INFECTIOUS DISEASES AND COGNITION: DO WE HAVE TO WORRY?

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Running title: Infectious diseases and cognition

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Author Contributions

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ABSTRACT

Objectives: age-related physiological changes, particularly immune system decline, may contribute to greater vulnerability to infectious diseases in older individuals. A growing body of evidence shows that both, acute and chronic infections may be accompanied by cognitive disturbances as part of their manifestations. Given the importance of cognition in aging trajectories, the objective of this article was to review current knowledge on cognitive outcomes of infectious diseases in older adults, and to emphasize the importance of considering cognition as a domain of interest in its own rights in these diseases.

Methods: A MEDLINE/PubMed database search was conducted to identify articles reporting cognitive impairment associated with various severe acute infections and specific chronic infectious conditions such as Human immune-deficiency virus, the Herpes Virus family, Hepatitis C virus, Lyme borreliosis, *Helicobacter pylori*, periodontitis, and emerging pathogens like SARS-CoV-2, as well as potentially preventive strategies like vaccination.

Results / Conclusions: Taken together, the studies examined in the present review emphasize that numerous acute and chronic infectious diseases share mechanisms that, when added to specific risk factors frequently found in older persons, contribute to considerably increase the risk of cognitive outcomes such as cognitive decline and dementia. This review may help to appreciate the role that infectious diseases play in cognitive trajectories and thus promote further investigation on the topic.

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Introduction

Due to certain particularities of the aging process, such as the relative decline of the immune system (immunosenescence), the potentially accompanying chronic low-grade inflammation (inflammaging), and a higher prevalence of chronic comorbidities and their treatment, older adults are more vulnerable to infectious diseases. Moreover, they are more likely to develop severe forms of infections and have a higher risk of long-term exposure to chronic infections and repeated acute infections. [1]

The role that some infectious diseases play in the development of adverse health outcomes, including increased short and long-term mortality, is well known. However, a growing body of evidence in the field of infectious diseases points to another area of health that is frequently affected by these conditions and is highly relevant to the older population: cognition.

In a variety of chronic infections and acute infectious episodes, an impact on cognition is not uncommon. [2, 3] Moreover, cognitive decline may be part of the reported clinical manifestations of specific infections if appropriate interventions are not undertaken in a timely manner, and this observation is not only limited to those infections primarily affecting the central nervous system (CNS). [4, 5]

Given the relevance of mental health issues among older adults, along with their higher risk of contracting infectious diseases, the objective of this paper is to review the reasons, but also the challenges for considering cognition as an outcome of interest in the field of infectious diseases in this population. For this, we address in this review several acute and chronic systemic diseases for which there is convincing epidemiological evidence showing an increased risk of adverse cognitive outcomes. Some pathophysiological mechanisms that these conditions may have in common or at the individual level potentially explaining the impact on cognition are developed, however, an in-depth or pathogen-dependent physio pathological review is beyond the scope of this publication. Similarly, this article does not cover those diseases that exclusively involve the CNS, since obviously, the cognitive manifestations in these infections are not new findings.

Specificities of the older persons that increase their risk of infectious diseases

The complex changes in the immune system that are associated with the aging process are collectively known as immunosenescence, and links between this phenomenon and potential higher risks of infectious diseases among older persons have been proposed since its earliest characterizations. [6, 7] Despite the absence of a formal consensus on the specific changes that encompass immunosenescence, some of its most frequently reported manifestations include a decline in cellular immunity that increases susceptibility to infections, cancer, and autoimmune diseases, as well as the development of a pro-inflammatory cellular phenotype, which has been proposed as the substrate for a chronic low-grade inflammatory state termed *inflammaging* (potentially linked to other age-related chronic conditions such as cardiovascular diseases, diabetes, sarcopenia, and frailty), and a relatively decreased antibody response (which may hamper for example, response to vaccinations). [1, 8] Whilst this process has frequently been addressed from a predominantly negative perspective, recent publications propose that some components of both immunosenescence and inflammaging may not be solely detrimental or inappropriate. Still under debate, the hypothesis is that the reactive development of an increased inflammatory state due to a relatively reduced immune response would be an adaptive homeostatic mechanism or immune remodeling, which may be more suitable for the state of the organism in advanced age. [9, 10]

Beyond these immunological changes, it is important to bear in mind (as usual in geriatric medicine) that it is not one factor, but the combination of several conditions that may render an individual more vulnerable to a given outcome. For most older adults, the decline, or changes in their immune system during the aging process will not be significant enough to be considered pathological or the sole cause of increased infectious risk. In the same vein, such changes do not represent a state of immunodeficiency either. For many individuals, it is the multiplicative effect of the declining immune function and their individual morbidity risk profile that will trigger the risk of infectious diseases. [11]

As previously stated, the immune system is not independent from the other components of the organism; thus, other age-related particularities also contribute to the increased risk of organ-specific infections. These changes include the waning of physical barriers (i.e., the skin), decreased cough reflex in frail individuals, urological alterations such as incomplete bladder voiding or mucosal atrophy in women, and changes in microbiota. [6, 12, 13]

Common chronic conditions in older adults, such as diabetes (particularly long-standing poor glycemic control) and chronic kidney disease, can further compromise the immune system which increases the risk of infections. [12, 14, 15] Likewise, multimorbidity increases the likelihood of exposure to medical procedures (e.g., permanent venous accesses, pacemakers, urinary catheters,

prosthetic joints, etc.), which may represent risk factors for specific infections. [16] In the same vein, geriatric syndromes as immobility, malnutrition, polypharmacy (e.g., sedatives, anticholinergic drugs, and proton pump inhibitors increase the risk for pneumonia), disabilities in activities of daily living, and frailty, not only increase the risk of developing infectious diseases, but also of developing severe forms of diseases, as the organism is in a more vulnerable state. [6, 17] This is particularly relevant for the frailty syndrome, as this condition is characterized by poor resilience. In addition, severe forms of infectious diseases in this already vulnerable subgroup of the older population may lead to additional functional decline, reducing the likelihood of returning to a baseline state. [18] Consequently, this process may precipitate a spiral of various negative health-related outcomes (including further infections) such as institutionalization, permanent disability, and increased mortality. [18-20] Likewise, atypical presentations of infectious diseases (i.e., absence of fever, delirium as the sole manifestation) are more common in older adults, which may also contribute to delay the diagnosis of the underlying infection, and consequently, contribute to adverse outcomes. [21, 22]

Figure 1 illustrates the constellation of factors contributing to the risk of infectious diseases in older adults.

As aging is a highly heterogeneous process, different aging trajectories are to be expected. [23] While some individuals maintain a good level of autonomy allowing them to continue to live in the community, others require the support of long-term care facilities, which will also increase their risk of contracting multidrug-resistant organisms. [24] Likewise, while some persons do not contract many infectious diseases throughout their lives, others develop repeated episodes of acute infections, or chronic (even lifelong) exposures to certain pathogens, and thus, age with a significant burden of infectious diseases. [25] The cumulative effect of infectious diseases is a relevant dimension to consider, as both the higher burden of infections, and living with specific chronic infectious diseases have been associated with cognitive decline. [19, 25]

Cognition and cognitive decline as domains of interest in the field of infectious diseases

Knowing that older persons are at higher risk of infectious diseases, it may be relevant to pay a particular attention to mental health consequences, as mental health is not exclusively affected in the acute phase of infectious diseases (e.g., delirium) or by those that directly affect the CNS (vasculitis or neuro-infections). There is a growing evidence showing cognitive manifestations in a wide variety of systemic infections, and a long-term impact on cognitive function due to the exposure to certain others.

- **Severe acute infections and their impact on cognition**

Severe infections are a common cause of emergency admissions in older adults (particularly pneumoniae, urinary tract infections, and bloodstream infections). They usually impose enormous physiological disturbances for the body to overcome, which in turn can lead to acute manifestations of disease such as delirium, short-term mortality, as well as long-term negative outcomes such as frailty, functional decline, institutionalization, and cognitive impairment. [2, 3, 12, 19]

Delirium is one of the most frequent neuropsychiatric manifestations of acute infections in older persons. This syndrome is characterized by an acute onset of cognitive disturbances that fluctuates over time, with orientation in time and space, attention, and working memory being the most frequently affected cognitive domains, although delirium can affect almost any cognitive domain. [22] Delirium can be considered both as a marker of underlying cognitive vulnerability and a risk factor, as older individuals who develop delirium are at higher risk of subsequent cognitive decline, dementia, and worsened cognitive trajectories in individuals who already have dementia. [22] Therefore, delirium may be a warning sign of cognitive vulnerability.

Beyond delirium, recent evidence has shown that in older individuals, infections severe enough to require in-hospital treatment may be independent risk factors for cognitive decline and all-cause dementia. [4, 26] According to several epidemiological studies, frequent infections, regardless of etiology, such as pneumoniae (viral or bacterial etiology), urinary tract infections, skin, and soft tissue infections, as well as sepsis from diverse origins are associated with an increased risk of cognitive decline, vascular dementia, and Alzheimer's disease. Actually, the risk of unspecified dementia would be doubled compared with individuals without a history of severe infectious episodes. [4, 26-28] Moreover, a study suggested a risk gradient, with higher infectious burdens associated with higher cognitive risks: an all cause dementia risk of about 1.4 for a history of one episode of hospital-treated infection, and about 2.5 for two episodes. [27]

- **Specific chronic infections and cognition**

Over the next section of the article, we describe specific examples of chronic infectious diseases and their associations with cognitive-related outcomes, as distinct changes in cognition may be part of their typical clinical manifestations.

1. **Human immune-deficiency virus (HIV)**

HIV represents one of the chronic infectious diseases with the largest evidence for cognitive outcomes. Almost from the beginning of the HIV pandemic, neurocognitive manifestations of the

disease were identified, and eventually the term HIV-associated neurocognitive disorder (HAND) was coined. [29] This term has been used for more than fifteen years to describe a range of HIV-related cognitive changes, and the classification criteria proposed by Antinori *et al*. remain the most frequently used to date. [30] These clinical criteria, based on neuropsychological assessment (and its impact on daily functioning), classify HAND into three possible states: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

In parallel, great advances have been made in the treatment of HIV, and the effect that combined antiretroviral therapy (cART) has had on minimizing the severe negative AIDS and HIV-related outcomes, including HAD is undeniable. Despite these advances in the cART era, HAND remains a frequent condition, particularly among the most vulnerable individuals, such as pre-frail, or frail older adults. [31] However, relevant transitions in HAND subtypes and neuropsychological profiles have been reported. [32] Regarding HAND and its subtypes, the estimated prevalence for HAND ranges from 15% to55%, and currently, the more common subtypes would be ANI and MND (with ANI accounting for approximatively 70% of cases), with HAD becoming a rare event. [29] In terms of the neuropsychological profiles of HAND, while a shift toward a more "cortical" profile has been suggested for persons under cART (potentially related to interactions between HIV and the aging process, as persons living with HIV live longer), evidence still supports a "subcortical" neuropsychological pattern in HAND characterized by impairments in tasks involving processing speed and executive functioning. [33] With respect to cognitive trajectories, the still scarce longitudinal data pertaining to the cART era suggests that ANI status is still associated with a higher risk of cognitive decline compared with cognitively "*normal*" peers without HIV. For instance, a cohort study reported that ANI was associated with a two to six-fold increased risk of developing symptomatic HAND (assessed by self-reported or objective performance), and another one reported that 13% of participants with HAND showed deterioration over 4 years of follow-up. [34, 35] Nonetheless, it seems that the largest proportion (61% to 77%) of persons on optimal HIV treatment remains stable in terms of cognitive functioning, and a small proportion may even improve (10% to 16.5%). [34, 36] However, a limitation shared by many of these studies is that the proportion of older adults included is relatively small, as most focus on middle-aged persons living with HIV. As we currently have an ever-growing population of older adults living with HIV for whom these issues could overlap with age-related conditions (including neurodegenerative diseases), the issue of cognitive function in HIV is gaining momentum and a substantial amount of collaborative work between Geriatrics and HIV-medicine is underway.

It is important to mention that HIV, and particularly AIDS can cause a number of neurological complications like toxoplasmosis, Epstein-Barr virus related lymphomas, JC polyomavirus, etc.. They are not detailed in this review since, as mentioned in the introduction, conditions directly affecting the CNS are outside the scope of this review.

2. Herpesviridae

Infections from the Herpes Virus family have long been studied as potential risk factors for cognitive impairment, particularly infections with herpes simplex virus (HSV) type 1, a very frequent infection worldwide, with no curative treatment (i.e., viral eradication). The interest for cognitive issues is justified by the neurotropic properties of the virus leading to *Herpes Simplex* encephalitis, its recurring nature, and the biological and epidemiological associations between HSV reactivations / infection and cognitive decline, and the higher reported risks for Alzheimer's disease. [37, 38, 39]

Recent evidence emphasizes the neurotropism of HSV, and points to brain areas most vulnerable to this infection, such as the hippocampal region, a critical area for episodic memory. [40] In addition, a recent study reports that early imaging markers of Alzheimer's disease such as microstructural alterations in para-hippocampal regions, and lower hippocampal volume are more frequent in older adults with high anti-HSV 1 IgG titers. Additionally, the same work reports a higher risk of developing Alzheimer's disease in APOE E ε4 allele carriers with high IgG levels than in allele carriers with lower IgG titers. [41] These results are interesting in light of other findings from a population-based longitudinal study suggesting an association between HSV-1 carriage and episodic memory decline in older persons. Indeed, the proportion of participants with episodic memory decline was higher in those aged ≥ 65 years with HSV-1 IgG antibodies (9.8% vs 0.0% without anti-HSV IgG), and even higher among APOE E ε4 allele carriers (23.5% vs 0.0% without anti-HSV IgG). [42] Regarding the potential effect of antiviral treatment on cognitive outcomes, a retrospective analysis of Taiwan's Health Insurance Research Database found that patients who received antiviral treatment during an active HSV episode had a reduced risk of developing all-cause dementia compared with patients who did not. [43] However, these findings need to be replicated in longitudinal studies.

Following the same trend, epidemiological studies have reported that previous Varicella Zoster Virus (VZV) infection may also increase the risk for cognitive decline and dementia. [39, 44, 45] For example, a Taiwanese nationwide population-based survey reported a higher risk of incident all-cause dementia in individuals with a history of herpes zoster compared with those without. [45] Noteworthy, another retrospective cohort study reported an almost three-fold increased risk of dementia in VZV infection with ophthalmologic involvement. [44] The proposed rationale for this association is

lifelong viral latency, induction of chronic inflammation, direct neurotropic involvement, and the recurrent nature of the infection. [39, 44]

Other herpes viruses such as Cytomegalovirus, and Epstein-Barr virus are also highly prevalent either alone, or as co-infections with other viruses like HIV. Their potential role on cognitive outcomes has been examined, but the evidence is inconclusive when considering their stand-alone effect. [39]

3. Hepatitis C virus

In the last few years, significant progress has been made in the understanding of the pathophysiological mechanisms of Hepatitis C Virus (HCV) infection. Furthermore, we are witnessing the first generation of patients treated with potentially curative approaches such as the direct antiviral agents (DAAs). HCV is a primary hepatotropic virus that is relatively frequent in older adults. Although initially affecting the liver, this infection is considered a systemic condition owing to its many extra-hepatic manifestations, including cognitive impairment. [46] Mechanisms that induce CNS dysfunction such as neurotransmitter disturbances (particularly in the serotoninergic and dopaminergic systems of the midbrain and basal ganglia), direct viral damage (viral entry through the peripheral mononuclear system with subsequent infection of microvascular endothelial cells), and immune-mediated vascular damage (HCV-associated mixed cryoglobulinemia) are suspected to be the drivers of the cognitive manifestations of the disease. [47-49] Several cognitive functions can be affected by HCV including attention, working memory, episodic memory, psychomotor speed, and executive functions. [47, 50, 51] Given that the elderly population represents the main group affected by the infection, and that HCV may contribute to worsening cognitive decline, efforts have been made not only to include this group in clinical trials of DAAs (which have reported excellent responses to treatment), but also in studies with outcomes that focus on cognitive measures. [52, 53] As with all studies evaluating novel medical interventions, the results should be taken with some hindsight, but a new and exciting chapter is probably opening in the field of HCV infection, as the preliminary results from these studies suggest an improvement of cognitive functioning as assessed by a comprehensive neuropsychological evaluation following HCV treatment with DAAs. [53] If confirmed, these results would indicate a potential reversibility of cognitive deficits after treatment.

4. Lyme borreliosis

Lyme disease or Lyme borreliosis is a common tick-borne infection caused by a group of spirochetes of the *Borrelia burgdorferi* group. [54] Three clinical stages have been described for Lyme borreliosis (early-localized, early-disseminated, and late-disseminated), and systemic manifestations of the disease may develop during its course, including neurological symptoms. [55] The potential cognitive

manifestations of Lyme borreliosis remain a rich and ongoing field of research. Indeed, due to the controversies surrounding definitions and classification criteria (for other states of disease out of the previously mentioned stages), and the different age groups considered in the studies, inconsistent results regarding the potential chronic manifestations of the disease are reported in the literature. Post-treatment Lyme disease syndrome (PTLDS) is a consensus-based classification created as a potential tool to detect individuals who have persistent symptomatology after a proper diagnosis and treatment of Lyme borreliosis, and for whom other common conditions have been excluded. [56] Memory complaints are frequent in PTLDS, and a few studies have suggested an association with cognitive decline; for instance, a case series of a well-characterized group of PTLDS patients reported that 26% of the participants endorsed a significant level of cognitive decline compared with an estimate of premorbid functioning, predominantly in measures of verbal memory and processing speed. [57] However, when considering only prior positive serological status, a longitudinal population-based study showed no association with subsequent negative trajectories of cognitive aging, as no association was found with cognitive decline, functional decline or risk of dementia. [58]

5. *Helicobacter pylori*

While the prevalence of *H. pylori* varies by geographic area, the infection remains common worldwide and affects approximately half of the world population. [59] Likewise, this infection represents one of the main causes of chronic gastritis, but this condition is not necessarily symptomatic, and can therefore remain undiagnosed or untreated throughout life, as it is usually contracted during childhood. [59] As for other chronic infectious diseases with systemic impact, extra-gastric manifestations of *H. pylori* are emerging as a topic of interest. Protracted *H. pylori* infections have been associated with chronic inflammatory states. This chronic inflammation along with other factors such as folate malabsorption, immune dysregulation, and bacteria entry into the CNS through the systemic circulation, have been proposed as potential mechanisms linking *H. pylori* to neurodegeneration and Alzheimer's disease. [60-62] A systematic review and meta-analysis conducted by Shindler-Itskovitch *et al*, reported that, compared with individuals without a history of *H. pylori*, patients with *H. pylori* infection have a 1.7 increased likelihood of developing all-cause dementia. [60] Specifically in older adults, a French longitudinal population-based cohort with a 20-year of follow-up found that after controlling for various conditions including APOE ε4 status, *H. pylori* infection remained a risk factor for incident all-cause dementia. [63] Similarly, an analysis of national surveys from the US found an association between *H. pylori* seropositivity and incident Alzheimer's disease and all-cause dementia. [61] Contrasting results have also been reported. For instance, a population-based cohort from the Netherlands found that IgG seropositivity to *H.pylori*

was not associated with a higher risk of dementia in a follow-up of 13.3 years. [64] However, some methodological differences that may have contributed to these discrepant results have been suggested, such as a possible underestimation of the proportion of patients with a prior infection as complementary long-lasting antibodies were not assessed. [65] Given these findings, further longitudinal studies focusing on mechanistic or physiopathological associations between *H. pylori* infection and dementia, as well as clinical trials assessing the impact of *H. pylori* treatment on cognitive outcomes are expected, as this is a treatable condition, and hence a potentially modifiable risk factor.

6. Periodontitis

Periodontal disease, particularly chronic periodontitis, has gained ground as a health marker in older adults, because of its prevalence and its potential association with many negative outcomes, including neurocognitive disorders. [66-68] Various periodontal disease-causing microorganisms have been associated with these outcomes, with *Porphyromonas gingivalis* being one of the most frequently reported. A recent analysis of a national survey from the US reported longitudinal associations between clustered bacterial periodontal markers (IgG) for *Porphyromonas gingivalis* and *Campylobacter rectus* with incident Alzheimer's disease. [69] According to the systematic review and meta-analysis conducted by Hu *et. al,* irrespective of the specific microorganisms, periodontal disease would be associated with mild cognitive impairment (MCI) and Alzheimer's disease with a 1.6 higher risk for MCI, and around 1.8 for Alzheimer's disease in persons with a history of periodontal disease, and a nearly five-fold higher risk of Alzheimer's disease in persons with severe periodontal disease. [68]

The mechanisms behind the link between chronic periodontitis and cognitive disorders remain unclear; however, the induction of chronic inflammation and the potential ability of periodontal pathogens to cross the blood-brain barrier have been frequently suggested as potential drivers of this association. [67, 68]

7. Emerging Pathogens

Over the past two years, we have seen the impact of an emergent pathogen on basically all the domains of daily life. We still do not know for sure the role of SARS-CoV-2 and COVID-19 as a long-term chronic condition, but we cannot deny the enormous initial impact on the elderly population, nor can we deny the growing body of evidence for the persistent disease manifestations and their potential longitudinal implications. The World Health Organization has already developed a working clinical case definition for post COVID-19 conditions. Even though these conditions are referred-to by

various terms (e.g.; "post-acute COVID syndrome", "post-acute sequelae of SARS-CoV-2 infection"), they share common elements such as the lack of return to a usual state of health after COVID-19 infection, and the fact that the symptoms cannot be better explained by an alternative diagnosis. [70, 71] Frequently reported persistent manifestations of COVID-19 include cognitive complaints, with attention difficulties (estimated frequency 27%) and memory loss (estimated frequency 16%) being the most frequently reported, along with fatigue, and respiratory symptoms. [72] Persistent hypo/anosmia and hypo/ageusia are thought to be predictive of future cognitive impairment. [73-75] Likewise, results from the first longitudinal case-series focusing on brain metabolic correlates of persisting neuropsychiatric symptoms and sensory dysfunction report that distinct patterns of brain hypo metabolism can be distinguished over time after SARS-CoV-2 infection. [76-78] While hypometabolic changes in the frontal cortex, olfactory/rectus gyrus, anterior cingulate, and insular regions can be observed in the acute phase of disease, patients with persistent neuropsychiatric and olfactory symptoms show hypometabolic changes in areas involved in cognition such as the hippocampal, para-hippocampal, and fusiform gyri. [76-78]

As with the other infections previously mentioned, systemic involvement, and direct neurotropism have been described for SARS-CoV-2. Direct invasion through the olfactory mucosa, disruption of the blood-brain barrier, or retrograde axonal transport have been proposed as potential routes of entry of the virus into the brain. [79] However, these assumptions are under debate. In particular, the neuro-invasive properties of the virus, and the precise mechanisms behind cognitive manifestations of the disease are yet to be fully understood. [79, 80]

8. Vaccination and cognition

Knowing the potential impact of certain infectious diseases on cognitive decline or dementia, one may wonder whether specific public health interventions against those diseases could affect cognitive outcomes. Particularly, the hypothesis of a reduced risk of dementia in vaccinated older adults has been more thoroughly explored in recent years due to a growing body of epidemiological data on the topic. These studies have shown a consistent reduction of the risk of dementia among older adults with a history of vaccination against Influenza, VZV and Tetanus, Diphtheria and Pertussis (Tdap). [81-83, 84] For example, a recent analysis from a US veterans cohort reported a 42% reduction of the risk of incident dementia in individuals with a history of Tdap vaccination compared with those who did not receive the vaccine. [82]

Given the consistent findings of risk reductions results for various types of vaccines and comorbidity profiles, these studies share the suggestion that the effects are not vaccine-specific, but rather a non-

specific immune response to the vaccines, or that they represent general immune conditioning/training over time. [81, 82, 85] Even for infections for which there is no clear epidemiological evidence of an increased risk of dementia such as influenza, some studies have reported a decreased risk in post-vaccinated individuals. [86] Indeed, annual influenza vaccination may reduce the risk of dementia with a dose-response effect, with more annual doses resulting in lower risks in older adults, as shown in a Taiwanese nationwide retrospective cohort analysis (HR of about 0.8 for 2 to 3 prior years of vaccination, and HR of about 0.4 for 4 prior vaccinations in patients with chronic obstructive pulmonary disease). [83]

However, many of these studies share specific limitations; some of the vaccines considered are not mandatory. Therefore, the individuals receiving these vaccines may not be representative of the general population, and the reported risk reductions may be due to indirect associations, as vaccination could be a marker of a healthy lifestyle. [87] Nonetheless, studies regarding vaccination and reduced risks of dementia provide valuable information, as their findings are not only consistent with the reported associations between infectious diseases and cognitive outcomes but may also strengthen the role of vaccination as an already valuable public health intervention as well as a prevention strategy promoting healthy aging.

Mechanisms underlying brain dysfunction in infectious diseases

The role that infections play as precipitating and participating factors in neuropathology and neurodegeneration represents a vast field of investigation and a myriad of basic-research studies are available. However, frequently reported mechanisms that may ultimately induce neuropathology or neurodegeneration, and that various pathogens share, are the induction/interaction of systemic and neurologic inflammation, vascular damage, direct damage (neurotropism), hyperphosphorylation of tau protein, and abnormal aggregation of peptides and proteins such as beta-amyloid, and alpha-synuclein. [88-91]

Associations between conditions that are associated with systemic inflammation and cognitive decline or dementia have been extensively studied through activation of brain microglia. [88] Given that severe acute infections and various chronic infectious diseases trigger systemic and neurologic inflammation, both have been proposed as potential contributors to cognitive decline, and a dose-response association between the severity of infections (i.e. the underlying severity of inflammation) and the risk of dementia has been suggested. [26, 27] This idea may be important to consider in the context of aging, as an individual may experience many infectious episodes over the course of a

lifetime. [92] Likewise, persistent exposure to inflammatory signals triggered by chronic infections may lead to an eventual decline in T-cell function called "*T-cell exhaustion*"; which may also participate in suboptimal responses against infections. [93]

Beyond these studies, basic-research and animal-model studies have shown that systemic inflammation causes vascular (capillary) damage, and that severe infections induce blood-brain barrier dysfunctions (allowing transient exposure to neurotoxic substances and pathogens), which may contribute to the higher risks of vascular dementia observed in older adults with a history of severe infections. [89, 94] In addition, there is evidence that points towards a role of beta-amyloid, and alpha-synuclein as antimicrobial proteins. The underlying hypothesis is that both beta-amyloid peptide, and alpha-synuclein protein have active properties against various pathogens, and that repeated infections throughout life could increase the production of beta-amyloid or alpha-synuclein, leading to the formation of pathologic aggregates. Such beta-amyloid and alpha-synuclein aggregates are thought to respectively promote the development of Alzheimer's disease and alpha-synucleinopathies such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, thereby explaining the potential link between infectious conditions and increased risk of neurodegenerative diseases. [90, 95]

Conclusions

Numerous other microorganisms/infectious diseases than those mentioned in this article (i.e., *Chlamydophila pneumonia*, Syphilis, the viruses that cause dengue or zika) have been associated with cognitive outcomes, alas; a pathogen-specific overview for all possible microorganisms was not the objective of this work. Nonetheless, it reminds us the tremendous variety of pathogens that may have an impact on cognition.

Should we be concerned about the relationship between infectious diseases and cognition? This mini review calls for a yes. A variety of interventions already exist among which vaccination, antivirals, anti-inflammatory therapy, but also healthy diet and physical activity which can potentially mitigate the cognitive impact of the infectious burden that older adults experience throughout their lives. For these reasons, but also given the relevance of cognitive issues in older adults, and their greater vulnerability to infectious diseases, the time has come to pay particular attention to the role of infectious diseases in age-related cognitive trajectories. As the global population is expected to grow older in the near future, this topic at the crossroads of Geriatrics, Neuropsychology, Infectious diseases, and Public Health is expected to develop.

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Figure 1. Constellation of factors contributing to the risk of infectious diseases in older adults.