Fostering healthy aging

Vetrano, Davide L; Triolo, Federico; Maggi, Stefania; Malley, Richard; Jackson, Thomas A; Poscia, Andrea; Bernabei, Roberto; Ferrucci, Luigi; Fratiglioni, Laura

DOI:
10.1016/j.arr.2021.101351

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Vetrano, DL, Triolo, F, Maggi, S, Malley, R, Jackson, TA, Poscia, A, Bernabei, R, Ferrucci, L & Fratiglioni, L 2021, 'Fostering healthy aging: the interdependency of infections, immunity and frailty', *Ageing Research Reviews*, vol. 69, 101351. https://doi.org/10.1016/j.arr.2021.101351

Ageing Research Reviews 69 (2021) 101351

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Fostering healthy aging: The interdependency of infections, immunity and frailty

Davide L. Vetrano [a,b,*], Federico Triolo [a], Stefania Maggi [c], Richard Malley [d], Thomas A. Jackson [e,f], Andrea Poscia [g], Roberto Bernabei [b], Luigi Ferrucci [h], Laura Fratiglioni [a,i]

[a] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[b] Centro Medicina dell'Invecchiamento, Fondazione Policlinico "A- Gemelli" IRCCS and Catholic University of Rome, Italy
[c] National Research Council, Neuroscience Institute, Padua, Italy
[d] Division of Infectious Diseases, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA
[e] Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[f] Department of Geriatrics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[g] Vaccination Office of Marche Region, Italy
[h] Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, USA
[i] Stockholm Gerontology Research Center, Stockholm, Sweden

ARTICLE INFO

Keywords:
Healthy aging
Frailty
Vaccination
Immunosenescence

ABSTRACT

Untangling the interdependency of infections, immunity and frailty may help to clarify their roles in the maintenance of health in aging individuals, and the recent COVID-19 pandemic has further highlighted such priority. In this scoping review we aimed to systematically collect the evidence on 1) the impact of common infections such as influenza, pneumonia and varicella zoster on frailty development, and 2) the role played by frailty in the response to immunization of older adults. Findings are discussed under a unifying framework to identify knowledge gaps and outline their clinical and public health implications to foster a healthier aging. Twenty-nine studies (113,863 participants) selected to answer the first question provided a moderately strong evidence of an association between infections and physical as well as cognitive decline – two essential dimensions of frailty. Thirteen studies (34,520 participants) investigating the second aim, showed that frailty was associated with an impaired immune response in older ages, likely due to immunosenescence. However, the paucity of studies, the absence of tools to predict vaccine efficacy, and the lack of studies investigating the efficacy of newer vaccines in presence of frailty, strongly limit the formulation of more personalized immunization strategies for older adults. The current evidence suggests that infections and frailty repeatedly cross each other pathophysiological paths and accelerate the aging process in a vicious circle. Such evidence opens to several considerations. First, the prevention of both conditions pass through a life course approach, which includes several individual and societal aspects. Second, the maintenance of a well-functioning immune system may be accomplished by preventing frailty, and vice versa. Third, increasing the adherence to immunization may delay the onset of frailty and maintain the immune system homeostasis, beyond preventing infections.

1. Background

As the population ages rapidly, new challenging scenarios are surfacing for both individuals and societies. Throughout the world, the older share of the population is expanding faster than the younger one, leading to an increasing prevalence of multimorbidity, disability and frailty (Vetrano et al., 2018b). One of the main goals in medicine is to prevent, or at least delay, the onset of these conditions, thus compressing the time that people live in poor health toward the very end of life. This will lead to meaningful advantages both at an individual and population level. The World Health Organization (WHO) promotes the concept of healthy aging as the process of developing and maintaining functional ability that enables wellbeing in older age, which should be the focus of all modern societies (WHO, 2015).

Alongside physical exercise and a healthy diet, immunization is considered to be one of the pillars to promote and maintain healthy

* Corresponding author at: Aging Research Center, Karolinska Institutet and Stockholm University, Tomtebodavägen 18 A, 10th floor, 171 65, Solna, Sweden.
E-mail address: davide.vetrano@ki.se (D.L. Vetrano).

https://doi.org/10.1016/j.arr.2021.101351
Received 16 December 2020; Received in revised form 16 April 2021; Accepted 3 May 2021
Available online 7 May 2021

aging (Teresa Aguado et al., 2018). Despite the commonly held belief that infectious diseases are less important than non-communicable diseases to health in high-income countries, this belief must be questioned when it comes to older adults. The COVID-19 pandemic is illustrative in this regard and teaches us painful but powerful lessons. Frail older people with multimorbidity and disability, and those living in residential facilities, are much more likely to be infected and to experience a higher case-fatality rate than the general population (Calderón-Larrañaga et al., 2020; Hewitt et al., 2020; Marengoni et al., 2020b).

Frailty, a condition of susceptibility and loss of resilience to even subliminal stress, is highly prevalent in older ages and is associated with increased risk of disability and mortality (Vetrano et al., 2018a, 2019; Zucchelli et al., 2019, 2018). Frailty is a negative prognostic factor during surgical or chemotherapy treatments and is associated with higher occurrence of infections and their adverse clinical course (Ethun et al., 2017; Wang et al., 2018). Indeed, pneumonia is one of the most frequent diagnoses in hospitalized older persons affected by disability and frailty, and may trigger a vicious cycle where pneumonia increases the severity of frailty and vice versa, leading to accelerated functional decline and mortality (Davydow et al., 2013; Quinton et al., 2018). Pneumonia, resulting from bacterial, influenza or other viral (e.g. coronaviruses) infections, is a frequent event especially in those who are living in long-term care institutions, where respiratory infections are associated with high disability burden, hospital care requirements, and mortality rate (Falcone et al., 2018; Kundi et al., 2019). Similarly, reactivations of varicella-zoster have been shown to be more frequent in the frailest older people, and to reduce functionality and quality of life (Bricout et al., 2015; Kundi et al., 2019; Mizukami et al., 2018; Zorzoli et al., 2018).

Influenza, pneumonia and zoster infections can be prevented through vaccination. In people of 65 years or older, influenza vaccination reduces the occurrence of influenza by 60 % and the occurrence of influenza-like illness by 40 % (Demicheli et al., 2018; Demurtas et al., 2020). Moreover, influenza vaccination reduces pneumonia hospitalizations by 9–12 %, and impacts survival reducing overall mortality by 5% in older vaccinated individuals (WHO, 2012). Similarly, in older people pneumococcal vaccination has been shown to reduce the occurrence of invasive pneumococcal disease by 73 % and the occurrence of pneumococcal pneumonia by 25 % (Falkenhorst et al., 2017). Finally, in this age-group, herpes zoster vaccination was reported to reduce shingles incidence by 51–92 % and post-herpetic neuropathy by 67–89 % (Cunningham et al., 2016; Gagliardi et al., 2019; Lal et al., 2015). However, there is strong evidence that older age is associated with reduced vaccination response, both serologically and in terms of infection rates. Reduced vaccination effectiveness has been connected with immunosenescence but the specific mechanisms are not clear and are the focus of extremely active research (Clegg et al., 2013; Pera et al., 2015).

Untangling the interplay between frailty, infections, and immunity may help to clarify their roles in increasing the risk of health deterioration and disability in older persons. In this report we aimed to summarize the scientific evidence concerning, on the one side, the role of major viral and bacterial infections in the development of frailty, and, on the other side, the role of frailty in blunting the efficacy of immunization in older persons. We achieved these aims by systematically reviewing the literature and discussing the findings under a unifying framework that may help in identifying the knowledge gaps that if addressed may lead to better strategies aimed at improving health, function and quality of life in old age.

2. Infections and frailty

Evidence suggests that frail individuals are susceptible to infectious diseases and more likely experience prolonged and complex clinical courses and long-term complications (Falcone et al., 2018; Hewitt et al., 2020; Kundi et al., 2019). However, less is known about the impact of infectious diseases on functional outcomes and frailty. We performed a systematic search of longitudinal studies investigating the role of influenza, pneumonia and varicella zoster infection on frailty (Box 1; **Fig. S1**).

Different measures and conceptualizations of frailty have been proposed over the years, but the most commonly employed are the physical phenotype model (Fried et al., 2001), and the frailty index model (Rockwood and Mitnitski, 2007). The first is based on the presence of at least three of the following five criteria: slow gait speed, low muscle strength, exhaustion, unintentional weight loss, and low physical activity levels. This model of frailty aims to capture physical impairments that reflect mostly muscle health, energy imbalance and nutrition aspects. The second is based on the assessment of a number of clinical and functional deficits (usually between 30 and 70) that together describe multiple aspects of health, representing a comprehensive proxy of biological age. Independent of its operationalization, frailty can successfully predict several negative health-related outcomes, and is increasingly being implemented in the assessment of older individuals,

Box 1
Systematic search methods.

Inclusion and exclusion criteria. PRISMA guidelines were followed for the present review. The three infectious diseases for which vaccination is highly recommended in all older adults (≥65 years) were considered: pneumococcus, influenza, and varicella zoster. Articles of interest were gathered from the following electronic databases: PubMed and Web of Science. Longitudinal (including intervention) studies were selected if they reported information on 1) The impact of infections on physical or cognitive function or frailty in older adults (aim 1); 2) The role of frailty on vaccine efficacy (aim 2). The following articles were excluded: a) Cross-sectional studies; b) Articles not in English; c) Articles involving individuals <18 years; d) Articles not based on human samples; e) Articles not providing definition of the outcomes or frailty; f) Guidelines, editorials, letters to the editor, and conference proceedings.

Search strategy. The search was carried out in two parallel tracks according to the two aims of the study, combining a) terms related to "infections" and "function"/ "frailty"; b) terms related to "immunization" and "frailty". The search was updated for the last time on 1 June 2020.

Study selection. Titles and/or abstracts of studies retrieved using the systematic literature search and those from additional sources were evaluated independently by two assessors to identify studies that potentially met the inclusion criteria outlined above. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by two review team members. Any disagreement was solved through discussion with a third co-author. A PRISMA flow-chart of the screening process is shown in **Fig. S1**.

Data extraction and synthesis. Standardized, pre-piloted tables were used to extract data from the studies. Extracted information includes author and year, setting, study population, study design, follow-up time, participant demographics, details on the intervention, frailty assessment, outcome definition, and main results.

both in geriatrics and other specialist settings (Hoogendijk et al., 2019). We consider both the Fried and the Rockwood models in our systematic search. Further, we explored also physical and cognitive impairments, which are two of the most important clinical manifestations of frailty (Fried et al., 2001; Grande et al., 2019a, b).

As summarized in Table 1 (complete information available in **Table S1**), 29 studies met the selection criteria and were examined, involving a total of 113,863 participants with an age range of 20–90 years. Studies were characterized by heterogeneity in study population (i.e. setting, age structure, gender distribution, ethnicity), inclusion criteria, length of follow-up, and operationalization of the functional measures. First, such variability is a strong indicator of the lack of established methodology in this research field. Second, it hinders the possibility to perform pooled analyses. Third, it challenges the direct comparisons as methodological differences might account substantially for findings inconsistency.

Table 1
Main findings from the selected studies on the relation between infections and the development of physical and cognitive decline, and frailty.

Study	N	Mean age years; (% female sex)	Significant impact of infections on		
			Physical function	**Cognitive function**	**Frailty**
Influenza					
Barker et al., 1998	243	n.a.; (82)	✓	–	–
Chen et al., 2017	56	n.a.	✓	–	–
Gozalo et al., 2012	2351	n.a.	✓	–	–
Pneumonia					
Binder et al., 2003	781	60+; (69)	✓	–	–
Bucks et al., 2007	42	20.3; (75)	–	✓	–
Büla et al., 2004	1324	85.7; (77)	✓	–	–
Caljouw et al., 2013	473	86; (67)	✓	–	–
Dalager-Pedersen et al., 2014	11,151	20–58; (46)	✓	–	–
Dalager-Pedersen et al., 2016	142	51–73; (54)	✓	–	–
Davydow et al., 2013	1434	77; (55)	✓	✓	–
Denke et al., 2018	42	42; (36)	✓	✓	–
El Solh et al., 2006	301	73.9; (40)	✓	–	–
Fried et al., 1997	312	n.a.; (68)	✓	–	–
Girard et al., 2018	67	57; (60)	–	✓	–
Goto et al., 2015	51	82; (57)	✓	✓	–
Hoogendijk et al., 2016	716	86; (76)	✓	–	–
Hughes et al., 2019	225	73; (59)	×	–	–
Kato et al., 2016	853	76.4 ; (42)	✓	–	–
Martín-Salvador et al., 2015	116	35–86; (43)	✓	–	–
Metlay et al., 1997	576	18+; (62)	✓	–	–
Shah et al., 2013	5888	73; (58)	–	✓	–
Tate et al., 2014	3069	79; (46)	–	✓	–
Varicella zoster					
Chen et al., 2018	78,410	50–59; (54)	–	✓	–
Duracinsky et al., 2014	609	70+; (60)	×	–	–
Grahn et al., 2013	42	50; (42)	–	✓	–
Mizukami et al., 2018	412	60+; (60)	✓	–	–
Schmader et al., 2007	160	71; (60)	✓	–	–
Tsai et al., 2017	3384	61; (50)	–	✓	–
Wang et al., 2016	633	74; (100)	–	–	×

✓ indicates a significant impact of the infection on function (physical and cognitive) and frailty; × indicates no effect.
"-" stands for "not investigated".
n.a. stands for "not available".

2.1. Frailty

Despite the high incidence of major infections in older adults, and the biological plausibility of their negative impact on frailty, there has been little investigation of this research field. A single longitudinal study investigated the impact of varicella zoster infection on frailty, reporting no association with incident physical frailty. This study only included older women, limiting the generalizability of its findings (Wang et al., 2016). To note, none of the selected studies investigated the impact of influenza and pneumonia on frailty, and the lack of studies on this topic is even more surprising when considering the strong rationale. The inflammatory response to acute infections such as influenza and bacterial pneumonia has systemic repercussions that involve virtually all organs and systems. First, during infections, most of the anabolic mechanisms responsible for the turnover of damaged macromolecules and organelles are inhibited, mainly through the downregulation of the signaling of growth factors, thus leading to the progressive accumulation of unrepaired damage in the tissues (Ferrucci and Fabbri, 2018). Second, the inflammatory response and the immobilization that always accompany acute infections may further lead to physical function deterioration and frailty (Welch et al., 2018). Third, infections may indirectly promote a frailty status by triggering specific pathological conditions, as suggested by a meta-analysis of case-control studies where recent respiratory infection was associated with increased myocardial infarction risk (Barnes et al., 2015). Further, a review reported that flu vaccination reduces the risk of major adverse cardiovascular events by 55 % in patients with recent acute coronary syndrome, and by 35 % in patients with chronic heart disease. Interestingly, influenza vaccination was shown to prevent myocardial infarction as effectively as currently accepted therapies for the prevention of ischemic heart disease (Demurtas et al., 2020).

2.2. Physical function

Twenty-one of the selected studies investigated the impact of major infections on physical function. Overall, pneumonia, influenza and varicella zoster infections appear to negatively affect physical function. Only two studies, one on pneumonia and one on varicella zoster infection, showed no association with reduced physical function (Duracinsky et al., 2014; Hughes et al., 2019). The assessment of physical function greatly varied across studies, with most of them employing disability scores (e.g. personal and instrumental activities of daily living [ADL]) or health status tests (e.g. 36-short form survey [SF-36]) as indicators of impaired physical function. Only three studies performed objective physical and motor function tests, which targeted different physical domains (e.g. 6-minute walking test, leg dynamometer, functional balance scale) (Denke et al., 2018; Goto et al., 2015; Martín-Salvador et al., 2015). Interestingly, despite the methodological heterogeneity, most studies support the hypothesis that infections impair physical function. The underlying mechanisms are multiple. Prolonged immobility during hospitalization accentuates muscle-atrophy and levels of proinflammatory cytokines, which further lead to muscle loss and sarcopenia (Iwashyna et al., 2010; Schweickert et al., 2009). Decreased caloric and nutritional intake is a common feature of infectious diseases; this can negatively affect muscle health and functionality. In the specific case of varicella zoster infections, post-herpetic pain may act as a mediator that contributes to impairing physical and motor function (Johnson et al., 2010).

2.3. Cognitive function

Overall, 10 studies support the possibility that pneumonia, and varicella-zoster infection to a lesser extent, negatively affect cognition.

Surprisingly, we could not find any longitudinal study that addressed the role of influenza on cognitive function. Cognitive evaluation was conducted with several methodologies across studies and included neuropsychological measures of global cognition (e.g., mini mental state examination [MMSE]), assessment of specific cognitive domains (e.g., cognitive tests battery) as well as clinical diagnoses of dementia. Among those studies that detected a cognitive decline after the occurrence of pneumonia and varicella zoster infection, three studies also found that pneumonia (Shah et al., 2013; Tate et al., 2014) and varicella zoster (Chen et al., 2018) were associated with a 2–3 fold increase risk of dementia. Several potential mechanisms have been hypothesized to explain the association of pneumonia and varicella zoster with cognitive aging. The neurotrophic propensity of the virus and the sustained pro-inflammatory status induced by the infection may trigger or accelerate neurodegenerative processes through increased deposition of beta-amyloid and microglia activation (Chiu, 2014; Hokkanen et al., 1997; Iwashyna et al., 2010; Reichenberg et al., 2001). Similarly, the systemic inflammatory status and the boost in the oxidative processes might explain the impact of pneumonia on cognition. Further, pneumonia-related hypoxia is also linked to neurodegeneration and cerebrovascular lesions, which has been shown to predispose individuals to cognitive impairment and dementia (Grande et al., 2020). Interestingly, 25 % of older people hospitalized for pneumonia develop delirium, which has been previously associated with an increased long-term risk of dementia (Davis et al., 2017; Pieralli et al., 2014). This has been observed also in older people hospitalized due to Covid-19 (Marengoni et al., 2020a).

In conclusions, in contrast with an almost complete lack of specific studies exploring the relation between infections and frailty, we found a moderately strong evidence showing an association between infections and physical as well as cognitive decline. Given that both physical and cognitive functions are considered essential dimensions of frailty, we interpret these data as supporting the link between infections and frailty, which may be eventually explained by immunosenescence, as discussed below.

3. Frailty, immunization and immunity

Immunosenescence hinders the effectiveness of response to previously and newly-encountered infective agents, and may reduce the immune surveillance that keeps chronic infection quiescent (e.g., herpes viruses) (Miller, 1996). At the same time, immunosenescence may affect the efficacy of active immunization. In light of the communalities and mutual influence between frailty and immunosenescence, active immunization for pneumococcus, influenza, and varicella zoster is likely to be influenced by individuals' frailty status (Appay and Sauce, 2014).

We conducted a systematic search looking for evidence in the literature about the modifier effect of frailty in the immune response to vaccinations (Box 1; **Fig. S1**). Table 2 presents a summary (complete information in **Table S2**) of the studies assessing the degree of vaccine efficacy across different frailty states, either defined by physical frailty criteria or a frailty index. Overall, 13 studies were selected: seven focused on influenza vaccination, four on pneumococcus vaccination and two on varicella zoster immunization. Overall, 34,520 individuals, aged over 60 years, were included.

These reports on the interaction between influenza vaccination and frailty provided mixed and sometimes contradictory results. Two studies, one using the frailty phenotype and one the frailty index, investigating the efficacy of a standard-dose trivalent inactivated seasonal influenza vaccine, showed that frail individuals have worse immunization outcomes, encompassing lower immune-protection and higher hospitalization compared to non-frail individuals (Andrew et al., 2017; Yao et al., 2011). Two studies examined the occurrence of clinical outcomes and showed that after flu vaccination, frail individuals experienced higher rates of flu-like illness compared to non-frail controls (Andrew et al., 2017; Yao et al., 2011). However, four other studies – one of which testing a high-dose inactivated vaccine – found no difference in serological response to influenza vaccination across different frailty levels (Bauer et al., 2017; DiazGranados et al., 2015; Narang et al., 2018; Van Epps et al., 2017). Notably, the study testing a high-dose vaccine, did not show significant differences in terms of lab-verified influenza in frail individuals when compared with a standard-dose inactivated one. Lastly, we identified one small study that reported an increased immunological activation following standard-dose trivalent influenza vaccination in frail individuals compared to non-frail ones (Moehling et al., 2018). However, the authors of this study did not provide strong justifications in support of such counterintuitive finding.

Table 2
Interplay between immunization and frailty: main findings from the selected studies.

Study	N	Mean age years; (% female sex)	Significant impact of frailty on immunization
Influenza vaccine			
Andrew et al., 2017	884	80; (55)	✓
Bauer et al., 2017	76	70+; (61)	×
DiazGranados et al., 2015	31,983	73; (56)	×
Moehling et al., 2018	106	62; (75)	×*
Narang et al., 2018	205	73; (62)	×
Van Epps et al., 2017	117	81; (4)	×
Yao et al., 2011	71	85; (78)	✓
Pneumonia vaccine			
Hamza et al., 2012	80	68; (60)	✓
Macintyre et al., 2014	312	70; (72)	✓
Macintyre et al., 2019	136	71; (50)	✓
Ridda et al., 2009	241	70; (55)	✓
Varicella zoster vaccine			
Choi et al., 2018	69	74; (51)	×
Lelic et al., 2016	240	60+; (n.a.)	×

✓ indicates detrimental effect of frailty on vaccination response; × indicates no effect.
* This study reports higher serological response in frail individuals compared to robust controls after influenza vaccination.

The methodological pitfalls and diversities encountered may explain the overall inconclusive evidence on the role of frailty in modifying active influenza immunization. Furthermore, no study compared the occurrence of clinical influenza-related conditions in vaccinated vs. non-vaccinated frail individuals. Finally, the lack of studies testing newer vaccines strongly limit the possibility to read these findings in the context of current immunization recommendations.

Four studies, three of them using the frailty index and one the frailty phenotype, investigated the hypothesis that frailty would reduce pneumococcal vaccination response, and all of them focused on the immune response to the vaccine and none on clinical outcomes. Of them, one study involved the 23-valent capsular polysaccharide (PPV) vaccine alone, one study compared the PPV with the 7-valent conjugate (PCV) and two compared the PPV with the PCV. All these studies suggested that the presence of frailty blunts serological response after anti-pneumococcal vaccination – affecting PCV more than PPV – compared to non-frail controls (Hamza et al., 2012; Macintyre et al., 2014; MacIntyre et al., 2019; Ridda et al., 2009). We found no evidence in the literature that pneumococcus vaccination is as effective in the prevention of pneumonia in frail and non-frail individuals.

As for varicella zoster vaccination, only two studies were found. Both of them tested the efficacy of a live attenuated vaccine, and no difference

in the serological response to vaccine between frail and non-frail individuals were observed upon immunization (Choi et al., 2019; Lelic et al., 2016). Notably, no study addressed the question of whether varicella zoster vaccination prevents shingles differently in frail and non-frail individuals. Given the close relationship between immunosenescence and frailty, it may be hypothesized that frailty plays a role not only in the virus reactivation, but also in the efficacy of the active immunization. Yet, the fact that no differences were identified between frail and non-frail individuals in response to varicella zoster immunization is puzzling and requires further investigation.

In conclusions, there is some evidence, although not strong, that frailty may decrease the immunization effect of vaccine against influenza. Indirect support derives from a meta-analysis including more than 11,000 older adults living in nursing homes – notoriously the frailest share of the older population. Influenza vaccination was associated with a 37 % reduction in pneumonia events, as well as a 34 % reduction in pneumonia- or influenza-related mortality (Chan et al., 2014; Fulop et al., 2009). A protective effect has been shown in spite of an incomplete strain-vaccine match (Dean et al., 2010). On the other hand, stronger and more concordant evidence shows that frailty blunts the immune response to pneumococcal vaccination. No effect was found for varicella zoster vaccination. Overall, in consideration of the higher risk of infections and poor outcomes in frail older adults, it can be argued that even a moderately effective vaccine may be valuable for this population.

4. A unifying framework

While evidence suggests frailty as an important substrate for the development of infections and their consequences, the impact of infections on frailty status has been less investigated so far. In our systematic search – focused on three major preventable infections through vaccination – we found that influenza, pneumococcus, and varicella zoster infectious events may interfere with healthy aging. The impact of such infections on physical function is well documented, while the effect on cognitive decline and dementia is less well established, yet consistent. Only one study explored the association between shingles and frailty, reporting no association (Wang et al., 2016). Since cognitive and physical impairments are two of the most important manifestations of frailty, despite the lack of dedicate studies we can reasonably infer that influenza, pneumococcal and varicella zoster infections also impact frailty status.

Our review suggests the existence of a vicious cycle that, upon being triggered, strongly reduces the chance of maintaining health in aging (Fig. 1). On one hand, frailty and infections are linked bi-directionally, acting both as risk factors and consequences of each other. On the other hand, immunosenescence both increases the risk of experiencing infections and decreases the effectiveness of vaccination. In this framework, the role played by immunization is currently unknown. Can immunization break the mutually-busting detrimental role of immunosenescence, frailty, and infections?

4.1. Biological rationale

Immunosenescence is characterized by impairment and dysregulation in the immune system function – encompassing innate and adaptive responses – and it is accompanied by a status of chronic low-grade inflammation, known as inflammaging (Fulop et al., 2017). Innate immunity is impaired, as evidenced by reduced phagocytic activity of neutrophils, macrophages, and natural killer cells. With respect to acquired immunity, aging individuals present with a progressive reduction in the number of naïve T cells, an increase in the percentage of memory T cells, mostly CD8+, and a shift toward dysfunctional effector T cells, which are responsible for a less effective response to new antigens, as in the case of neoplastic cells, infective agents, and vaccines (Appay and Sauce, 2014; Nguyen et al., 2018; Pawelec, 2017). It has been hypothesized that chronic infections, as for example Cytomegalovirus, may be a driver of the over-accumulation, progressive functional exhaustion, and senescence of memory T cells (Pawelec, 2014).

Immunosenescence and inflammaging fuel each other; a higher release of pro-inflammatory molecules negatively impacts the adaptive immune response. Conversely, an impaired adaptive immune response can also reinforce the stimulation of the innate immune response, leading to a further release of pro-inflammatory cytokines. Immunosenescence and inflammaging are involved in most of the pathological conditions observed in older age, among which multimorbidity, frailty, and recurrent and severe infections (Christensen et al., 2009; Furman et al., 2019). The biomolecular changes characterizing aging immune cells, as well as several other organs and systems (e.g. muscle and consequently frailty), overlap to some extent, and are identified as the hallmarks of aging (López-Otín et al., 2013). Among them, defective autophagy and altered mitochondrial turnover have been described to be highly relevant for immunosenescence (Bektas et al., 2019). Such bio-molecular deficits are largely involved in the development and

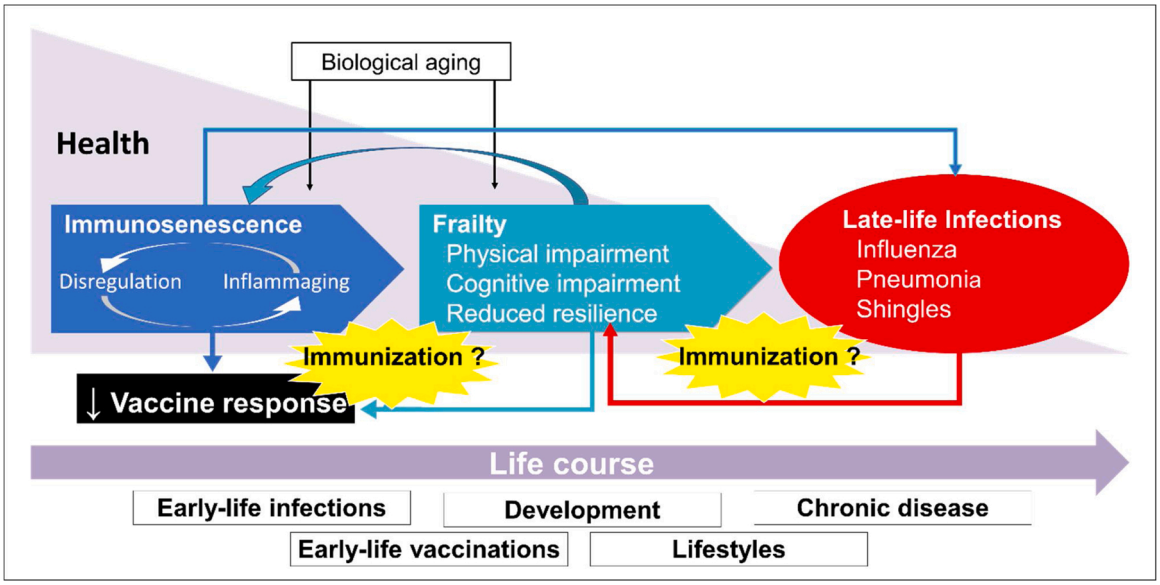

Fig. 1. PRISMA flow-chart of study selection (as of 1 June 2020).

progression of frailty, suggesting interdependence between immunosenescence, frailty, and aging (Ferrucci et al., 2018; Wilson et al., 2020).

Strong evidence supports the role of inflammation in frailty, possibly as a result of inflammaging. Several pro-inflammatory cytokines, including IL-6, C-reactive protein, and tumor necrosis factor-α (TNFα) are overexpressed in frail older individuals, compared to non frail (Collerton et al., 2012; Hubbard et al., 2009; Leng et al., 2007; Qu et al., 2009). Notably, a meta-analysis found that, frail older adults in their sixth and seventh decades – but not older – presented with twice the likelihood to be seropositive to Cytomegalovirus, one of the most common sources of chronic stimulation for our immune system (Araújo Carvalho et al., 2018).

One theoretical confounder not elucidated in the studies we found is the role of antibiotics in these alterations of the immune system. Antibiotics are often prescribed during influenza and pneumonia episodes, acting not only on pathogenic bacteria but also affecting the resident gut microbiota, altering its composition, reducing its diversity and sometimes promoting the growth of damaging species (Ianiro et al., 2016). The pathophysiology of several diseases has been linked to gut microbiota alterations, among which conditions characterized by a dysfunctional activation of the immune system (e.g., inflammatory bowel disease, rheumatoid arthritis) (Khan et al., 2019; Maeda and Takeda, 2019). Indeed, alterations of the gut microbiome have been linked to immunosenescence and inflammaging, as well to neuroinflammation, sarcopenia and frailty per se, suggesting that the integrity of the gut microbiome is indeed pivotal for healthy aging (Amsterda et al., 2018; Di Sabatino et al., 2018; Picca et al., 2018; Ticinesi et al., 2018; Vaiserman et al., 2017).

5. Knowledge gaps

Several knowledge gaps hamper our ability to most effectively use immunization to improve the qualtiy of life of older adults. The major points are summarized in Table 3.

First, whereas we have substantial evidence that infections can have a detrimental effect on physical and cognitive functioning – except for influenza on cognition (Andrew et al., 2017; Macintyre et al., 2014; Yao et al., 2011) – little is known on their effect on frailty. It is plausible though to expect that reducing the risk and consequences of infections slows frailty development and increases life years spent in good health. Moreover, it is not clear if infections extert a direct effect on physical and cognitive functions or there are intermediate conditions that take part to the chain of events (e.g., acute events, chronic diseases) as mediators or facilitators (Barnes et al., 2015).

Second, although several common mechanisms leading to both frailty and immunosenescence have been hypothesized, they have not been thoroughtly investigated in dedicated studies (Clegg et al., 2013). The discovery of common pathways may lead to the study of common preventive and therapeutic strategies, that can eventually promote healthy aging and improve the response to vaccines. For example, physical exercise and diet interventions have been shown in separate studies to delay the onset of frailty and improve vaccine response (Clegg et al., 2014; Edwards and Booy, 2013; Kohut et al., 2004; Kohut and Senchina, 2004; Langkamp-Henken et al., 2006; Lesourd, 2004). The investigation of the efficacy of multimodal interventions jointly on frailty and immunosenescence represents a priority for future studies.

Third, we currently do not have biomarkers to identify individuals likely to respond poorly to vaccines. Frailty syndrome itself was scarcely investigated as possible effect modifier in the immune response to vaccines, with an inconsistent utilization of the frailty index and the frailty phenotype models, which prevents us from concluding which construct better fits the data. Such information might steer more personalized immunization practices in older individuals. Moreover, low-entity stress-induced stimulations of the immune system, as in the case of

Table 3
Identified knowledge gaps.

RESEARCH FIELD	GAPS	IMPORTANCE
Infections and frailty	While the impact of pneumonia and shingles have been investigated in relation to both physical and cognitive health, the impact of influenza on cognition is still unclear.	*Documenting the impact of influenza on cognition could help motivate older adults to get vaccinated and also support more aggressive efforts to promote vaccination of older adults against influenza.*
	The impact – transient or permanent – of infections on frailty development remains to a large extent unexplored, and frailty is one of the main factors limiting healthy aging.	*Quantifying the impact of infections on frailty development would help to better understand their role as barrier to the goal of healthy aging.*
	No studies formally investigated factors mediating the association of major infections with functional decline and frailty, including single diseases and multimorbidity. In addition no studies evaluated potential interventions to reduce the impact of infections on frailty.	*The understanding of how infections lead to accelerated aging may steer interventions to delay the onset of frailty.*
Immunosenescence and frailty	Shared biological mechanisms between immunosenescence and frailty are highly plausible but have not been investigated.	*Discovering those underlying mechanisms may pave the way to the identification of common biomarkers and novel preventive interventions to promoting healthy aging.*
	Exercise and nutritional interventions have been separately shown to delay the onset of frailty and improve vaccine response. No data are available for joint interventions.	*The design of randomized trials based on multidomain interventions could shed light on the potential clinical and public health implications of joint interventions.*
	Despite weaker responses to vaccines have been reported in older frail individuals, biomarkers that predict vaccine efficacy in this population are not available.	*The discovery of biomarkers that can discriminate poor from good vaccine responders may help to personalize immunization recommendations.*
	As for several other stimuli (e.g. physical activity, fasting), a stress-resilience response to vaccine antigens positively modulating immunosenescence can be hypothesized, but evidence is missing.	*The proof of an hormetic impact of regular immunizations across life could add to the value of ensuring vaccination because of protective effects that go beyond infection prevention.*
Frailty and immunization	No studies investigated the occurrence of infections in frail vs. non-frail individuals.	*Quantifying the protection conferred by vaccines to frail individuals would ease realistic predictions of infections incidence and morbidity in such individuals after vaccination.*
	The reduced immunogenicity and higher disease rates observed in vaccinated frail individuals might be explained by the use of standard-dose and non-adjuvated vaccines.	*The evidence on newer vaccines efficacy in frail vs. non-frail individuals would guarantee more reliable expectations in relation to preparations recommended by current guidelines.*
	The occurrence side effects of vaccines commonly recommended in older adults has never been studied in relation to frailty.	*The knowledge of how the presence of frailty modifies the benefit/risk profile of old and newer vaccines may help to better personalize recommendations informing patients on more realistic expectations.*
	A limited number of studies investigating the impact of frailty on immunization used different frailty models (i.e., frailty index, frailty phenotype) and led to mixed results.	*Investigating alternative frailty models in the same study would provide useful insights about the most effective tools to predict a scarce immune response to vaccine and would increase knowledge of the mechanisms underlying this phenomenon.*

repeated minor infections or regular exposure to vaccine antigens, may slow down the immunosenescence process and reduce inflammaging (hormetic effect) (Calabrese et al., 2015; Fulop et al., 2017; Martucci et al., 2017). This has been hypothesized as a potential contributor to healthy aging, but has not been studied directly.

Finally, the effectiveness of high-dose and adjuvated vaccines, as well as their side effects in frail individuals is largely unknown, hindering a proper clinical appraisal of currently recommended vaccines.

The dramatic boost experienced by the research on immunization efficacy in older adults during the SARS-CoV-2 pandemic, and the large amount of observational data soon available, are likely to shed light on several of the knowledge gaps identified in the present review.

6. Pursuing immunization and frailty prevention in the society over the life course

Throughout life the combination of interactions between genetics and the external environment contributes to build our physical and cognitive reserve, fostering healthy aging, or predisposing us to develop frailty (Ben-Shlomo et al., 2016). The life-long sequence of exposures to infective agents, vaccines and endogenous antigens, contributes to shape our immune system and set the pace of immunosenescence. This set of events has been recently identified with the name of immunobiography (Franceschi et al., 2017). The influence of immunobiography on frailty supports the value of ensuring throughout life the development and the maintenance of a strong immune system, as well as physical and cognitive reserve (Calderon-Larranaga et al., 2019).

The positive consequences of immunization can be observed at any stage of life, and both direct and indirect benefits can be expected from large-scale immunization programs. However, in spite of solid evidence, the actual immunization coverage rates of older adults against vaccine preventable diseases is way below what recommended by the World Health Organization (Fedson et al., 2011; Gabutti et al., 2019; Hanquet et al., 2019; Jorgensen et al., 2018; Lode et al., 2013; Sheikh et al., 2018). Surprisingly, low coverage is often reported among the frailest individuals, for example those living in nursing home (Bardenheier et al., 2004). Several factors may limit an adequate vaccine uptake in older adults, including system- and individual-related factors, as well as policies' and clinicians' attitudes towards aging. The massive immunization campaign implemented during the SARS-CoV-2 pandemic is uncovering several of these factors (Jean-Jacques and Bauchner, 2021; Razai et al., 2021). At the systemic level, country-specific policies play a major role in vaccine provision and accessibility, above all the availability of a public and universal healthcare coverage (WHO, 2014). At the individual level, socioeconomic status and living conditions determine vaccine uptake the most. In fact, independently by multimorbidity and disability burden, the existence of socioeconomic disparities (e.g., immigrant status, living in deprived areas, living alone) has been reported as an important limiting factor for reaching adequate vaccine coverages (Bocquier et al., 2017; Crawford et al., 2011; Harrison et al., 2018; Jain et al., 2017; Vukovic et al., 2020). Finally, the concomitant existence of cognitive impairment further reduces the likelihood to get access to vaccines (Landi et al., 2005). These same characteristics have been shown to be involved in the development and progression of frailty, suggesting the possibility to act on common risk factors and pointing at the need to study these phenomena under a common framework (Feng et al., 2017; Gale et al., 2018; Trevisan et al., 2020). These factors should be considered collectively in the planning and implementation of effective immunization programs and should guide health professionals in the identification of older individuals at risk of being neglected. The neglected persons might be precisely those frail people with stronger immunization recommendations.

It has been suggested that preventive strategies against frailty such as diet and physical exercise may be implemented in order to further prevent frailty progression and age-related decline in immune response (Clegg et al., 2014). Chronic exercise or high levels of physical activity and nutrition interventions – effective treatments for the prevention of frailty – have been shown to improve vaccination immunogenicity in older adults. Interestingly, episodic exercise has been recently investigated as a potential adjuvant to vaccination, and studies on the effectiveness of other behavioral interventions, especially on nutrition, are ongoing (Edwards and Booy, 2013; Kohut et al., 2004; Kohut and Senchina, 2004; Langkamp-Henken et al., 2006; Lesourd, 2004).

6.1. A societal approach

In terms of infections – and consequently frailty – prevention in older adults thought of as a silo-like approach, targeting solely this age group would neither be effective nor sustainable (Korppi, 2018; Nanda et al., 2020; Nymark et al., 2017). Healthy aging is built over the entire life course, and the accumulation of "biological capital" – for example muscle strength and cognitive reserve – during younger ages has been recognized as a major factor counteracting physical and cognitive decline (Dekhtyar et al., 2019; Fratiglioni et al., 2020; Kuh and New Dynamics of Ageing (NDA) Preparatory Network, 2007). A life-long and wider perspective on immunization could successfully reduce infections in older age.

The implementation of effective immunization programs targeting children is of utmost importance for the protection of older adults. One important way that childhood vaccination can affect disease occurrence in older adults is through herd immunity. This has been observed with influenza and pneumococcal vaccination in several countries (Berical et al., 2016; Cohen et al., 2011; Haber et al., 2007; Prevention., 2009; Reichert et al., 2001; Tsaban and Ben-Shimol, 2017). In some settings, it has even been hypothesized that effective infant flu vaccination policies might make vaccinating older adults unnecessary (Hodgson et al., 2017). In light of similar results, US and Canada recently issued the indication to personalize the indication to pneumococcal immunization, not merely based on chronological age but accounting for comorbidity status and patients preferences (Matanock et al., 2019; National Advisory Committee on Immunization, 2018). Herd immunity also provides protection to a wider group beyond older adults, such as siblings that are too young to be vaccinated, classmates with special health conditions and those with limited access to vaccines living in the same community. Finally, immunization can also help protect older adults by reducing the use of antibiotics to treat vaccine-preventable diseases, and therefore limiting the development of antimicrobial resistance (Buckley et al., 2019; Jansen et al., 2018).

As part of a holistic approach to the prevention of infective diseases in older age, there is the need to diagnose frailty in a timely manner. Although this is currently recommended by some scientific societies, no clear recommendations have been issued by international public health bodies on the prevention and assessment of frailty (Morley et al., 2013; Turner and Clegg, 2014).

7. Conclusions

In this review we describe existing evidence about the bidirectional interplay between frailty and both vaccine-preventable infections in older adults and immunosenescence. Overall the evidence is not always consistent and there are several knowledge gaps, which we have described. First, the impact of major infections on frailty, rather than on physical or cognitive decline that likely contributes to frailty, needs to be formally assessed, and its pathophysiological mechanisms investigated. Second, an appraisal of the biomolecular mechanisms leading to frailty and immunosenescence is currently lacking, and multidomain interventions acting on both phenomena have not yet been designed. Third, no validated immunosenescence biomarkers or clinical criteria are available to predict the response to immunization of frail individuals, and the interaction between frailty and newer vaccines has been often overlooked so far. Filling these gaps is of utmost importance in consideration of the growing number of frail seniors in the world.

Moreover, answering to these open questions will help to implement effective and sustainable preventive programs to ensure a healthy aging to more and more individuals; to make available safe and effective vaccines also to frail individuals, which are forecasted to increase in the next decades, and to issue personalized recommendations for immunization, beyond the current indications based merely on age and presence of index diseases. Finally, in conjunction with the massive vaccination campaign against SARS-CoV-2, we are seeing a big push to vaccinate older adults; for this effort it would be useful to evaluate the efficacy of available vaccines in light of different levels of frailty.

Contributorship

Conception or design of the work: DLV, FT. Data extraction and syntesis: DLV, FT. Interpretation of the results: all authors. Drafting the article: DLV, FT, LF. Critical revision of the manuscript: all authors. Final approval of the manuscript: all authors. All the authors fulfil the ICMJE criteria for authorship.

Funding

This work was supported by the Karolinska Institutet-MSD Partnership (Ref.: 2-4646/2016).

The funder had no role in study design, data extraction and syntesis, decision to publish, or preparation of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

We thank Dr. Melvin Kohn for his critical feedback on the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101351.

References

Amsterdam, D., Ostrov, B.E., 2018. The impact of the microbiome on immunosenescence. Immunol. Invest. 47, 801–811.
Andrew, M.K., Shinde, V., Ye, L., Hatchette, T., Haguinet, F., Dos Santos, G., McElhaney, J.E., Ambrose, A., Boivin, G., Bowie, W., Chit, A., ElSherif, M., Green, K., Halperin, S., Ibarguchi, B., Johnstone, J., Katz, K., Langley, J., Leblanc, J., Loeb, M., MacKinnon-Cameron, D., McCarthy, A., McGeer, A., Powis, J., Richardson, D., Semret, M., Stiver, G., Trottier, S., Valiquette, L., Webster, D., McNeil, S.A., Serious Outcomes Surveillance Network of the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research, N, the Toronto Invasive Bacterial Diseases, N, 2017. The importance of frailty in the assessment of influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J. Infect. Dis. 216, 405–414.
Appay, V., Sauce, D., 2014. Naive T cells: the crux of cellular immune aging? Exp. Gerontol. 54, 90–93.
Araújo Carvalho, A.C., Tavares Mendes, M.L., Santos, V.S., Tanajura, D.M., Prado Nunes, M.A., Martins-Filho, P.R.S., 2018. Association between human herpes virus seropositivity and frailty in the elderly: a systematic review and meta-analysis. Ageing Res. Rev. 48, 145–152.
Bardenheier, B., Shefer, A., McKibben, L., Roberts, H., Bratzler, D., 2004. Characteristics of long-term-care facility residents associated with receipt of influenza and pneumococcal vaccinations. Infect. Control Hosp. Epidemiol. 25, 946–954.
Barnes, M., Heywood, A.E., Mahimbo, A., Rahman, B., Newall, A.T., Macintyre, C.R., 2015. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. Heart 101, 1738–1747.
Bauer, J.M., De Castro, A., Bosco, N., Romagny, C., Diekmann, R., Benyacoub, J., Vidal, K., 2017. Influenza vaccine response in community-dwelling German prefrail and frail individuals. Immun. Ageing 14, 17.
Bektas, A., Schurman, S.H., Gonzalez-Freire, M., Dunn, C.A., Singh, A.K., Macian, F., Cuervo, A.M., Sen, R., Ferrucci, L., 2019. Age-associated changes in human CD4(+) T cells point to mitochondrial dysfunction consequent to impaired autophagy. Aging (Albany N. Y.) 11, 9234–9263.
Ben-Shlomo, Y., Cooper, R., Kuh, D., 2016. The last two decades of life course epidemiology, and its relevance for research on ageing. Int. J. Epidemiol. 45, 973–988.
Berical, A.C., Harris, D., Dela Cruz, C.S., Possick, J.D., 2016. Pneumococcal vaccination strategies. An update and perspective. Ann. Am. Thorac. Soc. 13, 933–944.
Bocquier, A., Fressard, L., Paraponaris, A., Davin, B., Verger, P., 2017. Seasonal influenza vaccine uptake among people with disabilities: a nationwide population study of disparities by type of disability and socioeconomic status in France. Prev. Med. 101, 1–7.
Bricout, H., Haugh, M., Olatunde, O., Prieto, R.G., 2015. Herpes zoster-associated mortality in Europe: a systematic review. BMC Public Health 15, 466.
Buckley, B.S., Henschke, N., Bergman, H., Skidmore, B., Klemm, E.J., Villanueva, G., Garritty, C., Paul, M., 2019. Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. Clin. Microbiol. Infect. 25, 1213–1225.
Calabrese, E.J., Dhawan, G., Kapoor, R., Iavicoli, I., Calabrese, V., 2015. What is hormesis and its relevance to healthy aging and longevity? Biogerontology 16, 693–707.
Calderon-Larranaga, A., Vetrano, D.L., Ferrucci, L., Mercer, S.W., Marengoni, A., Onder, G., Eriksdotter, M., Fratiglioni, L., 2019. Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. J. Intern. Med. 285, 255–271.
Calderón-Larrañaga, A., Dekhtyar, S., Vetrano, D.L., Bellander, T., Fratiglioni, L., 2020. COVID-19: risk accumulation among biologically and socially vulnerable older populations. Ageing Res. Rev., 101149
Chan, T.C., Fan-Ngai Hung, I., Ka-Hay Luk, J., Chu, L.W., Hon-Wai Chan, F., 2014. Effectiveness of influenza vaccination in institutionalized older adults: a systematic review. J. Am. Med. Dir. Assoc. 15, 226.e221–226.e226.
Chen, V.C., Wu, S.I., Huang, K.Y., Yang, Y.H., Kuo, T.Y., Liang, H.Y., Huang, K.L., Gossop, M., 2018. Herpes zoster and dementia: a nationwide population-based cohort study. J. Clin. Psychiatry 79.
Chiu, M.J., 2014. Systemic infections may cause cognitive deterioration and neurodegeneration. Crit. Care Med. 42, 1282–1283.
Choi, J.Y., Kang, M.G., Park, K.U., Park, W.B., Kim, K.I., Kim, E.S., Kim, H.B., Song, K.H., Kim, C.H., 2019. Immunogenicity of the varicella-zoster vaccine in community-dwelling non-robust elderly individuals compared to robust elderly individuals: a prospective cohort study. J. Gerontol. A Biol. Sci. Med. Sci. 74, 1225–1230.
Christensen, K.L., Holman, R.C., Steiner, C.A., Sejvar, J.J., Stoll, B.J., Schonberger, L.B., 2009. Infectious disease hospitalizations in the United States. Clin. Infect. Dis. 49, 1025–1035.
Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381, 752–762.
Clegg, A., Barber, S., Young, J., Iliffe, S., Forster, A., 2014. The Home-based Older People's Exercise (HOPE) trial: a pilot randomised controlled trial of a home-based exercise intervention for older people with frailty. Age Ageing 43, 687–695.
Cohen, S.A., Chui, K.K., Naumova, E.N., 2011. Influenza vaccination in young children reduces influenza-associated hospitalizations in older adults, 2002-2006. J. Am. Geriatr. Soc. 59, 327–332.
Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C.M., Isaacs, J., Kolenda, C., Parker, C., Dunn, M., Catt, M., Jagger, C., von Zglinicki, T., Kirkwood, T.B.L., 2012. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. Mech. Ageing Dev. 133, 456–466.
Crawford, V.L., O'Hanlon, A., McGee, H., 2011. The effect of patient characteristics upon uptake of the influenza vaccination: a study comparing community-based older adults in two healthcare systems. Age Ageing 40, 35–41.
Cunningham, A.L., Lal, H., Kovac, M., Chlibek, R., Hwang, S.-J., Díez-Domingo, J., Godeaux, O., Levin, M.J., McElhaney, J.E., Puig-Barberà, J., Vanden Abeele, C., Vesikari, T., Watanabe, D., Zahaf, T., Ahonen, A., Athan, E., Barba-Gomez, J.F., Campora, L., de Looze, F., Downey, H.J., Ghesquiere, W., Gorfinkel, I., Korhonen, T., Leung, E., McNeil, S.A., Oostvogels, L., Rombo, L., Smetana, J., Weckx, L., Yeo, W., Heineman, T.C., 2016. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N. Engl. J. Med. 375, 1019–1032.
Davis, D.H.J., Muniz-Terrera, G., Keage, H.A.D., Stephan, B.C.M., Fleming, J., Ince, P.G., Matthews, F.E., Cunningham, C., Ely, E.W., MacLullich, A.M.J., Brayne, C., ft.E.C.Si. E.C. Members, 2017. Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. JAMA Psychiatry 74, 244–251.
Davydow, D.S., Hough, C.L., Levine, D.A., Langa, K.M., Iwashyna, T.J., 2013. Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. Am. J. Med. 126, 615–624 e615.
Dean, A.S., Moffatt, C.R., Rosewell, A., Dwyer, D.E., Lindley, R.I., Booy, R., MacIntyre, C. R., 2010. Incompletely matched influenza vaccine still provides protection in frail elderly. Vaccine 28, 864–867.
Dekhtyar, S., Marseglia, A., Xu, W., Darin-Mattsson, A., Wang, H.X., Fratiglioni, L., 2019. Genetic risk of dementia mitigated by cognitive reserve: a cohort study. Ann. Neurol. 86, 68–78.
Demicheli, V., Jefferson, T., Di Pietrantonj, C., Ferroni, E., Thorning, S., Thomas, R.E., Rivetti, A., 2018. Vaccines for preventing influenza in the elderly. Cochrane Database Syst. Rev. 2, Cd004876.
Demurtas, J., Celotto, S., Beaudart, C., Sanchez-Rodriguez, D., Balci, C., Soysal, P., Solmi, M., Celotto, D., Righi, E., Smith, L., Lopalco, P.L., Noventa, V., Michel, J.P., Torbahn, G., Di Gennaro, F., Pizzol, D., Veronese, N., Maggi, S., 2020. The efficacy and safety of influenza vaccination in older people: an umbrella review of evidence from meta-analyses of both observational and randomized controlled studies. Ageing Res. Rev. 62, 101118.

Denke, C., Balzer, F., Menk, M., Szur, S., Brosinsky, G., Tafelski, S., Wernecke, K.D., Deja, M., 2018. Long-term sequelae of acute respiratory distress syndrome caused by severe community-acquired pneumonia: delirium-associated cognitive impairment and post-traumatic stress disorder. J. Int. Med. Res. 46, 2265–2283.
Di Sabatino, A., Lenti, M.V., Cammalleri, L., Corazza, G.R., Pilotto, A., 2018. Frailty and the gut. Dig. Liver Dis. 50, 533–541.
DiazGranados, C.A., Dunning, A.J., Robertson, C.A., Talbot, H.K., Landolfi, V., Greenberg, D.P., 2015. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine 33, 4565–4571.
Duracinsky, M., Paccalin, M., Gavazzi, G., El Kebir, S., Gaillat, J., Strady, C., Bouhassira, D., Chassany, O., 2014. ARIZONA study: is the risk of post-herpetic neuralgia and its burden increased in the most elderly patients? BMC Infect. Dis. 14, 529.
Edwards, K.M., Booy, R., 2013. Effects of exercise on vaccine-induced immune responses. Hum. Vaccin. Immunother. 9, 907–910.
Ethun, C.G., Bilen, M.A., Jani, A.B., Maithel, S.K., Ogan, K., Master, V.A., 2017. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J. Clin. 67, 362–377.
Falcone, M., Russo, A., Gentiloni Silverj, F., Marzorati, D., Bagarolo, R., Monti, M., Velleca, R., D'Angelo, R., Frustaglia, A., Zuccarelli, G.C., Prina, R., Vignati, M., Marnati, M.G., Venditti, M., Tinelli, M., 2018. Predictors of mortality in nursing-home residents with pneumonia: a multicentre study. Clin. Microbiol. Infect. 24, 72–77.
Falkenhorst, G., Remschmidt, C., Harder, T., Hummers-Pradier, E., Wichmann, O., Bogdan, C., 2017. Effectiveness of the 23-Valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS One 12 e0169368.
Fedson, D.S., Nicolas-Spony, L., Klemets, P., van der Linden, M., Marques, A., Salleras, L., Samson, S.I., 2011. Pneumococcal polysaccharide vaccination for adults: new perspectives for Europe. Expert Rev. Vaccines 10, 1143–1167.
Feng, Z., Lugtenberg, M., Franse, C., Fang, X., Hu, S., Jin, C., Raat, H., 2017. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: a systematic review of longitudinal studies. PLoS One 12 e0178383.
Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15, 505–522.
Ferrucci, L., Levine, M.E., Kuo, P.L., Simonsick, E.M., 2018. Time and the metrics of aging. Circ. Res. 123, 740–744.
Franceschi, C., Salvioli, S., Garagnani, P., de Eguileor, M., Monti, D., Capri, M., 2017. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front. Immunol. 8, 982.
Fratiglioni, L., Marseglia, A., Dekhtyar, S., 2020. Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference? Lancet Neurol. 19, 533–543.
Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56, M146–156.
Fulop, T., Pawelec, G., Castle, S., Loeb, M., 2009. Immunosenescence and vaccination in nursing home residents. Clin. Infect. Dis. 48, 443–448.
Fulop, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E.H., Cohen, A.A., Witkowski, J.M., Franceschi, C., 2017. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front. Immunol. 8, 1960.
Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstreuer, N., Slavich, G.M., 2019. Chronic inflammation in the etiology of disease across the life span. Nat. Med. 25, 1822–1832.
Gabutti, G., Bolognesi, N., Sandri, F., Florescu, C., Stefanati, A., 2019. Varicella zoster virus vaccines: an update. Immunotargets Ther. 8, 15–28.
Gagliardi, A.M.Z., Andriolo, B.N.G., Torloni, M.R., Soares, B.G.O., de Oliveira Gomes, J., Andriolo, R.B., Canteiro Cruz, E., 2019. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst. Rev.
Gale, C.R., Westbury, L., Cooper, C., 2018. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age Ageing 47, 392–397.
Goto, R., Watanabe, H., Tanaka, N., Kanamori, T., Yanagi, H., 2015. Factors associated with recovery of activities of daily living in elderly pneumonia patients. Gen. Med. 16, 68–75.
Grande, G., Haaksma, M.L., Rizzuto, D., Melis, R.J.F., Marengoni, A., Onder, G., Welmer, A.K., Fratiglioni, L., Vetrano, D.L., 2019a. Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: systematic review and meta-analysis. Neurosci. Biobehav. Rev. 107, 96–103.
Grande, G., Triolo, F., Nuara, A., Welmer, A.K., Fratiglioni, L., Vetrano, D.L., 2019b. Measuring gait speed to better identify prodromal dementia. Exp. Gerontol. 124, 110625.
Grande, G., Qiu, C., Fratiglioni, L., 2020. Prevention of dementia in an ageing world: evidence and biological rationale. Ageing Res. Rev., 101045
Haber, M., Barskey, A., Baughman, W., Barker, L., Whitney, C.G., Shaw, K.M., Orenstein, W., Stephens, D.S., 2007. Herd immunity and pneumococcal conjugate vaccine: a quantitative model. Vaccine 25, 5390–5398.
Hamza, S.A., Mousa, S.M., Taha, S.E., Adel, L.A., Samaha, H.E., Hussein, D.A., 2012. Immune response of 23-valent pneumococcal polysaccharide vaccinated elderly and its relation to frailty indices, nutritional status, and serum zinc levels. Geriatr. Gerontol. Int. 12, 223–229.
Hanquet, G., Krizova, P., Valentiner-Branth, P., Ladhani, S.N., Nuorti, J.P., Lepoutre, A., Mereckiene, J., Knol, M., Winje, B.A., Ciruela, P., Ordobas, M., Guevara, M., McDonald, E., Morfeldt, E., Kozakova, J., Slotved, H.-C., Fry, N.K., Rinta-Kokko, H., Varon, E., Corcoran, M., van der Ende, A., Vestrheim, D.F., Munoz-Almagro, C., Latasa, P., Castilla, J., Smith, A., Henriques-Normark, B., Whittaker, R., Pastore Celentano, L., Savulescu, C., 2019. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. Thorax 74, 473–482.
Harrison, S.M., Wei, M.Y., Lamerato, L.E., Petrie, J.G., Toth Martin, E., 2018. Multimorbidity is associated with uptake of influenza vaccination. Vaccine 36, 3635–3640.
Hewitt, J., Carter, B., Vilches-Moraga, A., Quinn, T.J., Braude, P., Verduri, A., Pearce, L., Stechman, M., Short, R., Price, A., Collins, J.T., Bruce, E., Einarsson, A., Rickard, F., Mitchell, E., Holloway, M., Hesford, J., Barlow-Pay, F., Clini, E., Myint, P.K., Moug, S.J., McCarthy, K., Davey, C., Jones, S., Lunstone, K., Cavenagh, A., Silver, C., Telford, T., Simmons, R., Mutasem, T.E.J., Singh, S., Paxton, D., Harris, W., Galbraith, N., Bhatti, E., Edwards, J., Duffy, S., Bisset, C., Alexander, R., Garcia, M., Sangani, S., Kneen, T., Lee, T., McGovern, A., Guaraldi, G., 2020. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health.
Hodgson, D., Baguelin, M., van Leeuwen, E., Panovska-Griffiths, J., Ramsay, M., Pebody, R., Atkins, K.E., 2017. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. Lancet Public Health 2, e74–e81.
Hokkanen, L., Launes, J., Poutiainen, E., Valanne, L., Salonen, O., Sirén, J., Iivanainen, M., 1997. Subcortical type cognitive impairment in herpes zoster encephalitis. J. Neurol. 244, 239–245.
Hoogendijk, E.O., Afilalo, J., Ensrud, K.E., Kowal, P., Onder, G., Fried, L.P., 2019. Frailty: implications for clinical practice and public health. Lancet 394, 1365–1375.
Hubbard, R.E., O'Mahony, M.S., Savva, G.M., Calver, B.L., Woodhouse, K.W., 2009. Inflammation and frailty measures in older people. J. Cell. Mol. Med. 13, 3103–3109.
Hughes, M.M., Praphasiri, P., Dawood, F.S., Sornwong, K., Ditsungnoen, D., Mott, J.A., Prasert, K., 2019. Effect of acute respiratory illness on short-term frailty status of older adults in Nakhon Phanom, Thailand-June 2015 to June 2016: a prospective matched cohort study. Influenza Other Respir. Viruses 13, 391–397.
Ianiro, G., Tilg, H., Gasbarrini, A., 2016. Antibiotics as deep modulators of gut microbiota: between good and evil. Gut 65, 1906–1915.
Iwashyna, T.J., Ely, E.W., Smith, D.M., Langa, K.M., 2010. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 304, 1787–1794.
Jain, A., van Hoek, A.J., Boccia, D., Thomas, S.L., 2017. Lower vaccine uptake amongst older individuals living alone: a systematic review and meta-analysis of social determinants of vaccine uptake. Vaccine 35, 2315–2328.
Jansen, K.U., Knirsch, C., Anderson, A.S., 2018. The role of vaccines in preventing bacterial antimicrobial resistance. Nat. Med. 24, 10–19.
Jean-Jacques, M., Bauchner, H., 2021. Vaccine distribution—equity left behind? JAMA 325, 829–830.
Johnson, R.W., Bouhassira, D., Kassianos, G., Leplège, A., Schmader, K.E., Weinke, T., 2010. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. BMC Med. 8, 37.
Jorgensen, P., Mereckiene, J., Cotter, S., Johansen, K., Tsolova, S., Brown, C., 2018. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine 36, 442–452.
Khan, I., Ullah, N., Zha, L., Bai, Y., Khan, A., Zhao, T., Che, T., Zhang, C., 2019. Alteration of gut microbiota in inflammatory bowel disease (IBD): cause or consequence? IBD treatment targeting the gut microbiome. Pathogens 8.
Kohut, M.L., Senchina, D.S., 2004. Reversing age-associated immunosenescence via exercise. Exerc. Immunol. Rev. 10, 6–41.
Kohut, M.L., Arntson, B.A., Lee, W., Rozeboom, K., Yoon, K.J., Cunnick, J.E., McElhaney, J., 2004. Moderate exercise improves antibody response to influenza immunization in older adults. Vaccine 22, 2298–2306.
Korppi, M., 2018. Universal pneumococcal vaccination provides marked indirect beneficial effects through herd immunity. Acta Paediatr.
Kuh, D., New Dynamics of Ageing (NDA) Preparatory Network, 2007. A life course approach to healthy aging, frailty, and capability. J. Gerontol. A Biol. Sci. Med. Sci. 62, 717–721.
Kundi, H., Wadhera, R.K., Strom, J.B., Valsdottir, L.R., Shen, C., Kazi, D.S., Yeh, R.W., 2019. Association of frailty with 30-day outcomes for acute myocardial infarction, heart failure, and pneumonia among elderly adults. JAMA Cardiol. 4, 1084–1091.
Lal, H., Cunningham, A.L., Godeaux, O., Chlibek, R., Diez-Domingo, J., Hwang, S.-J., Levin, M.J., McElhaney, J.E., Poder, A., Puig-Barberà, J., Vesikari, T., Watanabe, D., Weckx, L., Zahaf, T., Heineman, T.C., 2015. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N. Engl. J. Med. 372, 2087–2096.
Landi, F., Onder, G., Carpenter, I., Garms-Homolova, V., Bernabei, R., 2005. Prevalence and predictors of influenza vaccination among frail, community-living elderly patients: an international observational study. Vaccine 23, 3896–3901.
Langkamp-Henken, B., Wood, S.M., Herlinger-Garcia, K.A., Thomas, D.J., Stechmiller, J. K., Bender, B.S., Gardner, E.M., DeMichele, S.J., Schaller, J.P., Murasko, D.M., 2006. Nutritional formula improved immune profiles of seniors living in nursing homes. J. Am. Geriatr. Soc. 54, 1861–1870.
Lelic, A., Verschoor, C.P., Lau, V.W., Parsons, R., Evelegh, C., Bowdish, D.M., Bramson, J. L., Loeb, M.B., 2016. Immunogenicity of varicella vaccine and immunologic predictors of response in a cohort of elderly nursing home residents. J. Infect. Dis. 214, 1905–1910.
Leng, S.X., Xue, Q.L., Tian, J., Walston, J.D., Fried, L.P., 2007. Inflammation and frailty in older women. J. Am. Geriatr. Soc. 55, 864–871.

Lesourd, B., 2004. Nutrition: a major factor influencing immunity in the elderly. J. Nutr. Health Aging 8, 28–37.
Lode, H., Ludwig, E., Kassianos, G., 2013. Pneumococcal infection–low awareness as a potential barrier to vaccination: results of a European study. Adv. Ther. 30, 387–405.
López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Macintyre, C.R., Ridda, I., Gao, Z., Moa, A.M., McIntyre, P.B., Sullivan, J.S., Jones, T.R., Hayen, A., Lindley, R.I., 2014. A randomized clinical trial of the immunogenicity of 7-valent pneumococcal conjugate vaccine compared to 23-valent polysaccharide vaccine in frail, hospitalized elderly. PLoS One 9, e94578.
MacIntyre, C.R., Ridda, I., Trent, M.J., McIntyre, P., 2019. Persistence of immunity to conjugate and polysaccharide pneumococcal vaccines in frail, hospitalised older adults in long-term follow up. Vaccine 37, 5016–5024.
Maeda, Y., Takeda, K., 2019. Host-microbiota interactions in rheumatoid arthritis. Exp. Mol. Med. 51, 1–6.
Marengoni, A., Zucchelli, A., Grande, G., Fratiglioni, L., Rizzuto, D., 2020a. The impact of delirium on outcomes for older adults hospitalised with COVID-19. Age Ageing 49, 923–926.
Marengoni, A., Zucchelli, A., Vetrano, D.L., Armellini, A., Botteri, E., Nicosia, F., Romanelli, G., Beindorf, E.A., Giansiracusa, P., Garrafa, E., Ferrucci, L., Fratiglioni, L., Bernabei, R., Onder, G., 2020b. Beyond chronological age: frailty and multimorbidity predict in-hospital mortality in patients with coronavirus disease 2019. J. Gerontol. A Biol. Sci. Med. Sci.
Martín-Salvador, A., Torres-Sánchez, I., Sáez-Roca, G., López-Torres, I., Rodríguez-Alzueta, E., Valenza, M.C., 2015. Age group analysis of psychological, physical and functional deterioration in patients hospitalized for pneumonia. Archivos de Bronconeumología (English Edition) 51, 496–501.
Martucci, M., Ostan, R., Biondi, F., Bellavista, E., Fabbri, C., Bertarelli, C., Salvioli, S., Capri, M., Franceschi, C., Santoro, A., 2017. Mediterranean diet and inflammaging within the hormesis paradigm. Nutr. Rev. 75, 442–455.
Matanock, A., Lee, G., Gierke, R., Kobayashi, M., Leidner, A., Pilishvili, T., 2019. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the advisory committee on immunization practices. MMWR Morb. Mortal. Wkly. Rep.
Miller, R.A., 1996. The aging immune system: primer and prospectus. Science 273, 70–74.
Mizukami, A., Sato, K., Adachi, K., Matthews, S., Holl, K., Matsuki, T., Kaise, T., Curran, D., 2018. Impact of herpes zoster and post-herpetic neuralgia on health-related quality of life in japanese adults aged 60 years or older: results from a prospective, observational cohort study. Clin. Drug Investig. 38, 29–37.
Moehling, K.K., Nowalk, M.P., Lin, C.J., Bertolet, M., Ross, T.M., Carter, C.E., Susick, M., Saul, S.G., Kaynar, A.M., Bromberger, J.T., Zimmerman, R.K., 2018. The effect of frailty on HAI response to influenza vaccine among community-dwelling adults &/= 50 years of age. Hum. Vaccin. Immunother. 14, 361–367.
Morley, J.E., Vellas, B., van Kan, G.A., Anker, S.D., Bauer, J.M., Bernabei, R., Cesari, M., Chumlea, W.C., Doehner, W., Evans, J., Fried, L.P., Guralnik, J.M., Katz, P.R., Malmstrom, T.K., McCarter, R.J., Gutierrez Robledo, L.M., Rockwood, K., von Haehling, S., Vandewoude, M.F., Walston, J., 2013. Frailty consensus: a call to action. J. Am. Med. Dir. Assoc. 14, 392–397.
Nanda, A., Vura, N.V.R.K., Gravenstein, S., 2020. COVID-19 in older adults. Aging Clin. Exp. Res. 32, 1199–1202.
Narang, V., Lu, Y., Tan, C., Camous, X.F.N., Nyunt, S.Z., Carre, C., Mok, E.W.H., Wong, G., Maurer-Stroh, S., Abel, B., Burdin, N., Poidinger, M., Tambyah, P.A., Bosco, N., Visan, L., Ng, T.P., Larbi, A., 2018. Influenza vaccine-induced antibody responses are not impaired by frailty in the community-dwelling elderly with natural influenza exposure. Front. Immunol. 9, 2465.
National Advisory Committee on Immunization, 2018. Update on the Use of Pneumococcal Vaccines in Adults 65 Years of Age and Older - A Public Health Perspective. Public Health Agency of Canada.
Nguyen, T.H.O., Sant, S., Bird, N.L., Grant, E.J., Clemens, E.B., Koutsakos, M., Valkenburg, S.A., Gras, S., Lappas, M., Jaworowski, A., Crowe, J., Loh, L., Kedzierska, K., 2018. Perturbed CD8(+) T cell immunity across universal influenza epitopes in the elderly. J. Leukoc. Biol. 103, 321–339.
Nymark, L.S., Sharma, T., Miller, A., Enemark, U., Griffiths, U.K., 2017. Inclusion of the value of herd immunity in economic evaluations of vaccines. A systematic review of methods used. Vaccine 35, 6828–6841.
Pawelec, G., 2014. Immunosenenescence: role of cytomegalovirus. Exp. Gerontol. 54, 1–5.
Pawelec, G., 2017. Immunosenescence and cancer. Biogerontology 18, 717–721.
Pera, A., Campos, C., Lopez, N., Hassouneh, F., Alonso, C., Tarazona, R., Solana, R., 2015. Immunosenescence: implications for response to infection and vaccination in older people. Maturitas 82, 50–55.
Picca, A., Fanelli, F., Calvani, R., Mulè, G., Pesce, V., Sisto, A., Pantanelli, C., Bernabei, R., Landi, F., Marzetti, E., 2018. Gut dysbiosis and muscle aging: searching for novel targets against Sarcopenia. Mediators Inflamm. 2018, 7026198.
Pieralli, F., Vannucchi, V., Mancini, A., Grazzini, M., Paolacci, G., Morettini, A., Nozzoli, C., 2014. Delirium is a predictor of in-hospital mortality in elderly patients with community acquired pneumonia. Intern. Emerg. Med. 9, 195–200.
Prevention, Cf.D.Ca., 2009. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus Pneumoniae 2010.
Qu, T., Walston, J.D., Yang, H., Fedarko, N.S., Xue, Q.-L., Beamer, B.A., Ferrucci, L., Rose, N.R., Leng, S.X., 2009. Upregulated ex vivo expression of stress-responsive inflammatory pathway genes by LPS-challenged CD14(+) monocytes in frail older adults. Mech. Ageing Dev. 130, 161–166.
Quinton, L.J., Walkey, A.J., Mizgerd, J.P., 2018. Integrative physiology of pneumonia. Physiol. Rev. 98, 1417–1464.
Razai, M.S., Osama, T., McKechnie, D.G.J., Majeed, A., 2021. Covid-19 vaccine hesitancy among ethnic minority groups. BMJ 372, n513.
Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmächer, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. Arch. Gen. Psychiatry 58, 445–452.
Reichert, T.A., Sugaya, N., Fedson, D.S., Glezen, W.P., Simonsen, L., Tashiro, M., 2001. The Japanese experience with vaccinating schoolchildren against influenza. N. Engl. J. Med. 344, 889–896.
Ridda, I., Macintyre, C.R., Lindley, R., Gao, Z., Sullivan, J.S., Yuan, F.F., McIntyre, P.B., 2009. Immunological responses to pneumococcal vaccine in frail older people. Vaccine 27, 1628–1636.
Rockwood, K., Mitnitski, A., 2007. Frailty in relation to the accumulation of deficits. J. Gerontol. A Biol. Sci. Med. Sci. 62, 722–727.
Schweickert, W.D., Pohlman, M.C., Pohlman, A.S., Nigos, C., Pawlik, A.J., Esbrook, C.L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G.A., Bowman, A., Barr, R., McCallister, K.E., Hall, J.B., Kress, J.P., 2009. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373, 1874–1882.
Shah, F.A., Pike, F., Alvarez, K., Angus, D., Newman, A.B., Lopez, O., Tate, J., Kapur, V., Wilsdon, A., Krishnan, J.A., Hansel, N., Au, D., Avdalovic, M., Fan, V.S., Barr, R.G., Yende, S., 2013. Bidirectional relationship between cognitive function and pneumonia. Am. J. Respir. Crit. Care Med. 188, 586–592.
Sheikh, S., Biundo, E., Courcier, S., Damm, O., Launay, O., Maes, E., Marcos, C., Matthews, S., Meijer, C., Poscia, A., Postma, M., Saka, O., Szucs, T., Begg, N., 2018. A report on the status of vaccination in Europe. Vaccine 36, 4979–4992.
Tate, J.A., Snitz, B.E., Alvarez, K.A., Nahin, R.L., Weissfeld, L.A., Lopez, O., Angus, D.C., Shah, F., Ives, D.G., Fitzpatrick, A.L., Williamson, J.D., Arnold, A.M., DeKosky, S.T., Yende, S., Investigators, G.E.M.S., 2014. Infection hospitalization increases risk of dementia in the elderly. Crit. Care Med. 42, 1037–1046.
Teresa Aguado, M., Barratt, J., Beard, J.R., Blomberg, B.B., Chen, W.H., Hickling, J., Hyde, T.B., Jit, M., Jones, R., Poland, G.A., Friede, M., Ortiz, J.R., 2018. Report on WHO meeting on immunization in older adults: geneva, Switzerland, 22-23 March 2017. Vaccine 36, 921–931.
Ticinesi, A., Tana, C., Nouvenne, A., Prati, B., Lauretani, F., Meschi, T., 2018. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. Clin. Interv. Aging 13, 1497–1511.
Trevisan, C., Grande, G., Vetrano, D.L., Maggi, S., Sergi, G., Welmer, A.K., Rizzuto, D., 2020. Gender differences in the relationship between marital status and the development of frailty: a swedish longitudinal population-based study. J. Womens Health (Larchmt).
Tsaban, G., Ben-Shimol, S., 2017. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: a systematic review of the literature. Vaccine 35, 2882–2891.
Turner, G., Clegg, A., 2014. Best practice guidelines for the management of frailty: a british geriatrics society, age UK and royal college of general practitioners report. Age Ageing 43, 744–747.
Vaiserman, A.M., Koliada, A.K., Marotta, F., 2017. Gut microbiota: a player in aging and a target for anti-aging intervention. Ageing Res. Rev. 35, 36–45.
Van Epps, P., Tumpey, T., Pearce, M.B., Golding, H., Higgins, P., Hornick, T., Burant, C., Wilson, B.M., Banks, R., Gravenstein, S., Canaday, D.H., 2017. Preexisting immunity, not frailty phenotype, predicts influenza postvaccination titers among older veterans. Clin. Vaccine Immunol. 24.
Vetrano, D.L., Calderon-Larranaga, A., Marengoni, A., Onder, G., Bauer, J.M., Cesari, M., Ferrucci, L., Fratiglioni, L., 2018a. An international perspective on chronic multimorbidity: approaching the elephant in the room. J. Gerontol. A Biol. Sci. Med. Sci. 73, 1350–1356.
Vetrano, D.L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., Lopez Samaniego, L., Rodriguez-Manas, L., Bernabei, R., Onder, G., 2018b. Frailty and multimorbidity: a systematic review and meta-analysis. J. Gerontol. A Biol. Sci. Med. Sci.
Vetrano, D.L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., Lopez Samaniego, L., Rodríguez-Mañas, L., Bernabei, R., Onder, G., 2019. Frailty and multimorbidity: a systematic review and meta-analysis. J. Gerontol. A Biol. Sci. Med. Sci. 74, 659–666.
Vukovic, V., Lillini, R., Lupi, S., Fortunato, F., Cicconi, M., Matteo, G., Arata, L., Amicizia, D., Boccalini, S., Bechini, A., Prato, R., Stefanati, A., Panatto, D., de Waure, C., 2020. Identifying people at risk for influenza with low vaccine uptake based on deprivation status: a systematic review. Eur. J. Public Health 30, 132–141.
Wang, G.C., Han, C., Detrick, B., Casolaro, V., Levine, D.M., Fried, L.P., Walston, J.D., 2016. Herpesvirus infections and risk of frailty and mortality in older women: women's health and aging studies. J. Am. Geriatr. Soc. 64, 998–1005.
Wang, J., Zou, Y., Zhao, J., Schneider, D.B., Yang, Y., Ma, Y., Huang, B., Yuan, D., 2018. The impact of frailty on outcomes of elderly patients after major vascular surgery: a systematic review and meta-analysis. Eur. J. Vasc. Endovasc. Surg. 56, 591–602.
Welch, C., Hassan-Smith, Z.K., Greig, C.A., Lord, J.M., Jackson, T.A., 2018. Acute sarcopenia secondary to hospitalisation - an emerging condition affecting older adults. Aging Dis. 9, 151–164.
WHO, 2012. Background paper on influenza vaccines and immunization. In: SAGE Meeting 2012. Geneve, Switzerland.
WHO, 2014. European Vaccine Action Plan 2015-2020.
WHO, 2015. World Report on Ageing and Health. World Health Organization, Geneva, Switzerland.
Wilson, D., Drew, W., Jasper, A., Crisford, H., Nightingale, P., Newby, P., Jackson, T., Lord, J.M., Sapey, E., 2020. Frailty is associated with neutrophil dysfunction which

is correctable with phosphoinositol-3-kinase inhibitors. J. Gerontol. A Biol. Sci. Med. Sci. 75, 2320–2325.
Yao, X., Hamilton, R.G., Weng, N.P., Xue, Q.L., Bream, J.H., Li, H., Tian, J., Yeh, S.H., Resnick, B., Xu, X., Walston, J., Fried, L.P., Leng, S.X., 2011. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine 29, 5015–5021.
Zorzoli, E., Pica, F., Masetti, G., Franco, E., Volpi, A., Gabutti, G., 2018. Herpes zoster in frail elderly patients: prevalence, impact, management, and preventive strategies. Aging Clin. Exp. Res. 30, 693–702.
Zucchelli, A., Vetrano, D.L., Marengoni, A., Grande, G., Romanelli, G., Calderón-Larrañaga, A., Fratiglioni, L., Rizzuto, D., 2018. Frailty predicts short-term survival even in older adults without multimorbidity. Eur. J. Intern. Med. 56, 53–56.
Zucchelli, A., Vetrano, D.L., Grande, G., Calderón-Larrañaga, A., Fratiglioni, L., Marengoni, A., Rizzuto, D., 2019. Comparing the prognostic value of geriatric health indicators: a population-based study. BMC Med. 17, 185.