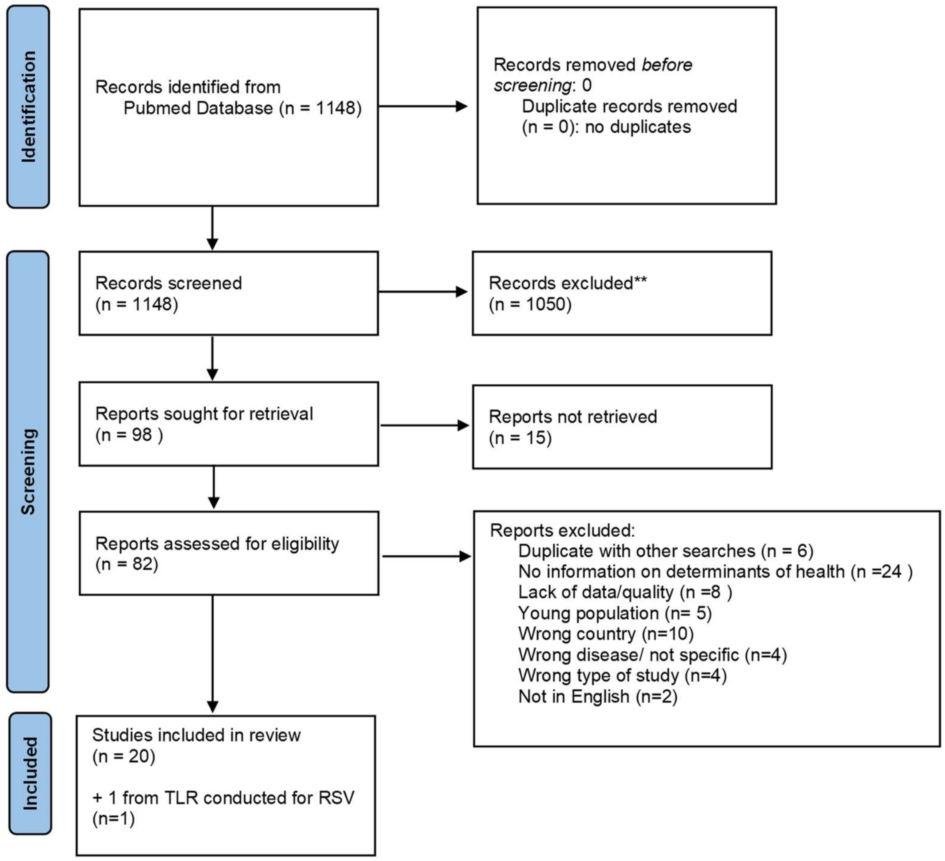


Figure 12: PRISMA 2020 flow diagram for targeted literature review performed for Influenza virus respiratory infections in Pubmed database.

As illustrated in figure 13, a total of 429 records related to Streptococcus Pneumoniae respiratory infections have been identified in Pubmed database and screened on title and abstract. No duplicate has been detected. 11 papers have not been retrieved for full text assessment. 13 papers have been included in the selection based on eligibility criteria.

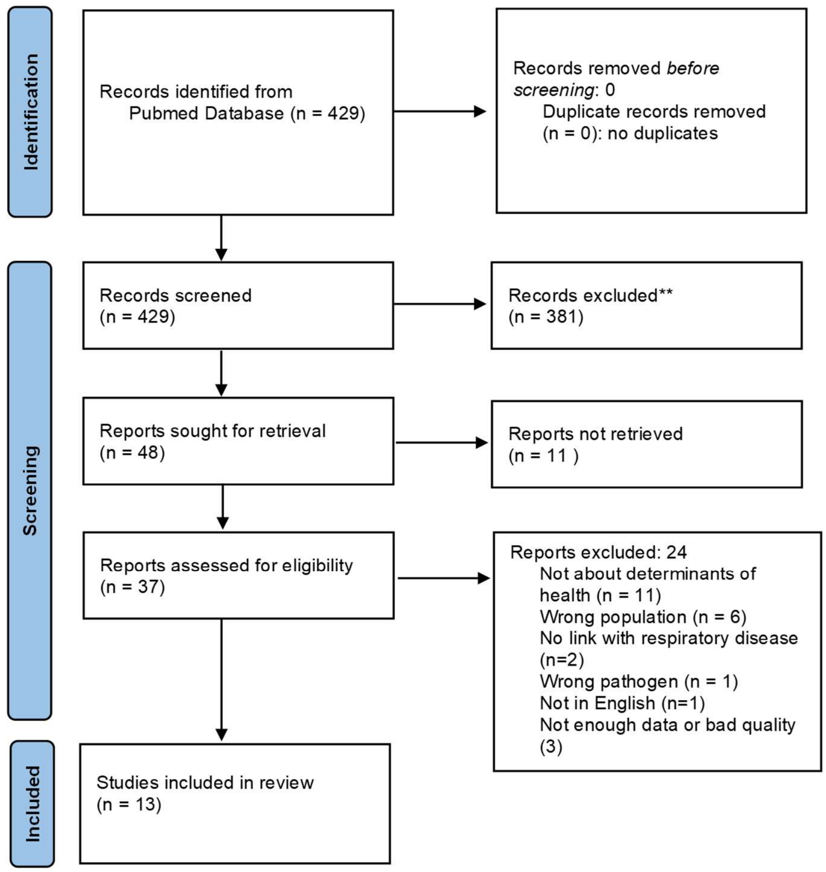


Figure 13: PRISMA 2020 flow diagram for targeted literature review performed for Streptococcus Pneumoniae respiratory infections in Pubmed database.

131 publications have been screened in Pubmed database for RSV based on title and abstract. 112 were excluded, 18 were assessed for eligibility based on full text and 1 publication was not retrieved. One publication related to influenza only and meeting eligibility criteria was kept in the selection and move to the influenza selected publications (see also figure 12). Finally, 3 publications have been selected as illustrated in figure 14.

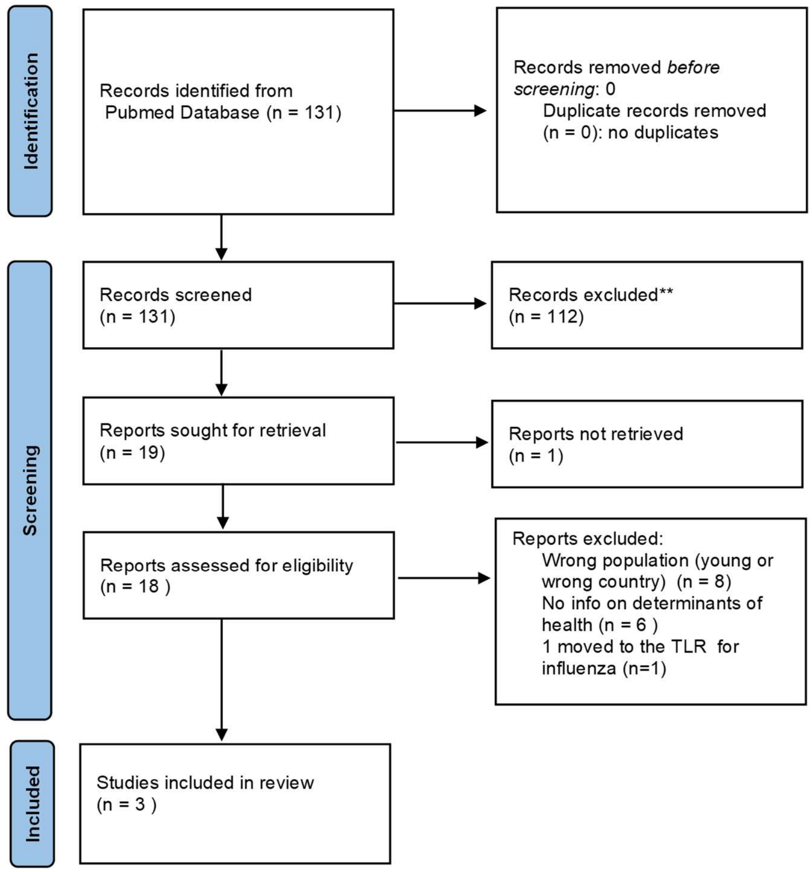


Figure 14: PRISMA 2020 flow diagram for targeted literature review performed for RSV infections in Pubmed database.

The additional research in EBSCO host database did not provide any additional information as all the papers retrieved from database (n=307) and screened for title and abstract (n=304 after removal of 3 duplicates) and based on full text (n=8) did not meet the eligibility criteria (data not shown).

When considered together, a total of 37 publications have been selected for this literature review. The list of the publications selected and the full references can be found in appendix 3. The determinants of health in context of influenza were the most explored in scientific literature with 21 publications retrieved on influenza only. On top, 2 from the 3 publications selected for RSV were also addressing influenza infections. The impacts of determinants of health on RSV infections are the less documented with only 3 publications retrieved. 13 publications have been retrieved for Streptococcus Pneumoniae.

Quality of all selected publications has been confirmed based on the Joanna Briggs Institute (JBI) critical appraisal tools and on the classification according to the robustness of the study design referring to the evidence-based medicine classification. Figure 15 shows the matrix with final quality scores of each selected studies based on these 2 criteria. Each study is represented by a square with a study ID, colored in orange for influenza, grey for RSV and blue for Streptococcus infections. Full reference of the selected publications corresponding to the study ID can be found in appendix 3. Most of the studies selected for influenza are RWE database analysis studies, with a robustness score of 2 and a quality score varying from 3 to 1. The type of study design was more heterogenous in the publications related to Streptococcus Pneumoniae, with a higher quality level overall. One cohort study was addressing both RSV and influenza. The 2 other studies on RSV were database analysis, with one common to RSV and influenza.

		Quality assessment score (based on JBI)			
		High	Medium	Low	Very Low (**)
Robustness (EBM classification)	score	3	2	1	0
Meta-analysis & SLR	5		10		
randomised controled trials	N/A (*)				
cohort study	4	1, 5, 17, 26	3, 6, 14, 14, 27		
case-control study	3	4, 9, 12, 24			
Cross-sectional study - RWE Database analysis studies- Ecological studies	2	28, 31, 32, 33, 34	8, 18, 19, 20, 30, 36	13, 15, 15, 16, 21, 22, 25, 29, 35, 37	
case-series/ case -report	1	2, 11	7, 23		
animal/in vitro search	N/A (*)				
expert experience & opinion	N/A (*)				

Figure 15: Positioning of each selected publication in quality matrix. Legend: Blue squares represent publication related to Streptococcus Pneumoniae, grey squares represent publications related to RSV and orange squares represent publication related to influenza virus. Numbers refers to the study ID attributed to each publication for which the corresponding full references can be found in appendix 3. (*) out of scope as per eligibility criteria. (**) Not included. RWE = real world evidence, JBI = Joanna Brigss Institute quality checklists.

3.1.1. Study Characteristics

A total of 37 publications have been retained from the targeted literature review: 13 publications on Streptococcus Pneumoniae, 1 on RSV, 2 on RSV and influenza and 21 on influenza.

Geographic footprints of the selected publications are illustrated in figure 16.

All studies on Streptococcus Pneumoniae were conducted in Europe, except for the systematic review from Smith et al. which includes data from outside Europe, predominantly in high income countries. Amongst the 21 studies selected for Influenza virus infections, 8 were conducted in the USA and 13 in Europe (1 in Germany, 5 in Italy, 1 in Denmark, 2 in the UK, 2 in France, 1 in Spain and 1 in Sweden). One of the studies selected for RSV (and influenza) infections was conducted in France and the 2 other studies (on RSV and on RSV and influenza) were conducted in the USA.

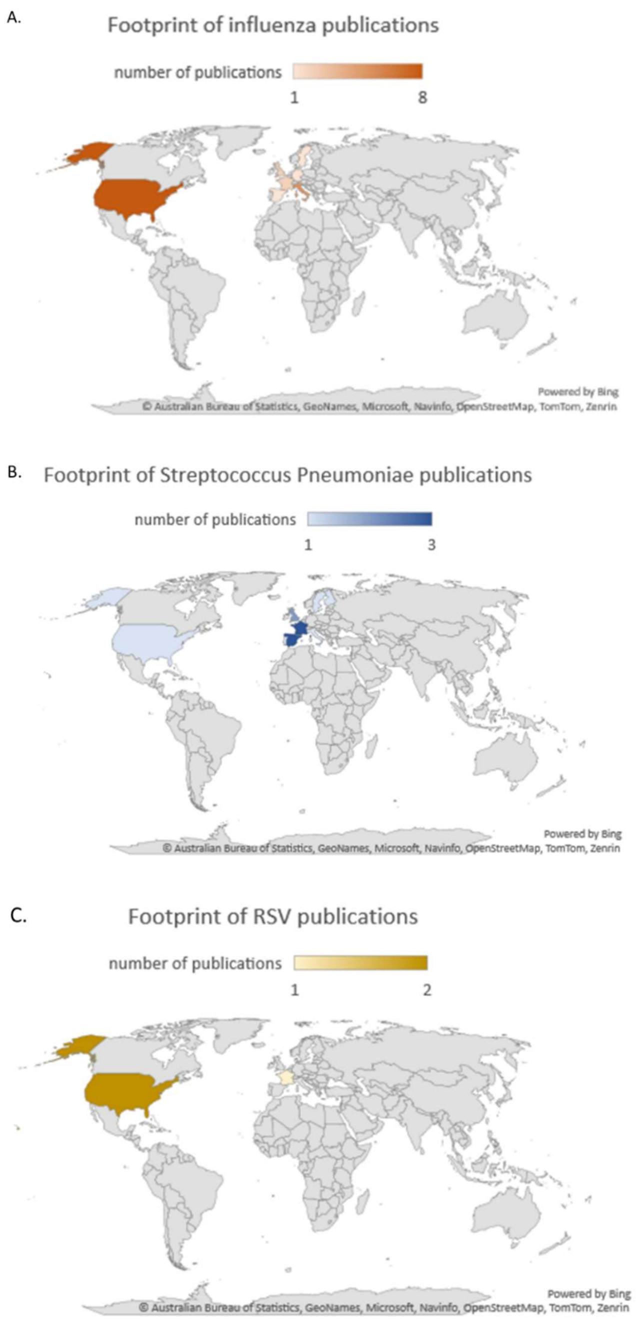


Figure 16: Geographic footprint of selected publications for each disease. A. Number of studies conducted on influenza in each country; B. Number of studies conducted on Streptococcus Pneumoniae in each country; C: Number of studies conducted on RSV for each country.

Studies selected for Streptococcus Pneumoniae covered a period from 1998 to 2020. While one French RSV study was conducted in 2012, the other studies referred to data from a period between 1999 to 2018. Influenza related studies covered a period from 1988 to 2019.

As illustrated by orange squares in figure 17, most of the studies on influenza are based on real world evidence database analysis (18 studies/21+2) using mortality rates data (9 studies/18), data from flu monitoring registers reporting cases of flu confirmed by laboratory test (5 studies/18) or from recorded cases based on clinical diagnosis (4 studies/18). The determinants of health reported using such database are the socio-economic status, race and ethnicity, place of residence, gender, occupation, education but also living conditions (pollution, large population centers, meteorological conditions) and behaviors (smoking)(76-92). Two studies were defined as cohort studies by the authors. One of them was using newly collected data combined with extracts from previous records in a database(93) and the other used real world evidence database (94). Figure 18A shows how the exposure to influenza infections has been measured in the selected publications. Besides database analyses, a case-series reports influenza outbreaks in nursing home where influenza was confirmed based on clinical symptoms and laboratory test(95). A case-control study explored the link between smoking and influenza in patients with laboratory confirmed influenza infection(96). Two cohort studies evaluate the incidence of influenza through virus nasal carriage in a cohort of Hajj pilgrims before and after pilgrimage(97, 98).

	Place of Residence	Race/ Ethnicity	Occupation	Gender	Religion	Education	Socio Economic Status	Behaviours	Living Conditions
Meta-analysis and SLR	10			10				10	10
Cohort study	1	26	3	26	6, 14, 14, 27		26	1, 5, 26	1, 17
Case-control			12				4, 9	9, 24	
Cross-sectional study/ Database analysis	19, 21, 22, 34	15, 16, 21, 25, 29, 31, 15, 34	32	8, 16, 25, 30, 36, 37		18, 28, 33, 34	16, 18, 21, 28, 30, 33, 34, 35, 36	13	13, 16, 19, 20, 30, 34, 36
Case/ series (Outbreak) - report			2, 7						11, 23

Figure 17: Matrix showing the type of studies (lines) and the determinant of health (columns) discussed in each selected publication identified by its study number. Blue squares represent publication related to Streptococcus Pneumoniae, grey squares represent publications related to RSV and orange squares represent publication related to Influenza virus. Numbers refers to study ID attributed to each publication (full references can be found in appendix 3). SLR= systematic literature review, RWE= real world evidence.

Blue squares on figure 17 represents the publications on Streptococcus Pneumoniae. The determinants of health potentially associated with Streptococcus Pneumoniae respiratory infections in older adult population are occupation, place of residence, socio-economic status, gender and religion. Behaviors like smoking, alcohol consumption and dental hygiene are also reported as associated with Streptococcus Pneumoniae infections, as well as living conditions like living in a nursing home, contact with school-age children or crowding in the household. As illustrated in figure 18B, exposure to Streptococcus Pneumoniae respiratory disease has been measured through bacterial carriage in 4 studies(99-102) and through clinical symptoms of pneumoniae with laboratory confirmed results in 5 studies(103-107). Two studies have assessed exposure using database records of pneumonia or IPD cases recorded from official public health monitoring programs(108, 109), one study used mortality rates data from death certificates(110). One study looked at exposure to risk factors associated with Streptococcus Pneumoniae infections(111) and was therefore classified in the “other” category (figure 18B).

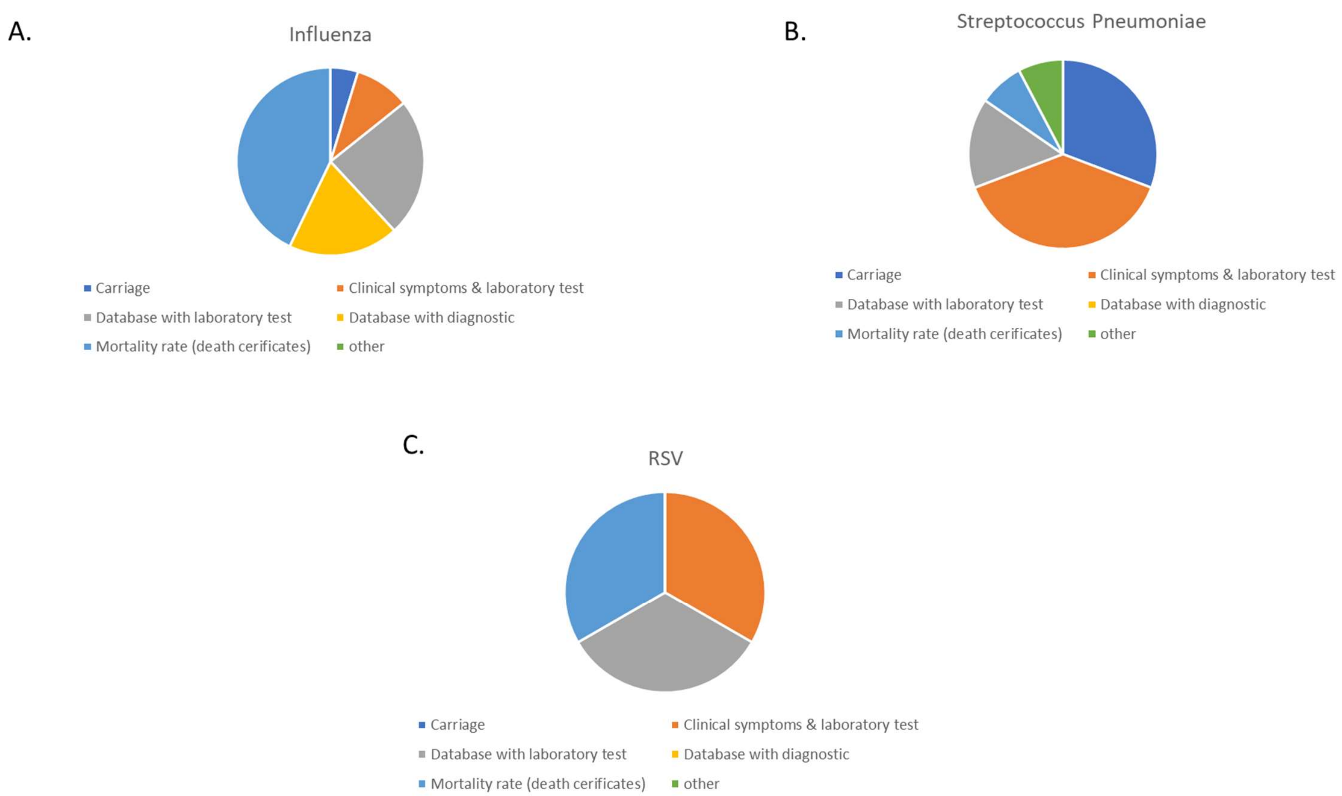


Figure 18: Measurement of disease exposure in the selected publications. A. Proportion of studies related to influenza where exposure was measured through virus carriage (dark blue), data based on clinical diagnostic confirmed by a laboratory test (grey), mortality rate assessed through death certificates (light blue), clinical symptoms and confirmatory laboratory test (orange) or data based on clinical diagnostic only (yellow). B. Proportion of studies related to Streptococcus Pneumoniae infections where exposure was measured through bacterial carriage (dark blue), data based on clinical diagnostic confirmed by a laboratory test (grey), mortality rate assessed through death certificates (light blue), clinical symptoms and confirmatory laboratory test (orange) or in another method like a survey (green). C. Proportion of studies related to RSV infections where exposure was measured through data based on clinical diagnostic confirmed by a laboratory test (grey), mortality rate assessed through death certificates (light blue) or clinical symptoms and confirmatory laboratory test (orange).

One of the studies selected for RSV and influenza infections has assessed the impact of the Hajj Pilgrimage through number of cases of RSV and influenza identified amongst pilgrims (through clinical symptoms and laboratory confirmation test)(98). Amongst the two studies conducted in the USA, one had assessed the impact of race on RSV and influenza infection using data from death certificates(81), the second one has evaluated the impact of socio-economic status on RSV infection using data from laboratory confirmed RSV cases from RSV surveillance system database(112) (grey squares in figure 17 and figure 18C).

3.1.2. Determinants of health of interest in the context of respiratory infectious diseases in older adults

To ensure a comprehensive analysis of the determinants of health in the context of infectious disease in the older adult population, the definition of determinants of health has been based on the "*conceptual framework for action on the social determinants of health*" proposed by Solar and Irwin(74, 75). A first finding from the targeted literature review is that scientific literature reports both structural and intermediary determinants of health being associated with respiratory infections cause by Streptococcus Pneumoniae, RSV and Influenza virus in older adults as depicted in figure 19.

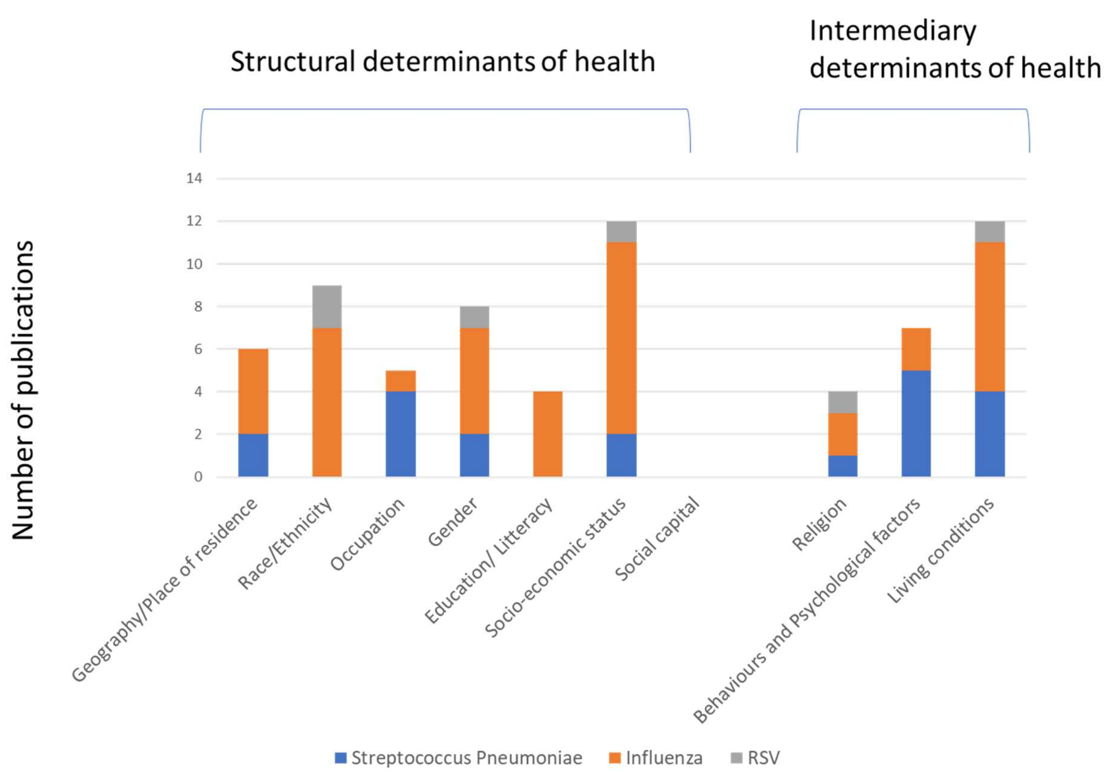


Figure 19: Overview of the number of publications studying each structural and intermediary determinants of health in the context of Streptococcus Pneumoniae (blue), Influenza (orange) and RSV (grey) in older adults.

Another framework useful to ensure proper data extraction and analysis of equity in the scientific literature is the PROGRESS framework(113). A combination of both approaches has been used in this analysis of infectious respiratory diseases in older adults, starting from a description of determinants of health using the PROGRESS framework that was complemented by a deeper analysis of the intermediary determinants of health. Multiple aspects are falling in the intermediary determinants of health category, which are specific for the respiratory diseases and the older adult population.

3.1.2.1. Determinants of health under PROGRESS framework

The PROGRESS framework classification of the determinants of health is an acronym referring to Place of residence, Race and ethnicity, Occupation, Gender, Religion, Education, Socio-economic status and Social capital(113). As shown in figure 20, socio-economic status is more frequently reported to be associated with the three respiratory diseases. The impact of race and ethnicity is also frequently discussed, but only for influenza and RSV infections. In the context of Streptococcus Pneumoniae infections, occupation is the most frequently reported determinant of health being associated with the disease.

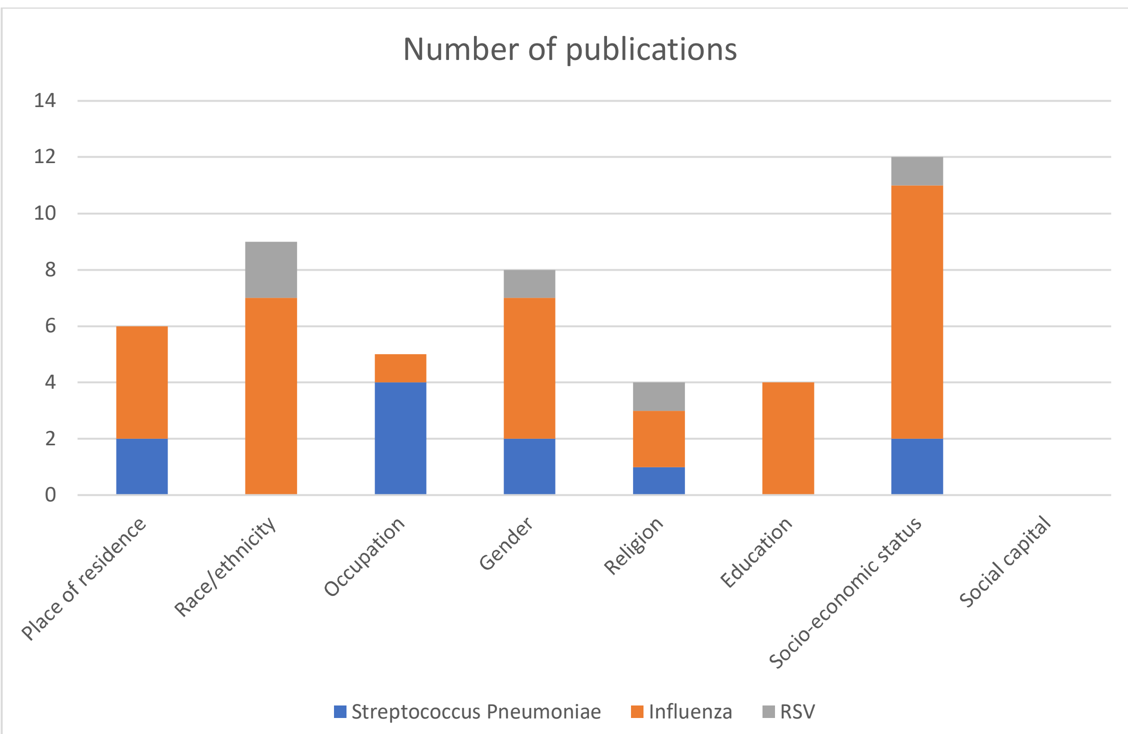


Figure 20: Frequency of publication studying the structural determinants of health in the context of Streptococcus Pneumoniae (blue), influenza (orange) and RSV (grey) infections in older adults.

3.1.2.1.1 Socio-economic status

The impact of socio-economic status is described mostly in the context of Influenza virus infections. Despite studies have been conducted in various places in the USA and Europe (Italy, UK, Sweden) and throughout several seasons, there is a common observation that number of flu cases and/or mortality associated with flu is higher in the more socio-economically deprived groups (78, 82, 83, 85, 88-91, 94). The ways socio-economic status is assessed vary amongst studies and is often based on a composite measure taking into consideration multiple variables. As a common ground, an economic indicator has been usually included which is either income (76, 83, 88), employment and occupation(82, 83, 85, 94) or level of poverty(76, 89).

Some social indicators are also included like marital status, household crowding (i.e., family dimension), number of school-age children per household, percent of single-parent household or female headed household(76, 82, 85, 89, 94). Studies conducted in Italy have used a local socio-economic and health deprivation index (SEDHI) which is based on economic-educational and socio-familial factors(82, 85), and was adapted in some cases to include specificities of the older adult population (like old age index, index of structural dependence, % of widows/widowers)(90, 91).

Distinction of the effect of socio-economic status and other determinants of health like education, race and ethnicity, place of residence or gender is not so straightforward and the effect of these determinants of health is often analyzed simultaneously. Level of education is considered either as a variable of the composite socio-economic index(82, 83) or as a distinct determinant of health(88, 89). Place of residence is also integrated with socio-economic status in some studies linking spatial analysis of influenza clusters with socio-economic variables, allowing to consider impact of population density, or highlighting higher rate of influenza in places characterized by higher poverty(76, 78, 89). Spatial analysis of potential risk factors for influenza is also reported to be linked to racial disparities(78, 89) and with percentage of female-headed household(89). Two studies showed that the relationship between deprivation and flu mortality is not linear in men but is linearly positive in women, suggesting that this group has a greater economic and social fragility(85, 91).

Suffering of social disadvantaged situation is also found to be a risk factor for developing community acquired pneumoniae(108) and a higher number of patients with pneumococcal disease is observed in those being without income or with a replacement income(104).

Similar observation is made in the context of RSV infections, where higher census tract poverty is associated with higher incidence of RSV-associated hospitalizations in adults(112). The authors highlighted that this association is likely to be multifactorial with poverty unlikely being the sole explanatory component. They observed that amongst adults with RSV-associated hospitalizations in higher poverty group, there were more individuals who identified as Black compared to White. Overall, there were also more women with RSV hospitalizations (59%)(112).

3.1.2.1.2. Race and Ethnicity

In contrast with socio-economic status, no consensus can be retrieved in the analysis of the literature on the impact of race and ethnicity on the incidence of the respiratory infectious diseases. Except for one report from the UK, all the studies from the selection exploring the effect of race on influenza or RSV incidence have been conducted using databases from the USA and reports characteristics for the population in the USA. They usually distinguish race and Hispanic origin as non-Hispanic White, non-Hispanic Black, non-Hispanic American Indian or Alaska Native, non-Hispanic Asian or Pacific Islander and Hispanic(80, 84, 86). When looking globally on leading cause of death in the USA in 2017, influenza and pneumonia ranked differently amongst race groups, being seventh in non-Hispanic Asian or Pacific Islander, eight for non-Hispanic White population, ninth for non-Hispanic American Indian or Alaska Native. For non-Hispanic Black and Hispanic population, influenza and pneumonia was not ranked in the 10 leading causes of death(80). Results from studies exploring the effect of race and ethnicity as potential risk factor for influenza infections show some discrepancies. Jeganathan et al. have observed higher mortality rates from influenza for the period between 2010 to 2019 in non-Hispanic White people followed by non-Hispanic Native Americans and non-Hispanic Black. Rates were the lower in Hispanic and non-Hispanic Asian(84). On the opposite, O-Halloran et al. observed higher hospitalization and ICU admission rates for non-Hispanic Black and American Indian or Alaska Native persons compared with non-Hispanic White persons for the season 2009-2010(86). Similarly, despite they both investigate mortality burden for influenza for the period between 1999 to 2018, two groups reached opposite conclusions. Hansen et al. observed, based on death certificates, that 80% underlying influenza death occurred in non-Hispanic White individuals, while non-Hispanic Black adults had the lowest mortality for influenza, but not for all-cause mortality(81). However, Donaldson et al.

observed from CDC epidemiology data that age-adjusted mortality rate for influenza and pneumonia was higher in non-Hispanic Blacks than in non-Hispanic White(78). Donaldson et al. analyzed more precisely the disparities by region and showed some variations. The disparities were greater in New York, New Jersey, California, Arizona, Hawai and Nevada. No racial disparities were observed in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming and Alaska, Idaho, Oregon, Washington(78). A potential partial explanation of these regional disparities might be the different vaccination coverage. Indeed, the CDC's influenza vaccination reports for 2010 to 2011 showed non-significant lower rated of vaccination in non-Hispanic Blacks compared to non-Hispanic White in the New York and New Jersey regions where disparities for flu mortality are higher(78).

One study based on influenza cases recorded in the UK biobank from 2016 to 2020 highlighted that South-Asians were at increased risk of developing influenza (risk ratio=2,20). Ethnicity was coded as White, South-Asian, Black or mixed/other(94).

Effect of race and ethnicity on the incidence of RSV infection has been assessed by Hansen et al. using death certificates in the USA population for the period between 1999 to 2018. They showed that mortality for RSV is mainly reported in non-Hispanic White population (60 %) and that non-Hispanic Black adults aged of 65 years old and above had the lowest mortality for RSV and unspecified bronchiolitis(81). On the opposite, Holmen et al. observed that, when combined with socio-economic analysis, there were more Black individuals compared to White in the adults with RSV-associated hospitalization in the higher poverty group(112).

There are no publications in the selection on the impact of race and ethnicity in the incidence of respiratory infection caused by Streptococcus Pneumoniae in older adults.

Overall, these observations suggest that if there is an effect linked to race and ethnicity in the incidence of influenza and RSV, it needs to be assessed in perspective of other confounding factors like, for example, socio-economic and political context and other determinants of health like socio-economic position, education and living conditions (see below).

3.1.2.1.3. Place of residence

There are various aspects that characterize the place of residence of older adults, and which may impact their susceptibility to respiratory infections. It can be environmental characteristics of the location itself like climate and the meteorological conditions or geopolitical and socio-economic context like level of urbanization or population density. In this section, we will cover the geographical, socio-economic and geopolitical aspects related to the place of residence. The living conditions that may be linked to the location (pollution…) or specific living context that can be determined by social and/or functional status of subject (nursing home) will be discussed as part the intermediary determinants of health in section 3.1.2.2..

Donaldson et al. have observed some variability amongst regions in the association between race and influenza mortality rate. Regions with large disparities in influenza mortality rates between non-Hispanic Black and non-Hispanic White individuals (New York, New Jersey, California, Arizona, Hawai and Nevada) include two or the largest cities in the USA (New York city and Los Angeles). These large central metropolitan areas are characterized by high density population, with extremely high rates of non-Hispanic Black population with high rates of poverty, lack of well-paying jobs and limited access to quality healthcare and preventative services. Such characteristics differ from small metropolitan and micropolitan areas, where no racial disparities in mortality to influenza are observed, which have a relatively small non-Hispanic Black population, an overall lower mortality rate and with only few large cities.

Using data from 2009 -2010 and 2013-2014 influenza season, Sloan et al. have also shown that geographic clustering of influenza hospitalization observed in Ohio, New York, Michigan and Connecticut (New Haven and Hartford County) may be influenced by socio-economic factors(89).

Geo-political context may also be a factor influencing the susceptibility to infections. This is the hypothesis proposed by Fallani et al. to explain their observation that provinces located in Northern Italy displayed a higher mortality rate to pneumonia and influenza compared to Southern and central provinces(79). As in Italy, each region may either adopt the national recommendation or provide its own regional recommendation in term of influenza immunization programs, the authors suggest that the difference between regions might originate in the type of vaccines used, with different level of efficacy. The regions that have used a higher proportion of adjuvanted vaccine (with higher efficacy) showed significantly lower pneumonia and influenza mortality in the elderly independently of the influenza vaccination coverage, virus circulation pattern, and other potential confounder(79).

In their ecological study, Bota et al. have used socio-economic data from official statistics in Sweden to integrate median household income, number of children by household, fraction of people receiving social aid and population density with spatial localization and meteorological conditions to study the spreading of influenza. They concluded that spreading of influenza is driven by large population centers, the presence and size of outbreaks in neighboring municipalities and meteorological factors like humidity and temperature. Absolute humidity seemed to play a critical role while mean temperature contributed less(76).

Place of residence is a determinant of health which seems to play a role in susceptibility to Streptococcus Pneumoniae infections too. Two publications showed a higher risk of pneumococcal colonization in individuals living in rural area compared to those living in urban area(99, 102).

3.1.2.1.4. Occupation

The potential impact of occupation on societal hierarchy and socio-economic position is often integrated as a variable of the composite measure of the socio-economic status as mentioned in section 3.1.2.1.1. This chapter will focus on the exposure to specific occupational risks which impacts the incidence of respiratory infectious disease in older adults. This impacts more the “pre-aging” or younger part of older adult population, between 50 to 75 years old.

Occupation risk is well documented in the context of Streptococcus Pneumoniae infections, particularly for jobs involving metal fumes or respiratory irritants. Several outbreaks of invasive pneumococcal disease (IPD) associated with pneumonia have been reported in shipyards workers exposed to respiratory irritant in France and Finland(103, 107). In England and Wales, an excess mortality from pneumococcal pneumonia has been reported in welders for all working age for the period between 2001 to 2010(110). The increased risk of IPD with concomitant pneumonia carried by jobs involving exposure to metal fumes has been further demonstrated by a case-control study in Swedish population(109). Toren et al. have shown that welders manifest an increased odds of IPD with pneumonia (OR=3,28, 95% confidence interval (CI) from 1.80 to 3.43), using adjusted models with the following covariates: comorbid conditions, socio-economic status (evaluated as per education level defined dichotomously as university graduate vs less education) and ethanol abuse(109). When looking to a broader category of job exposed to fumes, association with increase odds for IPD with pneumonia is also observed (OR=1.17, 95%CI from 1.06 to 1.30)(109). The only job category for which similar significant risk of IPD with pneumonia was observed is jobs with high exposure to silica(109).

To investigate if there is any occupational risk associated with influenza infections, Ostergaard et al. used data on hospitalization with influenza and occupational data from Danish official registers(87). They observed that the crude rate of being hospitalized with influenza was the highest for people working in public transportation (2,7/10000 person years), followed by people working with garbage and recycling (1,5/10000 person years) and healthcare workers at hospitals and dentists (1,5/10000 person years). Interestingly, they observed that people working within farming and gardening and in metal industry had the lowest crude rate of being hospitalized with influenza (0,7/10,000 PY for both groups)(87). When comparing with public administration, only people working in public transportation had an increased rate of influenza-related hospitalization (Incidence rate ratio= IRR=2.54; 95% CI 1.79–3.58). When investigating hospitalization linked to pneumonia (without identification of infectious agent), the authors observed that people working in day care, sewers, public transportation, and nursing home care had an increased rate compared to people working within public administration(87).

3.1.2.1.5. Religion

The link between religion and respiratory infectious disease in older adults can be retrieved in the religious practices and behaviors. The only risk factor documented in the literature with regards to respiratory infections in older adults concerns the Islamic religion and is related to Hajj pilgrimage in Mecca in the Kingdom of Saudi Arabia.

In their prospective cohort study, Benkouiten et al. followed a cohort of 152 Hajj Pilgrims before, during and at the end of the pilgrimage in 2012 to measure their exposure to viral respiratory infectious disease. Most of the infections were caused by rhinoviruses. They detected 1 case of influenza C and they didn't detect any case of RSV infection(98). Similar approach was followed by Hoang et al. who measured virus carriage in a cohort of 109 pilgrim before and during the 2016 Hajj season(97). They detected influenza A virus in 23, 8% of Pilgrims during their stay in Saudi Arabia. The carriage was cleared in 100% of cases before they leaved Saudi Arabia but the majority of cases were still symptomatic (71,4%). Same authors have assessed bacterial carriage of Hajj pilgrims following participation to Hajj in 2015 in an observational study. They observed that prevalence of Streptococcus Pneumoniae significantly increased after participation in Hajj, compared to pre-Hajj status (from 1.8% pre-Hajj to 9.8% post-Hajj ($p = 0.01$)). Pilgrims vaccinated were seven time less likely to harbor Streptococcus Pneumoniae after the Hajj compared to unvaccinated pilgrims.

3.1.2.1.6. Education

Education is reported as determinant of health in the context of influenza infection, but not for Streptococcus Pneumoniae, neither for RSV(82, 83, 88, 89). Through a database study using data from influenza surveillance from season 2013/2014 to 2017/2018 in Rhode Island (USA), Otero et al. have assessed health disparities associated with influenza infection based on median household income and educational attainment, as two separate criteria(88). They observed that people with low educational attainment were more likely to have influenza-related hospitalization than people with higher educational attainment(88). In the other studies, education was considered as an element of the composite measure of the socio-economic status. As mentioned earlier, lower socio-economic status linked to lower education was associated with increased incidence of influenza(82, 83, 89).

3.1.2.1.7. Gender

Results vary in the literature on how gender may or not change the susceptibility to infectious respiratory disease in older adults. Ho et al. observed that influenza cases are more common in women (risk ratio=0,83 in men) based on influenza cases recorded in the UK biobank between 2006 and 2020(94) while Walter at al. did not observe any difference between male and female for susceptibility for influenza in their analysis of mandatory records of influenza cases in Germany for the period between 2001 to 2013(92). In the USA, influenza and pneumonia ranked as the ninth cause of death for men (causing 1,8% of death) while it ranked eight for women (2,1% of death) in 2017(80). In their evaluation of socio-economic impact on influenza, Lai et al. reported that relationship between deprivation and overall mortality is linearly positive in women but not in men. They attributed these results to greater economic and social fragility of aged women(85).

With regards to Streptococcus Pneumoniae infections, Smith et al. showed that male participants had significantly lower pneumococcal colonization than females (OR= 0,76, 95% CI 0,59–0,98)(114). When looking more specifically to known risk factors for pneumococcal infections, Ochoa-Gondor et al. observed that most underlying conditions are common in men and women. However, they report that prevalence of smoking, alcoholism and HIV infection are higher in men while prevalence of immuno-deficiency, immuno-suppressive treatment, severe renal failure, cerebrospinal fluid leaks and cochlear implants are higher in women(111).

When looking to RSV-associated hospitalizations in USA, Holmen et al. observed more of them in the women (59%)(112).

3.1.2.1.8. Social capital

Social capital characterizes the relations and interactions between individuals and groups. It can be seen as the personal resources that emerges from social networks like having better access to information, services and support. It is a multidimensional concept including social networks, social participation, social support and social trust. It may affect health through several mechanisms: norms and attitudes that influence health behaviors, psychosocial networks that increase access to healthcare and psychosocial mechanisms that enhance self-esteem(115).

There is no study reporting social capital as determinant of susceptibility to infectious disease in older adults. Some aspects of it are discussed in publications on the other determinants of health, suggesting that social capital explains part of the observations. For instance, Lai et al. explain the link between socio-economic deprivation and susceptibility to influenza in women by the fact that women often live alone and are therefore less likely to have adequate family support or easy access to healthcare or public social assistance(85).

3.1.2.2. Intermediary determinants of health

Beyond the determinant of health as per PROGRESS framework, several intermediary determinants of health are reported in the context of respiratory infectious diseases in older adults. As defined by Solar and Irwin, they are linked to a "*set of individual-level influences including health-related behaviors and psychological factors*" and they "*determine difference* *in exposure and vulnerability to health compromised conditions"(75).* They belong to two main categories: the behavioral factors and the material circumstances(75).

The figure 21 illustrates the number of publications from the selection which refers to behaviors and material circumstances in the context of Streptococcus Pneumoniae, Influenza virus and RSV infections. The behavioral factors include smoking, alcohol consumption and dental hygiene. Material circumstances refers here to living conditions, including physical environment around the housing location like pollution but also social aspects like the fact of living in nursing home, the household size and crowding, and the contact with young or school-aged children.

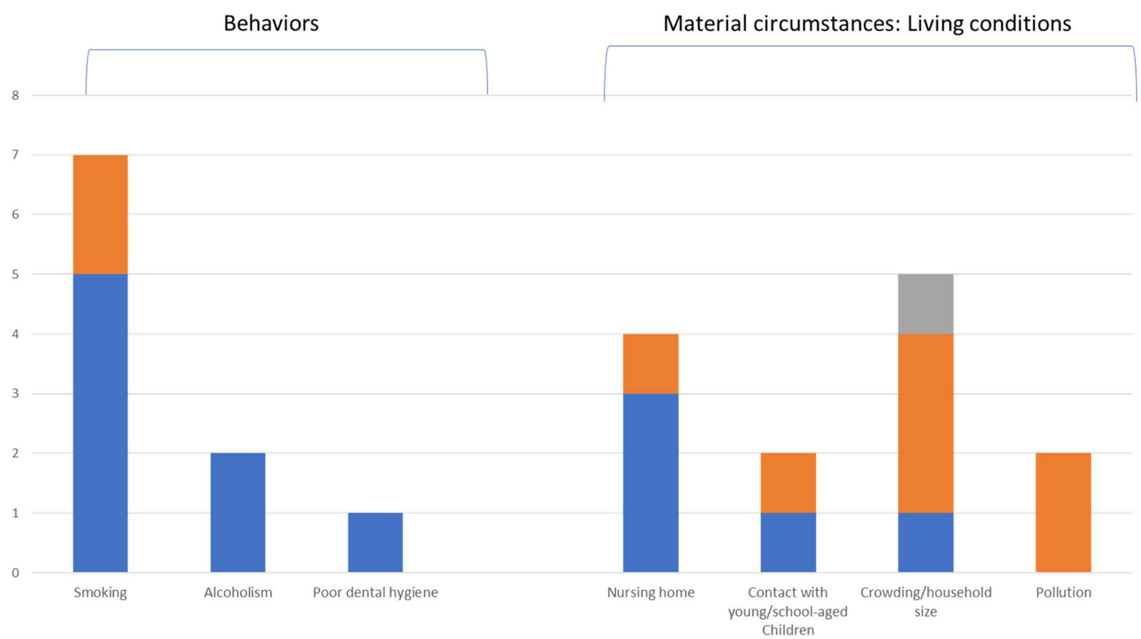


Figure 21: Frequency of publication studying the intermediary determinants of health in the context of Streptococcus Pneumoniae (blue), Influenza (orange) and RSV (grey) infections in older adults.

3.1.2.2.1. Behavioral factors

Not surprisingly, there is a consensus in the literature confirming that smoking is a risk factor for pneumococcal pneumonia and influenza infections(94, 96, 99, 101, 102, 105, 108). Current active smoking is associated with higher prevalence of pneumococcal colonization of the upper respiratory tract(99, 101, 102). Tramuto et al. have observed a dose-response trends with the odds of pneumococcal carriage increasing progressively with number of cigarettes smoked per day(101). Also, compared to the general population, patient with invasive pneumococcal disease (IPD) were more often smokers(105). Smoking is also associated with higher risk of influenza infections and hospitalization(94, 96). In their case-control study, Godoy et al. have observed that risk of influenza hospitalization was 30% higher in patients with a history of smoking (either active smokers or ex-smokers). The fraction of the risk of influenza hospitalization attributable to smoking was 24.2% (95% CI: 3.84% to -410.5%) in current smokers/ex-smokers(96).

High alcohol consumption or history of alcohol abuse is also reported as risk factor for pneumococcal pneumoniae and infection. Patient with invasive pneumococcal disease are more often alcohol abusers compared to general population(105, 108). Poor dental hygiene was also found to be a risk factor for community acquired pneumonia, but this is less documented(108).

3.1.2.2.2. Living conditions

Risk of infectious disease is inherent to the physical environment where people live. Level of exposure to pollution varies between individuals depending on their place of residence or place of work. Risk related to place of work has been covered in the section 3.1.2.1.4. as part of the occupation. This section will focus on environment where people live.

Park et al. have examined the prospective association of biomarkers of cadmium exposure with mortality related to influenza(93). Cadmium is known as environmental risk factor which promote lung inflammation and is immuno-toxic(116). They observed that Cadmium body burden measured as urinary concentrations is associated with higher risk of mortality from influenza or pneumonia among older adults representative of the general U.S. population. As the association of mortality is stronger with urinary compared to blood cadmium levels, the primary risk factor seems to be cadmium burden that has accumulated over time vs. recent cadmium exposure(93). Another indicator of air pollution is the level of fine particulate matter air pollution of 2,5 µm or less in diameter ($PM_{2,5}$). Croft et al. showed an association between an increased $PM_{2,5}$ concentration in the previous 5-7 days and an increased relative rate of emergency department visits for influenza. These increased relative rates were independent of temperature and relative humidity changes, as well as subject characteristics (e.g., age, race, sex, socio-economic status, previous health events) that were controlled by design in their case–cross-over study, confirming that air quality may influence susceptibility to respiratory infections(77).

With regards to the social environment, one characteristic of the older adult population is the significant proportion among the oldest subgroup (80 years old and above) living in nursing home, and potentially exposed to a higher risk of infectious diseases. Those living in nursing home compared to those living in community have increased rates of pneumococcal colonization as shown by Smith et al. through their systematic review of the literature and their meta-analysis(102) and by Almeida et al(99). Indeed, an outbreak of acute respiratory tract infection caused by Streptococcus Pneumoniae has been reported in a nursing home, despite a high rate of vaccination among residents(106). Similarly, several influenza outbreaks have been reported in French nursing homes (46 influenza outbreak /76 respiratory infections outbreaks in 14 sites) with an infection rate close to 30%(95). Gaspard et al. have shown increasing rates of infections among the older and the less autonomous residents who have higher risk of falling ill(95).

For those living in community, another important aspect of social live of older adults is the contact with young and/or school-aged children which is a risk factor for upper airway pneumococcal colonization(102). This seems to be linked to the proximity in which they are living, as pneumococcal carriage is inversely related to number of rooms in the house and directly related to household size(101). Number of school-age children per household has also a significant positive effect on influenza transmission(76). Home crowding and number of people per family can also be an indicator of the socio-economic status and is often taken into consideration in socio-economic status measurement and its impact on infectious disease (76, 85, 89, 91).

4. Discussion

The purpose of this work was to understand the value of vaccination beyond cost-effectiveness, in terms of social equity in older adults in North-Western high-income countries. The scope was to assess if vaccination, through reduction of susceptibility to infectious diseases, might reduce or erase the social inequities in such population.

The work consisted as a targeted literature review carried out in Medline and EBSCO host database to assess the current scientific knowledge on health disparities with regards to respiratory diseases caused by Influenza virus, Streptococcus Pneumoniae and RSV infections. A broad approach has been followed in the research queries to investigate potential causes of disparities using the determinants of health as per PROGRESS framework(113) complemented by intermediary determinants of health(75).

4.1. Complex interlink between structural and intermediary determinants of health that are involved in increased susceptibility to infection in older adults

The scientific literature reports both structural and intermediary determinants of health being associated with respiratory infections caused by Streptococcus Pneumoniae, RSV and Influenza virus in older adults.

4.1.1. Age

The study population of interest in this work is the older adults aged of 50 years and above. The rationale to include the pre-aging adults (from 50 to 64 years old) is that process of aging varies, with some heterogeneity in the biological mechanism of immuno-senescence between individuals that may start earlier for some and impact their susceptibility to respiratory infectious disease(27). These differences are partially linked to the environment in which they are living(28). This includes occupational risk exposure, which is usually measured in the pre-aging population, before retirement. Acknowledging that process of aging is not linear and may vary between individuals, age remains by itself a well-known risk factor for respiratory infectious disease(24).

A significant part of the older adult population, especially the oldest ones, lives in nursing home. For example, 2,4% of the older adults were living in nursing home in the USA in 2016, 3,8% in Canada in 2019, 8,8% in Belgium in 2014, 4,1% in France in 2019 and 4,2% in the UK in 2004 according to WHO and based on Organization for Economic Cooperation and Development (OECD) Stats data(117). As shown in the literature review, those living in nursing homes face a higher risk of respiratory infectious disease caused by Influenza virus and Streptococcus Pneumoniae. The lack of autonomy seems to be associated with higher rate of influenza infections, due to high level of dependency(95). This may be partially explained by the need for more frequent social contacts with nursing staff that may favor transmission of the disease. However, more active residents may be less fragile and/or have greater capacity for compliance in the infection control measures(95).

In the developed countries in scope of this work, vaccination campaigns of older adults against flu and Streptococcus Pneumoniae infection are implemented, but not yet for RSV. Compliance to vaccination seems to increase with age, with individuals older than 70 years old being more likely to be vaccinated compared to those aged of 65-69 years old (70, 118-120). Limited functional status and lack of social support may decrease the likelihood of vaccine uptake since access depends on transportation or assistance. Access may be easier for those living in nursing home increasing their compliance with vaccination (70).

4.1.2. Gender

The impact of gender in susceptibility to respiratory infectious disease is not consistent across the literature with a limited number of reports for each infection. Risk factors reported for men and women differs. Men are more at risk of non-healthy behaviors like smoking and alcoholism(111). However, older women are more at risk to be in a more socio-economic deprived position and of being isolated; they also are less likely to have adequate social support or easy access to healthcare assistance(85). With regards to vaccination behaviors, some studies report a difference between men and women in their likelihood to be vaccinated, while some studies found no difference by gender(70).

4.1.3. Socio-economic status

Socio-economic status is the most frequently reported determinants of respiratory infectious disease in older adults. There is a consensus in the literature that the socio-economically deprived groups are more susceptible to respiratory infections than privileged ones, with similar observations for the 3 diseases investigated. The way socio-economic status is measured vary between studies. Education is often integrated as a component of the socio-economic index. When assessed separately, people with lower educational attainment seems more sensitive to influenza when compared to those with higher educational level.

There are many ways on how socio-economic status may directly or indirectly influence respiratory function and health in older adults, including associated behaviors and living conditions. Some specific behaviors are socially patterned, like smoking. People who smoke are more likely to report lower income and less education compared to non-smokers in the population(121). As shown in the targeted literature review, there is a consensus in the scientific community to identify smoking as a risk factor for respiratory infectious disease in older adults. Both socio-economic deprivation and smoking behaviors might therefore exacerbate each other resulting in socio-economic disadvantaged smokers being more highly exposed to harm from tobacco(121). Moreover, smoking cessation programs are reported to be less likely successful for socially disadvantaged smokers(121).

Alcohol consumption is another behavior associated with higher risk of respiratory infectious disease in older adults. The scientific literature reports a positive relationship between alcohol use and socio-economic status such that those with higher socio-economic status engage in more frequent and heavier drinking compared with people with lower socio-economic status. This relationship may be influenced by moderating factors such as race, ethnicity and gender(122). However, socio-economic status seems to be inversely related to negative alcohol-related consequences(122).

Other important intermediary determinants of health highlighted in the literature review are the living conditions. The physical environment where people live and level of pollution to which they are exposed are also risk factors for respiratory infectious diseases in older adults. This is translated through the concept of "*environmental inequality*" referring to differentiated distribution of air pollution across different socio-economic groups(123). Results from air pollution studies vary depending on places. Studies conducted in North America suggest that lower socio-economic status individuals and communities are exposed to higher concentrations of criteria air pollutants while findings in the European literature is more mixed(123). Relationship between environmental inequality and health is complex. Health disparity driven by environmental factors may results from a higher exposure to air pollutants and other environmental hazard but also from an increased susceptibility to poor health is such population caused by poorer health status, psychosocial stressors (such as discrimination and chronic stress) and fewer opportunities to choose health-promoting behaviors(123). Indeed, in some places, higher socio-economic group live with higher concentration of air pollution but are not necessarily more exposed because they have resources that can protect themselves from increased exposure(123).

Such interlink between socio-economic status and intermediary determinants of health has also been extensively reported in context of covid-19 infection, with similar observations and conclusions. Factors like the use of public transportation, lack of adequate personal protective equipment, poor general health and nutritional status, housing conditions, living in poverty or deprivation, lack of insurance, household overcrowding, lower level of education, speaking in a language other than the national language in a country, being an immigrant and unemployment may have increase the exposure and mortality of covid-19(124). Also, lower education levels and lack of information may influence lifestyle and behavior leading to habits such as smoking, drinking and poor diet which are risk factors for severe forms of covid-19(124).

4.1.4. Social capital

Social capital can be conceptualized as personal resources that emerges from social networks(115). In our research, there is no publication addressing the importance of social capital per se, but elements of interpretations are provided through the analysis of the other determinants of health. Lai et al. interpreted the positive relationship between deprivation and overall mortality observed in women but not in men by the greater economic and social fragility of aged women(85). Because life expectancy varies with gender, women who lived longer are more likely to be widowed and not having support from a caregiving spouse(50).

Social capital is difficult to interpret as the social support may benefit to older adults for accessing healthcare and disease prevention(70) while social interactions that favor transmission like contact with children might be a risk factor(59, 76, 101, 102).

4.1.5. Race and ethnicity

There is no consensus in the literature on the impact of race and ethnicity on the incidence of respiratory infections in older adults. While the topic is extensively discussed in context of influenza and RSV infections, there were no publication related to race and ethnicity retrieved for Streptococcus Pneumoniae infections. Most of the studies have been conducted in the USA where social and health inequalities among ethnic groups are more documented. The discrepancies in the observations of susceptibility to the disease between races/ethnicities may be explained partially by the methodology used. Most of the studies are using databases which may suffer from reporting or selection bias.

Biological differences between races or ethnicities could be an explanation for some of the observed differences. Research on the potential racial difference in lung capacity and lung function is extremely controversial because of its tight link to history of racism in science(125, 126). For instance, "*difference of structure in pulmonary apparatus*" was used at some point to justify the condition of slaves in US slavery-based republic. Starting from the intend to define norms for spirometry, racial differences were finally used as an argument to justify superiority of white race vs the colored ones. Therefore, the idea of White people having naturally a higher lung capacity is now approached with some skepticism(125). With their systematic review on this topic, Braun et al. showed that definition of race is often lacking precision leading to a lack of consistency on how an individual is allocated to a specific group. They highlighted that most of the publications focus on anthropometric or inherent differences but did not consider race and ethnicity in the context of socio-economic status(127).

The role of potential confounding factors to explain the difference observed with regards of race or ethnicity in susceptibility to respiratory infections should be considered. An interesting finding from Donaldson et al. is that racial disparities vary with the location where they are studied(78), confirming some influence of socio-economic and geopolitical elements. Race and ethnicity should therefore be considered together with socio-economic status and place of residence. Aspects linked to urbanization, level of poverty and population density may also play a role. Indeed, places where most racial disparities are observed are also those where Black people live and experience with higher level of poverty and with limited access to quality healthcare and preventative services(78).

Complexity of confounding factors when assessing “racial differences” in respiratory disease has been recognized previously by van Sickle et al. who showed the contribution of socio-economic factors and education level to “racial differences” measured in lung function (128).

4.1.6. Occupational risk in the pre-aging population

Two types of occupational risk have been identified in the targeted literature review. The first one, documented in the context of Streptococcus Pneumoniae, is the exposure to metal fumes and respiratory irritants. Higher exposure to pollution in the place of residence is similarly associated with increased incidence of respiratory infectious diseases. For those with an occupation involving chronic exposure to such respiratory irritants, one hypothesis is that the risk may be even higher due to the chronicity of the exposure. This risk is impacting all categories of job exposed to fumes (welders, shipyard workers…) and silica(109). This association has led some authors to advocate strongly for specific vaccination campaign for welders in the UK(110). Recommendation of pneumococcal vaccination for welders and metal workers is now published on NHS website(129). UK remains precursor in such recommendation.

The second occupational risk, reported in the literature in the context of flu, is linked to social interactions and the subsequent risk of person to person and airway transmission of such contagious disease. Indeed, influenza viruses seems to spread mainly by droplets made when people with flu cough, sneeze or talk. These droplets can land in the noses or mouths or possibly inhaled into the lungs of other people nearby(130). The profession the most impacted by the disease is people working in public transportation characterized by closed and crowded environments(87).

In context of covid-19, similar risk of exposure to SARS-Cov-2 infection was directly related to the nature of people’s profession(124). A link was made between education level and occupational risk, with a trend that people with lower educational level often work in jobs that do not offer the opportunity to work remotely, increasing the exposure risk. Also, in the most deprived groups, social distancing was an inaccessible privilege as it was impossible for them to depart from work for the period necessary to carry out quarantine(124).

4.1.7. Religion and related practices as risk factor for infectious disease

Religion is not a risk factor for infectious disease per se. However, some religious practice may lead to an increase exposure. The most documented one in the literature is related to the Islam. Several studies have evaluated the risk of respiratory infectious disease related to Hajj pilgrimage in Mecca in the Kingdom of Saudi Arabia. There are nearly 2-3 million Muslims from countries across the globe that take part to the Hajj pilgrimage each year(131). They undergo rituals that are physically demanding and are exposed to crowded environment during most of the duration of the pilgrimage which lasts on average between 1 week to 1 month(97, 98, 100).

The type of risk to which pilgrims are exposed is linked to social interactions and crowded environment that favor transmission of the respiratory diseases. In the literature review, the risk has been reported for influenza and streptococcus Pneumoniae infections but not for RSV. This risk could be managed by ensuring adequate vaccination of the pilgrims before pilgrimage(100). Compliance to vaccination before Hajj pilgrimage could be increased by some awareness and information campaign on the specific needs of that sub-population.

4.2. Opportunities and challenges for vaccination to improve health equity

It is difficult to discriminate if the increased susceptibility to respiratory infectious disease observed in older adults from a more deprived socio-economic groups and in the less educated group results from a lower level of vaccination or to other factors like living conditions of non-healthy behaviors. Current knowledge in the scientific literature suggests multiples causes, including different behavior in term of prevention and vaccination. In the context of influenza disease and Streptococcus infections, public health authorities in high income countries have implemented vaccination programs targeting groups at high risk of morbidity and mortality such as older adults. Despite compliance is increasing, the targeted population in older adults is not yet fully vaccinated. Both influenza vaccination and pneumococcal vaccination campaigns are sub-optimal but immunization deficit is more important for pneumococcal vaccination(73). Compliance with vaccination tends increase with age in the older adult population and may be influenced by several factors such as economic status, education, household composition, comorbidities(70, 132)… Behaviors with regards to vaccination and vaccination uptake are largely discussed in the scientific literature, with various observations reported. For instance, direction of the association between socio-economic status and vaccination uptake varies(70, 73). Many studies showed that lower socio-economic status was found to correlate with lower vaccination uptake while patients with higher income were found to have significantly higher probabilities of vaccine uptake(70, 133-136). However, one study in Italy showed that influenza vaccination was more prevalent in lower social classes(70, 119). Lucyk et al. explain these discrepancies in the observations by the measures of socio-economic status that have been used(137). Socio-economic status is a multi-dimensional concept that may vary with context. It is measured indirectly by using the proxy measure of class (e.g. economic resources), prestige (e.g. community ranking), occupation (e.g. occupational class) and education (e.g. education level). Socio-economic status is measured using either a single a measure, or a combination of several variable (e.g. deprivation index). Lucyk et al. recommend employing as many measures as possible for socio-economic status and to consider how they interact in order to convey as much information as possible on the impact of socio-economic status(137).

Vaccination can help to address inequities as far as the determinants of health are considered in the design and implementation of vaccination campaigns. To increase access to vaccines for those who need it the most, access should be adapted to their functional status. Additional healthcare support should be considered for socio-economic deprived groups or when social support is deficient(70, 135). Another area for improvement is the acknowledgement of cultural values and socio-cultural aspects that influence vaccine uptake(70) as well as some racial disparities with regards to vaccination compliance(70, 133, 138). Effective interventions to promote vaccination should understand and be adapted to socio-cultural beliefs and practices, to better promote benefits of vaccination within communities which may doubt on the effectiveness of vaccines. One specific and concrete example highlighted in this work would be to increase awareness and/or good practice in terms of prevention and vaccination in context of Hajj pilgrimage for the Muslims' older adults.

Exposure to respiratory irritants for welders increase their risk to streptococcus infections and social interactions favor transmission of influenza which represents a significant risk for those working in public transportation. Tailored vaccination campaign for these sub-groups of workers should be considered more consistently for those older than 50 years old.

At individual level, behavior toward vaccination is influenced by multiples factors such as physician's advice, cost, convenience, perceived susceptibility, prior experiences, health status, personal beliefs, (mis)conception about the vaccine and the disease…which represent many opportunity to act to improve vaccine uptake(70, 73). Role of physician, family member and care givers to ensure and coordinate social support and management of psychological factors is key to improve vaccine acceptance in older adults.

Beyond individuals factors, the conceptual framework for action on the social determinants of health proposed by Solar and Irwin(75) emphasize the role of some political mechanisms that may generate health inequalities. Political decision in terms of vaccination may partially explain some difference observed in susceptibility to the infectious disease. In our review, Fallani et al. make the hypothesis that the higher mortality rate to influenza and pneumonia observed in Northern Italy compared to Southern and central provinces originates in political decision in this area to use a vaccine with less efficacy.

Overall, this work shows that there are still some opportunities to increase equity through vaccination. Our findings highlight some areas to improve to vaccination policies and public health immunization campaigns.

4.3. Challenges to generate evidence and demonstrate impact on equity of the vaccination of older adults in HTA

This research on determinants of health shows the complex interplay between structural determinants of health and between structural and intermediary determinants, which can't be totally isolated from each other. As discussed, it is recommended to conceptualize socio-economic status as a multi-dimensional concept and to assess it using as many measures as possible(137). The use of composite index combining several measures of economic and social status might help to better grasp the interconnection between determinants of health. For instance, in UK, the Index of Multiple Deprivation (IMD) is the most used. The IMD is a composite measure of social deprivation based on seven weighted domains: income; employment; health and disability; education skills and training; barriers to housing and other services; crime and living environment(83). In USA, the CDC has developed the Social Vulnerability Index (SVI) which considers several social factors including socio-economic status (poverty, employment, housing cost burden, education, health insurance), household characteristics (age, children, disabilities, single parent household, English language proficiency), racial and ethnical minority status, housing type and transportation (multi-unit structures, mobile home, crowding, no vehicle, group quarters(139). Our targeted literature review also highlighted the use of the socio-economic and health deprivation index (SEDHI) by several research groups in Italy(82, 90). Such indexes may help to define sub-groups of society in which benefits and opportunity cost associated with vaccination could be assessed to measure equity impact of vaccination. However, some reflection should take place to ensure some harmonization across countries in the measurement of determinants of health, including socio-economic status, especially in Europe, where some difficulties remain for HTA of vaccines, due to the high heterogeneity of processes for decision making between countries(4).

Another aspect to consider is the type, quality and completeness of data to be used. In our targeted literature review, we have observed the use of several database in the literature to generate knowledge in this area. Development of more robust and harmonized tools dedicated to infectious disease surveillance programs which would include data on vaccination status and information on determinants of health would help to generate evidence of the equity improvement provided through vaccination campaigns.

Generating such evidence on older adult population is also limited by their under-representation in biomedical research. This is further exacerbated in those belonging to social groups adversely impacted by social determinants of health that reduce access to health care but also the ability to participate in clinical trials(140). Overall, older adults are less likely to be eligible, screened, enrolled, or be interested in clinical studies(140). Barriers for research participation includes practical considerations (transportation to study sites), lack of methods to engage older communities, misunderstanding or confusion around study procedures and concerns over side effects. Some older adults might not be mentally competent of physically well enough to consent or adhere to research protocols. Barriers may also come from the investigators or physicians, like the perception of age as a risk with regards to potential adherence to study procedures or a risk of toxicity of experimental treatment. Opposition may also come from friends and family or from the perceived burden on caregivers(140). A lack of racial and ethnic diversity has also been reported in many studies(140). Improving participation of older adults, including those from racial minorities and socio-deprived group to research, can be reach by using methods of contact that are appropriate for older adults, including in-person contact for certain hard to reach sub-groups, with messaging that resonate for them and by incorporating patient perspective during the study. Recruiting from multiple sites like senior housing and local church, offering home visits, coordinate the research with routine care and financial incentives may help(140). Identifying and addressing barriers for study participation for older adults of low socio-economic status, racial and ethnical minorities(140) is key to include and retain them in clinical studies in order generate the information needed to demonstrate equity impact of vaccination.

4.4. Limitations of this work

This work has certain limitations. The selection of studies in the targeted literature review has been operated mainly by one reviewer (Julie Saliez). To limit impact, a sample of 5 % of the abstracts has been reviewed by a second reviewer (Sophie Lucas) to confirm consistency of the selection process. Full text review was performed only by one reviewer (Julie Saliez). Due to large number of abstracts screened, a double review during the entire selection process would have been beneficial to limit risk of inclusion bias.

Studies may have source bias as only two databases have been used (Pubmed and EBSCO host) and no search has been made in the grey literature. Most of the studies selected are real world evidence database, cross-sectional or ecological studies which may be less robust than cohort studies by design. To limit impact on the interpretations, quality of each study has been evaluated and studies judged too weak in terms of robustness have been eliminated.

Some publications were not accessible and could not be considered for full text assessment. They were eliminated by default.

Scope of this work was the impact of determinants of health on respiratory infectious disease in older adults in a non-pandemic context. Therefore, covid-19 infection has not been considered despite an important information in the scientific literature in this topic.

5. Conclusions and perspectives

Social inequalities in the context of vaccination can appear in susceptibility to infectious disease, in access to vaccines and in health outcomes following vaccination. To further understand the value of vaccination in terms of social equity, the scope of this work was to assess the impact of determinants of health on the incidence of vaccine preventable respiratory diseases in older adults in North-Western high-income countries. We have confirmed that many determinants of health may affect susceptibility to infectious disease in older adults, in particular the socio-economic status.

Overall, studying the determinants of health of importance in context of infectious respiratory disease in older adults has highlighted the complex interplay between several structural and intermediary determinants of health, which may re-enforce each other to define some trajectories of the diseases in sub-groups of this population. Such blurring lines between the different determinants of health represents a challenge to assess value that vaccination can bring in terms of social equity and highlight the needs for additional research in order to define a common framework to support equity assessment in future HTA and public health decision making.

We have highlighted the difficulty to discriminate if the increased susceptibility to respiratory infectious disease observed in older adults from a more deprived socio-economic groups results from a lower level of vaccination or from other factors like living conditions or non-healthy behaviors. The outcome of vaccination might also vary amongst older adults, which are characterized by a large heterogeneity in terms of immunosenescence. Therefore, to fully understand the value of vaccination in terms of social equity, the 2 remaining "*stairs of health inequality impact*" as referred by Cookson and Love-Koh (21) i.e., access to vaccination and health outcome following vaccination should be investigated through additional literature review and integrated in the full analysis.

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7. Appendices

7.1. Protocol of targeted literature review

1. Administrative information:

Title and Identification:

This targeted literature review is a part of a master thesis in Public Health.

The title of the master thesis is "Understanding value of vaccination improving health equity in older adults: the role of social determinants of health for vaccine preventable diseases.".

This protocol of targeted literature review is following the recommendation of PRISMA-P checklist(141).

Registration:

The protocol will be registered at the time of publication, if any, and references will be provided as per journal recommendation.

Authors and Support:

The targeted literature review is conducted by Julie Saliez under the supervision of Dr. Ekkehard Beck (GSK) and Pr. Sandy Tubeuf (UCLouvain).

This research work is part of the GSK Adult Immunization research program led by Ekkehard Beck who is Vaccines Value Evidence Portfolio Lead for Adult Immunization and is co-promotor of Julie Saliez's master thesis.

It is conducted as part of the academic program of Master in Public Health in UCLouvain where Julie Saliez is registered as student.

Sandy Tubeuf is Professor of Health Economic at UCLouvain and the promotor of Julie Saliez's master thesis.

Sophie Lucas will perform a second review in the selection process on a sample of titles and abstracts. Sophie Lucas is also registered as student in the academic program of Master in Public Health in UCLouvain.

2. Introduction:

Rationale:

Full benefit of vaccination might be underestimated in Health Technology Assessment (HTA). This work is part of a broader research program aiming to identify and increase knowledge on elements of value of vaccination to be consider in HTA in order to better capture the broader spillovers of vaccination. Previous work conducted by Postma et al. (2022) proposed three concepts to be considered for inclusion in HTA namely 1) macroeconomic gains (e.g. benefits to the economy and/or society), 2) social equity and ethics (e.g. equal distribution of health outcomes, reduced health/financial equity gaps) and 3) health system strengthening, resilience and security (e.g. efficiency gains, reduced disruption, increased capacity)(8, 9). This work aims to increase the knowledge on the value of vaccination in terms of social equity in older adults (OA) population.

Health equity is an important objective of health systems in many countries. It requires changes in systems and policies when they result in health disparities that can be considered as unfair. Health disparities are defined by the Center for Disease Control and Presentation in United states (CDC) as "*preventable difference is the burden of disease, injury, violence or opportunities to achieve optimal health that are experienced by populations that have been disadvantaged by their social or economic status, geographical location and environment" (14)*. As health disparities are considered as preventable through societal efforts, there is a growing interest in decision bodies in charge of HTA to better understand who gains and who loses from health programs, in order to better anticipate and address health inequalities. An important body of knowledge is currently under development to help decision makers to assess where to make trade-offs between classical cost-effectiveness analysis (CEA) and equity in the distribution of health-related outcomes(17).

Health conditions and outcomes are known to be influenced by non-medical factors called social determinants of health. WHO refers to them as "*the conditions in which people are born, grow, work, live and age and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems."* (20). The main social determinants of health are the place of residence, race and ethnicity, occupation, gender, religion, education, socio-economic status and social capital. To assess the impact of vaccination in terms of health equity, there is a need to understand which social determinants of health are relevant in the epidemiology of vaccine-preventable diseases. So far, reference to health equity criteria for decision making in HTA on vaccine is limited due to a lack of knowledge on the relevant social determinants of health in the case of vaccine preventable diseases. In many countries, there is no guidance on which risk factors to consider and this limits evidence generation and decision making.

In this work, we will focus on the social determinant of health representing risk factors for respiratory infections in the older adult population in western-developed countries. Infectious respiratory diseases are of particular interest as they represent a high medical burden in such population and vaccination can bring benefit as prophylactic intervention.

<u>Objectives:</u>

Purpose of this review is to investigate equity across the susceptibility to respiratory infectious diseases of older adult population. The aim is to identify the social determinants of health that are of interest when one assesses the value of vaccination across older adults and that would be relevant to be considered in HTA by advisory bodies and decisions makers. This TLR aims to provide a synthesis of the identified social determinants and their importance for respiratory infectious disease of older adult population.

This TLR will focus on three main infectious agents causing lower respiratory tract infection and death in older adults: Influenza, Respiratory Syncytial Virus (RSV) and Streptococcus Pneumoniae. There are vaccines available on the market already for Influenza and Streptococcus Pneumoniae and active research development ongoing for vaccines against RSV infections.

We consider a context of non-pandemic respiratory infectious diseases; therefore COVID-19 will be out of scope. The rationale for not including COVID-19 pandemic in this TLR is that there are already several systematic reviews available and ongoing on the question.

Research question:

"What are the social determinants of health impacting the incidence of lower respiratory tract infection caused by Flu or RSV or streptococcus pneumoniae in older adult population (50+ years old)?"

The research question has been established using the PECOS method as followed:

Population	Older adult population aged of 50+
Exposure	Lower respiratory tract infection caused by Flu, RSV or Streptococcus pneumonia. Focus is made on lower respiratory tract infections as they are critical outcomes against which vaccine efficacy is measured/ assessed.
Comparison	Stratification in sub-groups vs whole population (when applicable)
Outcome	Risk factors linked to social determinants of health or health inequities that might influence the incidence (and/ or prevalence) of the lower respiratory tract infections
Study-type	Quantitative studies: Epidemiology non-interventional studies: prospective observational cohort studies, retrospective studies, comparative studies, case-control studies Systematic literature reviews on respiratory infectious diseases of older adult population

3. Methods

<u>Information sources:</u>

Research will be conducted in the Pubmed and EBSCO host database.

Search Strategy:

Research in Pubmed will be based on MeSH terms related to the research question and identified in Pubmed MeSH thesaurus as described in the table below.

On top, some filters will be used in Pubmed:

- for language of publication: English
- for the period:
- 10 years for to pneumococcal or RSV infection.
- 5 years for influenza. Considering the medical burden of Influenza in older adult population, the number of publications on this topic is much higher. Period will therefore be limited to 5 years to limit the number of records identified while it will still allow a good overview of situations before, during and after the covid-19 pandemic.
- for the species: Humans
- for the age: Middle Aged +: Aged 45+ years, Middle Aged +: 45- 64 years, Aged 65+ years, 80 and over: 80+ years

ID	Topic	MeSH or filters
1	Older adults	No MeSH terms as filters will be used in Pubmed for the age: Middle Aged +: Aged 45+ years, Middle Aged +: 45-64 years, Aged 65+ years, 80 and over: 80+ years
2	Flu	Influenza, Human
4	RSV	Respiratory Syncytial Virus Infections
5	Streptococcus pneumoniae	Pneumococcal Infections
7	Lower respiratory tract infections	Respiratory tract infections Respiratory tract diseases
8	Social Determinants of Health (*)	Residence Characteristics Geography Medical Racial Groups Race Factors Occupations Sex Gender Identity Gender Role Gender Equity Sexual and Gender Minorities Sexism Religion Education Educational Status Education, Professional Minority Health Health Literacy Literacy Social Class Social Capital Behavior

		Culture ethnology
9	Study type	Epidemiology

(*) Both global terms referring to social determinants of health and more specific terms referring to the main ones (place of residence, race and ethnicity, occupation, gender, religion and culture, education, socio-economic status and social capital) have been selected in the MeSH thesaurus and included in the queries in order to have broad selection of publication on these risk factors.

Research of publications in Pubmed will be conducted in 3 steps, considering separately the 3 infectious agents of interest. Publications over a period of 10 years will be screened for studies related to pneumococcal or RSV infection and of 5 years for influenza. The different approach for screening period is due to the number of publications existing on the topic that are more important for influenza-related infections.

The search query for Influenza infections will be as followed:

"(Flu OR Influenza) AND (epidemiology) AND (Social Determinants of Health OR Healthcare Disparities OR Health Inequities OR Health Status Disparities OR Sociological Factors OR Residence Characteristics OR Geography Medical OR Racial Groups OR Race Factors OR Occupations OR Sex OR Gender Identity OR Gender Role OR Gender Equity OR Sexual and Gender Minorities OR Sexism OR Religion OR Education OR Educational Status OR Education, Professional OR Minority Health OR Health Literacy OR Literacy OR Social Class OR Social Capital OR Behavior OR Culture OR ethnology) "

On top, following filters will be used in Pubmed:

- for language of publication: English
- for the period: 5 years
- for the species: Humans
- for the age: Middle Aged +: Aged 45+ years, Middle Aged +: 45- 64 years, Aged 65+ years, 80 and over: 80+ years

The search query for pneumococcal infections will be as followed:

" (Pneumococcal Infections) AND (Epidemiology) AND (Social Determinants of Health OR Healthcare Disparities OR Health Inequities OR Health Status Disparities OR Sociological Factors OR Residence Characteristics OR Geography Medical OR Racial Groups OR Race Factors OR Occupations OR Sex OR Gender Identity OR Gender Role OR Gender Equity OR Sexual and Gender Minorities OR Sexism OR Religion OR Education OR Educational Status OR Education, Professional OR Minority Health OR Health Literacy OR Literacy OR Social Class OR Social Capital OR Behavior OR Culture OR Ethnology) "

On top, following filters will be used in Pubmed:

- for language of publication: English
- for the period: 10 years
- for the species: Humans
- for the age: Middle Aged +: Aged 45+ years, Middle Aged +: 45- 64 years, Aged 65+ years, 80 and over: 80+ years

The search query for RSV infections will be as followed:

(Respiratory Syncytial Virus Infections) AND (Epidemiology) AND (Older adults OR Aged OR Frail Elderly OR Age Groups OR Health Services for the Aged OR Homebound persons) AND (Social Determinants of Health OR Healthcare Disparities OR Health Inequities OR Health Status Disparities OR Sociological Factors OR Residence Characteristics OR Geography Medical OR Racial Groups OR Race Factors OR Occupations OR Sex OR Gender Identity OR Gender Role OR Gender Equity OR Sexual and Gender Minorities OR Sexism OR Religion OR Education OR Educational Status OR Education, Professional OR Minority Health OR Health Literacy OR Literacy OR Social Class OR Social Capital OR Behavior OR Culture OR Ethnology)

On top, following filters will be used in Pubmed:

- for language of publication: English
- for the period: 10 years
- for the species: Humans
- for the age: Middle Aged +: Aged 45+ years, Middle Aged +: 45- 64 years, Aged 65+ years, 80 and over: 80+ years

Same approach will be done for the research in EBSCO host, but only one research will be done, grouping the 3 infectious diseases. MeSH terms have been identified in the EBSCO host thesaurus as per research question as described in the table below:

<table>
<tr><th>ID</th><th>Topic</th><th>MeSH or filters</th></tr>
<tr><td>1</td><td>Older adults</td><td rowspan="2">Respiratory infection in old age
Influenza
Respiratory syncytial virus infections
Pneumococcal pneumonia</td></tr>
<tr><td>2</td><td>Lower respiratory tract infections (Influenza, RSV, Streptococcus pneumoniae)</td></tr>
<tr><td>3</td><td>Social Determinants of Health (*)</td><td>Social determinants of health
Social factors
Social capital
Racial inequality
Gender inequality
Social classes
Racism
Education
Minorities
Culture
Religion
Education & economics
Behavior
Health literacy</td></tr>
<tr><td>4</td><td>Type of study</td><td>epidemiology</td></tr>
<tr><td>5</td><td>Exclusion terms</td><td>COVID-19
Children
Avian Influenza</td></tr>
</table>

The search query will be:

(RESPIRATORY infections in old age OR INFLUENZA OR RESPIRATORY syncytial virus infections OR PNEUMOCOCCAL pneumonia) AND (EPIDEMIOLOGY) AND (SOCIAL determinants of health OR SOCIAL factors OR SOCIAL capital OR RACIAL inequality OR Gender inequality OR Social classes or RACISM OR EDUCATION OR Minorities OR CULTURE OR RELIGION OR EDUCATION & economics OR Behavior OR HEALTH literacy) NOT (COVID-19) NOT (CHILDREN) NOT (AVIAN Influenza)

The following filters will be used in EBSCO host:

- Full text
- References available
- Peer review
- Publication date from 2012
- Language: English

Duplicates will be removed from the records identified from the database search.

Selection of papers will be first based on titles and abstracts.

Full-text articles will then be assessed for eligibility. Articles will be included in the final list based on full text screening.

To ensure selection of relevant papers, a sample of 5% of the titles and abstracts will be assessed independently by a second reviewer (Sophie Lucas). The results will be compared, and deviations will be discussed. In case of doubt by both researchers, the title will be selected for full-text evaluation.

Process and outcome of screening and selection will be represented by a PRISMA flow chart.

Original articles and secondary literature such as systematic literature review will be selected as described in the eligibility criteria.

Eligibility criteria :

Inclusion :

Inclusion criteria are defined as per PECOS elements:

Population:

- Adult population aged of 50 year or above. The OA population will be divided in 3 groups for the analysis: 50 to 64; 65 to 79; 80 and above. It includes OA population living in community and in nursing home or any kind of institution.
- Northern Western setting: only studies conducted in populations from high income countries from North America or Northern and Western Europe will be selected (USA, Canada, UK, Austria, Belgium, France, Germany, Ireland, Luxembourg, Monaco, Netherland, Switzerland, Andorra, Portugal, Spain, Italy, Denmark, Norway, Sweden, Finland, Iceland) based on geographical location.

Exposure:

- Studies referring to respiratory tract infectious (pneumonia, bronchiolitis) caused by Influenza, RSV of pneumococcal infections. Focus is made on lower respiratory tract infections as they are critical outcomes against which vaccine efficacy is measured/ assessed.

Comparator:

- As the type of studies are non-interventional, there will be no comparator per se. Some subgroups with risk factors might be compared to whole population.
- Both vaccinated and non-vaccinated population will be included in the review. Purpose is to consider potential bias linked to vaccination uptake that might be different in the different social groups and then impacting incidence of the disease.

Outcomes:

- Any social determinants of health will be considered as per WHO Commission on Social Determinants of Health conceptual framework i.e. structural and intermediary determinants of health inequities. It includes the place of residence, race & ethnicity, occupation, gender, religion & culture, education, socio-economic status and social capital but also behaviors and material condition linked to those determinants.

Studies: The type of studies that will be considered for inclusion are:

- Quantitative studies: Epidemiology non-interventional studies: prospective observational cohort studies, retrospective studies, comparative studies, case-control studies, cross-sectional design, survey
- Systematic literature review.
- Publications in English

Exclusion:

Population:

- Young population and children,
- Population with comorbidities younger than 50 years old (or if no information on age is reported)
- Healthcare workers younger than 50 years old (or if no information on age is reported)
- Countries not included in inclusion criteria

Exposure:

- Studies focusing (only) on respiratory disease caused by SARS-COV-2 or other infectious agents
- Studies on avian flu and 1918 Flu pandemic

Comparator:

Outcomes:

Studies:

- Randomized controlled trial: These publications will be excluded as they might be not informative on risk factors distribution in older adult population due to process of randomization that aim to control potential impact of such distribution.
- Study focusing only on vaccine uptake, with no information on epidemiology of the disease.
- Studies focusing on clinical risk factors and/or comorbidities in global population not related to determinants of health
- Study on vaccine efficacy and vaccine efficiency.
- Studies based on modeling only, without detailed information on data input and/or data analysis.
- Studies related to Influenza published before 2017
- Studies related to RSV and Streptococcus Pneumoniae published before 2012
- Non-peer-reviewed publications indexed in Pubmed
- Studies focusing on healthcare occupation only, without comparison to the whole population

Study records:

Data management and selection process:

For each search, list of records identified in Pubmed and EBSCO host will be saved for tracking purpose in End-Note. Selection will be made in Rayyan. Selected abstracts and full study publication text will be saved in Endnote. Screening to remove duplicates will be performed in both systems.

Paper selected from secondary publications will be saved in a separate folder.

Selection will be made by one reviewer (Julie Saliez) with a 5% sample being confirmed by a second reviewer (Sophie Lucas). The screening and study selection will be documented in a flowchart using PRISMA 2020 statement template as reference.

A data extraction form will be created in excel where data on studies, population description, exposure, comparators and outcomes will be recorded.

Data items:

For each search, the following data will be collected:

Study:

- Study identifier
- Authors
- Date
- Journal
- DOI
- Type of study
- Aim of the study
- comments

Population description:

- Aged 50 to 64
- Aged 65 to 80
- Aged 80+
- Country

Exposure/ Intervention

- Infectious agent confirmation
- Disease/ reported symptoms
- Severity of the disease
- Treatment
- Incidence
- Prevalence

Information on vaccination:

- Vaccination: Y/N
- Type of Vaccine received
- Reported efficacy

Outcomes: Impact on disease incidence, prevalence will be sought for the following determinant of health

- Structural determinant of health:
    - Geography/place of residence
    - Ethnicity and race
    - Occupation
    - Gender
    - Culture, religion & societal values
    - Education and literacy
    - Socio-economic status/ position and social class
- Intermediate determinants of health:
    - Social capital
    - Behaviors and psychological factors
    - Living and working conditions (nursing home…)

Conclusions from the authors:

- discussion (if any) on the impact of the determinant in health on the disease
- recommendation (if any) to use it as equity stratifier and how
- Quality of the studies evaluated as followed:
- Quality of the studies assessed through the JBI appraisal tool (Critical Appraisal Tools | JBI)
- Robustness of study design based on Evidence-based Medicine classification

Bias:

Bias in study selection:

Bias of inclusion will be avoided as the purpose of this TLR is to report current knowledge on the impact of any health determinants on respiratory disease caused by infections. There is no pre-conceptual idea of the results. Eligibility criteria are quite broad to avoid pre-selecting some determinants of health vs others.

There is a risk of reporting bias as some determinants of health (like race and ethnicity) may have been more studied than others. Number of studies reported for each health determinant will be counted to further assess that risk.

Bias in individuals studies:

There is a risk that epidemiology of respiratory diseases and their distribution in social groups are impacted by vaccination uptake as confounding factor. Vaccination status may vary between social groups and impacts the distribution of respiratory diseases on top of other equity factors. To take that bias into consideration, information on vaccination status will be sought and documented.

Data synthesis:

The data synthesis will summarize the characteristic of the studies selected and the importance in the literature for each determinant of health (i.e., number of publications addressing each of them), for the 3 infectious agents and in total. Population covered by the studies will be described considering location (countries).

A summary of the key findings on the determinant of health of importance to understand epidemiology of infectious disease will be made. Interpretation of the results in order to identify the more vulnerable groups to the disease will be made.

7.2. List of studies selected in the targeted literature review and references

Study ID		Full reference
ID	first author & date	
1	Almeida, 2014	Almeida ST, Nunes S, Santos Paulo AC, Valadares I, Martins S, Breia F, et al. Low prevalence of pneumococcal carriage and high serotype and genotype diversity among adults over 60 years of age living in Portugal. PLoS One. 2014;9(3):e90974. Epub 20140306. doi: 10.1371/journal.pone.0090974. PubMed PMID: 24604030; PubMed Central PMCID: PMC3946249.
2	Cassir, 2020	Cassir N, Pascal L, Ferrieux D, Bruel C, Guervilly C, Rebaudet S, et al. Outbreak of pneumococcal pneumonia among shipyard workers in Marseille, France, January to February 2020. Euro Surveill. 2020;25(11). doi: 10.2807/1560-7917.Es.2020.25.11.2000162. PubMed PMID: 32209166; PubMed Central PMCID: PMC7096773.
3	Coggon, 2015	Coggon D, Harris EC, Cox V, Palmer KT. Pneumococcal vaccination for welders. Thorax. 2015;70(2):198-9. Epub 20141015. doi: 10.1136/thoraxjnl-2014-206129. PubMed PMID: 25319209; PubMed Central PMCID: PMC4445601.
4	Flamaing, 2015	Flamaing J, De Backer W, Van Laethem Y, Heijmans S, Mignon A. Pneumococcal lower respiratory tract infections in adults: an observational case-control study in primary care in Belgium. BMC Fam Pract. 2015;16:66. Epub 20150527. doi: 10.1186/s12875-015-0282-1. PubMed PMID: 26012956; PubMed Central PMCID: PMC4443659.
5	Grau, 2014	Grau I, Ardanuy C, Calatayud L, Schulze MH, Liñares J, Pallares R. Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. Int J Infect Dis. 2014;25:59-64. Epub 20140519. doi: 10.1016/j.ijid.2013.12.013. PubMed PMID: 24853638.
6	Hoang, 2019	Hoang VT, Meftah M, Anh Ly TD, Drali T, Yezli S, Alotaibi B, et al. Bacterial respiratory carriage in French Hajj pilgrims and the effect of pneumococcal vaccine and other individual preventive measures: A prospective cohort survey. Travel Med Infect Dis. 2019;31:101343. Epub 20181108. doi: 10.1016/j.tmaid.2018.10.021. PubMed PMID: 30415081; PubMed Central PMCID: PMC7110955.
7	Linkevicius, 2019	Linkevicius M, Cristea V, Siira L, Mäkelä H, Toropainen M, Pitkäpaasi M, et al. Outbreak of invasive pneumococcal disease among shipyard workers, Turku, Finland, May to November 2019. Euro Surveill. 2019;24(49). doi: 10.2807/1560-7917.Es.2019.24.49.1900681. PubMed PMID: 31822326; PubMed Central PMCID: PMC6905297.
8	Ochoa Gondar, 2017	Ochoa-Gondar O, Hospital I, Vila-Corcoles A, Aragon M, Jariod M, de Diego C, et al. Prevalence of high, medium and low-risk medical conditions for pneumococcal vaccination in Catalonian middle-aged and older adults: a population-based study. BMC Public Health. 2017;17(1):610. Epub 20170629. doi: 10.1186/s12889-017-4529-8. PubMed PMID: 28662648;
9	Rivero-Calle, 2019	Rivero-Calle I, Cebey-López M, Pardo-Seco J, Yuste J, Redondo E, Vargas DA, et al. Lifestyle and comorbid conditions as risk factors for community-acquired pneumonia in outpatient adults (NEUMO-ES-RISK project). BMJ Open Respir Res. 2019;6(1):e000359. Epub 20190312. doi: 10.1136/bmjresp-2018-000359. PubMed PMID: 31178994; PubMed Central PMCID: PMC6530500.
10	Smith, 2020	Smith EL, Wheeler I, Adler H, Ferreira DM, Sá-Leão R, Abdullahi O, et al. Upper airways colonisation of Streptococcus pneumoniae in adults aged 60 years and older: A systematic review of prevalence and individual participant data meta-analysis of risk factors. J Infect. 2020;81(4):540-8. Epub 20200617. doi: 10.1016/j.jinf.2020.06.028. PubMed PMID: 32562794; PubMed Central PMCID: PMC7532703.

11	Thomas, 2015	Thomas HL, Gajraj R, Slack MP, Sheppard C, Hawkey P, Gossain S, et al. An explosive outbreak of Streptococcus pneumoniae serotype-8 infection in a highly vaccinated residential care home, England, summer 2012. Epidemiol Infect. 2015;143(9):1957-63. Epub 20141009. doi: 10.1017/s0950268814002490. PubMed PMID: 25298247; PubMed Central PMCID: PMC9507245.
12	Toren, 2020	Torén K, Blanc PD, Naidoo RN, Murgia N, Qvarfordt I, Aspevall O, et al. Occupational exposure to dust and to fumes, work as a welder and invasive pneumococcal disease risk. Occup Environ Med. 2020;77(2):57-63. Epub 20191217. doi: 10.1136/oemed-2019-106175. PubMed PMID: 31848233; PubMed Central PMCID: PMC7029234.
13	Tramuto, 2017	Tramuto F, Amodio E, Calamusa G, Restivo V, Costantino C, Vitale F. Pneumococcal Colonization in the Familial Context and Implications for Anti-Pneumococcal Immunization in Adults: Results from the BINOCOLO Project in Sicily. Int J Mol Sci. 2017;18(1). Epub 20170106. doi: 10.3390/ijms18010105. PubMed PMID: 28067813; PubMed Central PMCID: PMC5297739.
14	Benkouiten, 2013	Benkouiten S, Charrel R, Belhouchat K, Drali T, Salez N, Nougairede A, et al. Circulation of respiratory viruses among pilgrims during the 2012 Hajj pilgrimage. Clin Infect Dis. 2013;57(7):992-1000. Epub 20130709. doi: 10.1093/cid/cit446. PubMed PMID: 23839997; PubMed Central PMCID: PMC7108031.
15	Hansen, 2022	Hansen CL, Viboud C, Chaves SS. The Use of Death Certificate Data to Characterize Mortality Associated With Respiratory Syncytial Virus, Unspecified Bronchiolitis, and Influenza in the United States, 1999-2018. J Infect Dis. 2022;226(Suppl 2):S255-s66. doi: 10.1093/infdis/jiac187. PubMed PMID: 35968872; PubMed Central PMCID: PMC9377031.
16	Holmen, 2021	Holmen JE, Kim L, Cikesh B, Kirley PD, Chai SJ, Bennett NM, et al. Relationship between neighborhood census-tract level socioeconomic status and respiratory syncytial virus-associated hospitalizations in U.S. adults, 2015-2017. BMC Infect Dis. 2021;21(1):293. Epub 20210323. doi: 10.1186/s12879-021-05989-w. PubMed PMID: 33757443; PubMed Central PMCID: PMC7986301.
17	Park, 2020	Park SK, Sack C, Sirén MJ, Hu H. Environmental Cadmium and Mortality from Influenza and Pneumonia in U.S. Adults. Environ Health Perspect. 2020;128(12):127004. Epub 20201216. doi: 10.1289/ehp7598. PubMed PMID: 33325772; PubMed Central PMCID: PMC7739956.
18	Bechini, 2018	Bechini A, Pieralli F, Chellini E, Martini A, Dugheri G, Crescioli F, et al. Application of socio-economic-health deprivation index, analysis of mortality and influenza vaccination coverage in the elderly population of Tuscany. J Prev Med Hyg. 2018;59(4 Suppl 2):E18-e25. Epub 20190228. doi: 10.15167/2421-4248/jpmh2018.59.4s2.1116. PubMed PMID: 31016263; PubMed Central PMCID: PMC6419307.
19	Bota, 2021	Bota A, Holmberg M, Gardner L, Rosvall M. Socioeconomic and environmental patterns behind H1N1 spreading in Sweden. Sci Rep. 2021;11(1):22512. Epub 20211118. doi: 10.1038/s41598-021-01857-4. PubMed PMID: 34795338; PubMed Central PMCID: PMC8602374.
20	Croft, 2019	Croft DP, Zhang W, Lin S, Thurston SW, Hopke PK, Masiol M, et al. The Association between Respiratory Infection and Air Pollution in the Setting of Air Quality Policy and Economic Change. Ann Am Thorac Soc. 2019;16(3):321-30. doi: 10.1513/AnnalsATS.201810-691OC. PubMed PMID: 30398895; PubMed Central PMCID: PMC6394122.
21	Donaldson, 2021	Donaldson SV, Thomas AN, Gillum RF, Mehari A. Geographic Variation in Racial Disparities in Mortality From Influenza and Pneumonia in the United States in the Pre-Coronavirus Disease 2019 Era. Chest. 2021;159(6):2183-90. Epub 20210102. doi: 10.1016/j.chest.2020.12.029. PubMed PMID: 33400931.

22	Fallani, 2021	Fallani E, Orsi A, Signori A, Icardi G, Domnich A. An exploratory study to assess patterns of influenza- and pneumonia-related mortality among the Italian elderly. Hum Vaccin Immunother. 2021;17(12):5514-21. Epub 20211229. doi: 10.1080/21645515.2021.2005381. PubMed PMID: 34965179; PubMed Central PMCID: PMC8916782.
23	Gaspard, 2019	Gaspard P, Mosnier A, Simon L, Ali-Brandmeyer O, Rabaud C, Larocca S, et al. Gastroenteritis and respiratory infection outbreaks in French nursing homes from 2007 to 2018: Morbidity and all-cause lethality according to the individual characteristics of residents. PLoS One. 2019;14(9):e0222321. Epub 20190924. doi: 10.1371/journal.pone.0222321. PubMed PMID: 31550261; PubMed Central PMCID: PMC6759171.
24	Godoy, 2018	Godoy P, Castilla J, Soldevila N, Mayoral JM, Toledo D, Martín V, et al. Smoking may increase the risk of influenza hospitalization and reduce influenza vaccine effectiveness in the elderly. Eur J Public Health. 2018;28(1):150-5. doi: 10.1093/eurpub/ckx130. PubMed PMID: 29020390.
25	Heron, 2019	Heron M. Deaths: Leading Causes for 2017. Natl Vital Stat Rep. 2019;68(6):1-77. PubMed PMID: 32501203.
26	Ho, 2020	Ho FK, Celis-Morales CA, Gray SR, Katikireddi SV, Niedzwiedz CL, Hastie C, et al. Modifiable and non-modifiable risk factors for COVID-19, and comparison to risk factors for influenza and pneumonia: results from a UK Biobank prospective cohort study. BMJ Open. 2020;10(11):e040402. Epub 20201119. doi: 10.1136/bmjopen-2020-040402. PubMed PMID: 33444201; PubMed Central PMCID: PMC7678347.
27	Hoang, 2019 (b)	Hoang VT, Sow D, Dogue F, Edouard S, Drali T, Yezli S, et al. Acquisition of respiratory viruses and presence of respiratory symptoms in French pilgrims during the 2016 Hajj: A prospective cohort study. Travel Med Infect Dis. 2019;30:32-8. Epub 20190308. doi: 10.1016/j.tmaid.2019.03.003. PubMed PMID: 30858034; PubMed Central PMCID: PMC7110710.
28	Hungerford, 2018	Hungerford D, Ibarz-Pavon A, Cleary P, French N. Influenza-associated hospitalisation, vaccine uptake and socioeconomic deprivation in an English city region: an ecological study. BMJ Open. 2018;8(12):e023275. Epub 20181219. doi: 10.1136/bmjopen-2018-023275. PubMed PMID: 30573483; PubMed Central PMCID: PMC6303586.
29	Jeganathan, 2021	Jeganathan N, Grewal S, Sathananthan M. Comparison of Deaths from COVID-19 and Seasonal Influenza in the USA. Lung. 2021;199(5):559-61. Epub 20210819. doi: 10.1007/s00408-021-00468-0. PubMed PMID: 34414503; PubMed Central PMCID: PMC8375609.
30	Lai, 2018	Lai A, Pisanu L, Casula L, Minerba L, Lillini R, Vercelli M. Influenza vaccination coverage and deprivation among the elderly in the municipality of Cagliari: results and perspectives. J Prev Med Hyg. 2018;59(4 Suppl 2):E65-e70. Epub 20190228. doi: 10.15167/2421-4248/jpmh2018.59.4s2.1197. PubMed PMID: 31016269; PubMed Central PMCID: PMC6419306.
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