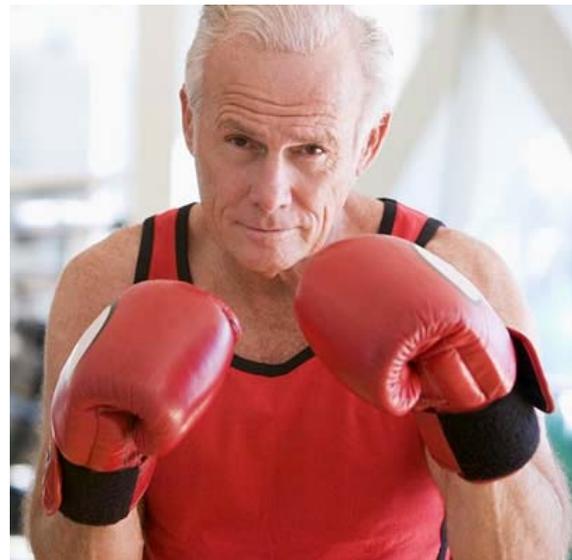


# Infectious Diseases and Aging

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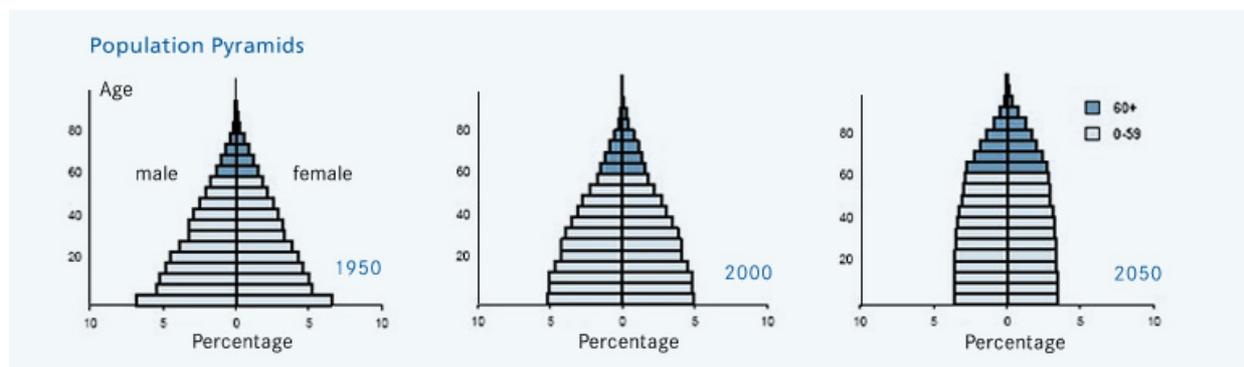
## Mankind's longevity

How old is old? For most of human history - from the Stone Age to modern times - the average life expectancy remained fairly constant: 20 to 35 years, just enough time to allow production of a few offspring, ensuring continuation of the human race. In the late 19th and the 20th centuries, however, life expectancy in industrialized nations was redefined, rising constantly and nearly doubling over the last 100 years. Average life expectancy is now ~75 years for men and somewhat over 80 years for women. Have we reached the maximum, or will future generations live even longer? There is no apparent slowing of the dramatic increase in live expectancy we've experienced during the last century - some 2.2 years per decade, nearly 5 hours per day – and nobody can predict where it will end. But as the baby boomers now reach retirement age, there is no doubt that our “old” or “elderly” population will increase even more dramatically over the coming decades.



While aging, the battle against infections gets harder © Monkey Business - Fotolia.com

Over millennia the human immune system has evolved to battle the ever-present (and co-evolving) threat of pathogenic microorganisms. But it is a relatively new challenge for the immune system to provide individuals with nearly a century of protection. And the strain is clear: the reduced ability of our immune system to generate protective immune responses – immune senescence – is a major cause of the increased susceptibility to infections and autoimmunity observed in aging organisms, including humans. Whether or not certain immune parameters vary with increased age is influenced by both the genotype and lifestyle of the individual, with enormous influence on the quality of life when humans reach octogenarian or even nonagenarian status.



In the year 2050 22% of the population will be aged 60+ © UN, Dept. of Economic and Social Affairs

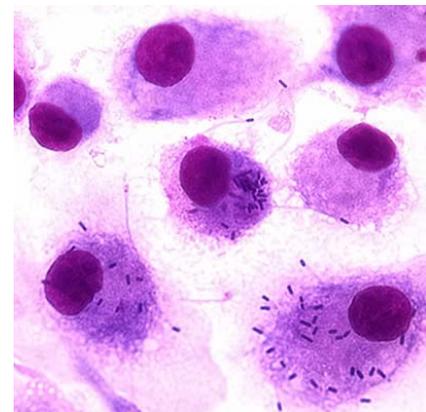
There is no doubt among researchers that immune function changes with age, but there are two viewpoints to describe those changes: Is it the result of defects in immune function, or does it instead reflect immune remodelling with reduced, unchanged or even increased function of the immune system? This question – and its answer – is increasingly important, as our aging world, in which the population aged 60+ is expected to rise from the current 10% to 22% in the year 2050, will present enormous challenges to society and increasing stress on health systems.

## Age-related changes in immunity

Two complementary forms of immunity protect us from pathogens and tumors: The evolutionary older innate immune system, which is found in all plants and animals, provides us with immediate but non-specific protection from invaders through phagocytosis, microbicidal activities and inflammatory mediators. It also helps activate the adaptive immune system, which generates long-lived specific immunity (memory) in humans (and other jawed vertebrates). Both types of immunity appear to change with increasing age.

The age-related modifications reported for innate immune function are somewhat contradictory, ranging from “relatively preserved” to “increased deterioration”. While some of the changes seem to be general transformations of the innate immune system with age, others may be specific for the frail elderly (individuals with clinical signs of infection, inflammation, malignancy, or abnormal organ function and those who take medication or have made unhealthy lifestyle choices).

The innate immune system is thought to play a central role in the chronic, low-grade, systemic inflammatory state that develops in aging individuals, also referred to as “inflammaging”; the pro-inflammatory genes that have helped us (and our ancestors) to resist pathogens, heal wounds and thus reach reproductive age become problematic later in life, contributing to age-related diseases such as cardiovascular diseases, Alzheimer's disease and diabetes. Macrophages are key to an effective innate immune response, engulfing invaders and then secreting inflammatory mediators (cytokines). Although studies in aging individuals have sometimes yielded contradictory results as to the impact of age on macrophage function, it is nevertheless widely believed that macrophages are a major component in the inflammatory imbalance that causes “inflammaging”.



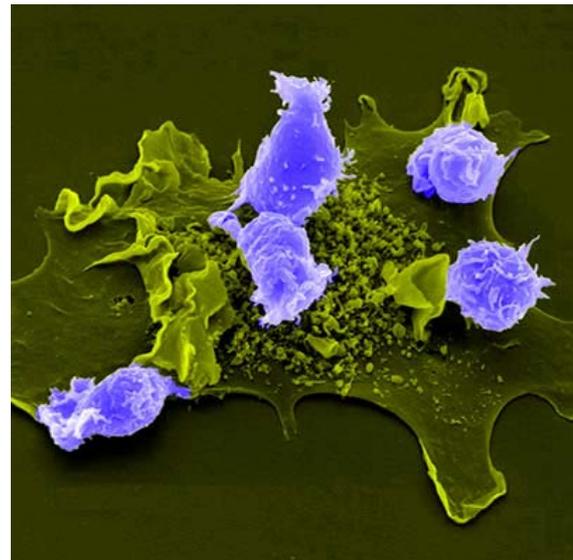
Macrophages play a key role during immune senescence © HZI

Cytokines secreted by macrophages recruit effector cells (neutrophils and natural killer cells) and initiate the maturation of dendritic cells. Neutrophils are one of the innate immune components consistently shown to change with increasing age. In young adults neutrophils are rescued from apoptosis by cytokines, growth factors and bacterial products, thereby allowing these cells to continue to produce the superoxide anions needed to kill pathogens they have engulfed. In the elderly the overall number of neutrophils does not change, but they are more susceptible to apoptosis and have reduced phagocytic capacity and killing ability (i.e. synthesis of reactive oxygen intermediates).

Natural killer (NK) cells are crucial for the recognition and killing of tumor cells and virus-infected cells. In aging individuals, their cytotoxicity can be attenuated due to inefficient signal transduction, increased expression of killer-inhibitory receptors or decreased secretion of chemokines, effects only partially compensated through an increase in their numbers. Finally, in frail elderly individuals, dendritic cells show a reduction in antigen presentation as well as impaired macropinocytosis, endocytosis and chemokine secretion; in healthy aging individuals they retain normal antigen-presenting function.

## The aging adaptive immune system

The adaptive immune system undergoes more profound age-related modifications, and the observed changes are more consistent in the literature. T lymphocytes are trained in the thymus, a gland located behind the breastbone. Pre-lymphocytes, derived from hematopoietic stem cells in the bone marrow, come into contact with endogenous and foreign antigens in the thymus, forming the basis for self/non-self recognition and building a repertoire of specific cytotoxic, helper and regulatory T cells. After birth the thymus begins to atrophy in a process called thymus involution, characterized by a reduction in size, changes in anatomy, loss of thymic epithelial cells, impairment of thymopoiesis and an increase in adipose tissue. As a result, the number of circulating naïve T cells declines, and oligoclonal memory and cytotoxic T cells accumulate in peripheral immune tissue. Nevertheless, studies of centenarians have revealed a functional T cell repertoire, with only a small reduction in the number of T lymphocytes and a relatively normal number of naïve and memory T cells.



The aging immune system has a surplus of oligoclonal memory and cytotoxic T cells  
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B cell development from lymphoid precursors starts in the bone marrow, with final maturation occurring in peripheral lymphoid organs. As hematopoietic tissue in the bone marrow decreases with age, it is probable that B cell development is decreased as well; such a decline has been shown in mice. B cells from aged humans and animals show impaired activation, a decrease in antibody production and less display of membrane-bound antibodies than B cells from younger animals. Furthermore, the production of specific antibodies in response to vaccination is significantly impaired in older individuals.

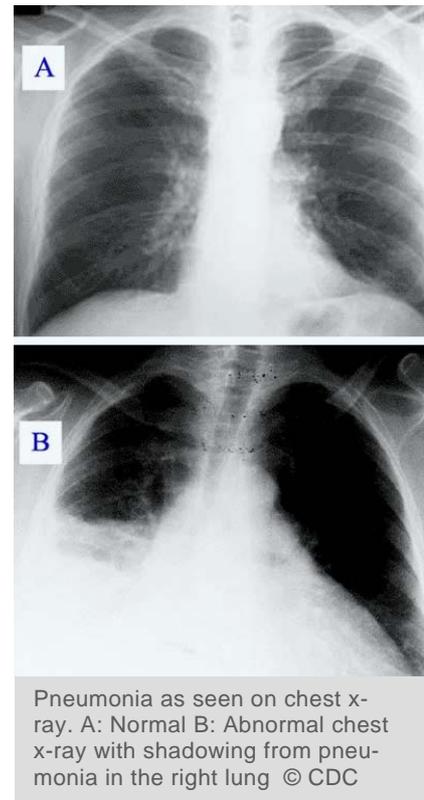
The development and function of the immune system are tightly regulated to ensure the generation of protective immune responses against invading pathogens while avoiding autoimmunity. During the aging process, the humoral and cell-mediated immune systems lose some of their ability to battle a variety of exogenous pathogens. Thus, the risk of infection increases in older individuals with faltering immune systems.

## Infections and Aging

Bacteria and viruses often encounter little resistance after invading the elderly. The aged immune system is not as efficient in recognizing and eliminating new invaders or in preventing their spread. Making the situation even more difficult, in older individuals the signs and symptoms of infection may be non-specific or hidden by underlying chronic conditions, resulting in delayed treatment and reduced response rates.

In developed countries, the major threat to elderly individuals comes from respiratory infections caused by a combination of classic bacteria (e.g. pneumococci) and respiratory viruses (e.g. influenza virus). Among respiratory infections, influenza is the most serious threat to persons over 65 years of age and, according to the World Health Organization (WHO), is responsible for the most deaths; the death rate for pneumonia is eight times higher in the elderly compared to younger adults. Urinary tract infections, often aided by indwelling urinary catheters, are caused by *Escherichia coli* (mainly in women), *Klebsiella spp.* (especially *K. pneumoniae*), *Proteus spp.* and *Morganella morganii* (mainly in men) and are the second most common type of infection in the geriatric population, with a prevalence 20-fold higher than in groups of younger individuals. Following close behind are infective endocarditis (caused by *Staphylococcus aureus* strains, which are often methicillin-resistant, as well as *Streptococcus bovis* and Enterococci) and septicemia, manifested through numerous bacteria in the blood. Infection with “unusual” pathogens such as *Cryptococcus spp.*, *Mycobacterium tuberculosis* and *Listeria spp.* is comparatively rare but nevertheless increased in the elderly and is often overlooked. Because of higher rates of hospitalization, older individuals are more susceptible to nosocomial infections, including those caused by antibiotic-resistant organisms (see also Perspective “[Infectious hospitals](#)”).

In less developed countries, malaria, hepatitis A and B and HIV are some of the most relevant infections with increased severity in older populations. Malaria caused by the parasite *Plasmodium* has a more severe clinical manifestation in the elderly; older patients have a greater parasite density, require a longer hospital stay and develop more complications, resulting in a significantly higher rate of mortality. Infection with Hepatitis A or Hepatitis B, viruses that are 50–100 times more infectious than HIV, cause both acute and chronic disease with a more severe and/or fatal outcome in the ageing population; the WHO reports that more than half of the documented deaths from hepatitis A occur in elderly persons in developing countries. Acute hepatitis B infection, which is rarely fatal in younger populations, can cause mortality as high as 10–15% in elderly populations (concrete



numbers for the impact of chronic hepatitis B on elderly populations are lacking). Finally, although data - especially from developing countries - are somewhat vague, a high prevalence of HIV/AIDS infection seems to be observed in older populations. In 2003, 30% of the reported AIDS cases in the USA were in individuals over the age of 45, and while the success of antiviral therapy certainly impacts these numbers in the Western world, new infections resulting from a lack of awareness are also a serious threat. Aging makes diagnosis more difficult, as early symptoms of HIV infection (night sweats, chronic fatigue, weight loss, dementia) are a normal part of the aging process. In Africa, the impact of aging on HIV/AIDS is even clearer; in addition to the secondary peak of HIV incidence that occurs with advancing age, faster progression from HIV infection to AIDS is observed in older individuals.

### Death is unavoidable...

... but might be postponed by a well-maintained immune system. The immune system that serves to protect us against the myriad of potentially pathogenic microorganisms has a major impact not only on how long we live but also on how well we feel as we reach octogenarian status and beyond. We are beneficiaries of the advances in sanitation, disinfection, vaccination and antibiotics that have drastically reduced the incidence and mortality of infectious disease, but a dysfunctional - or simply less functional - immune system is still a major threat to its "owner". How can we preserve immune function and prevent infectious disease in the elderly?

Vaccination would be a good start...if only it were as effective as in younger people; the influenza vaccine, for example, has an efficacy of only 30–40% in older individuals. And there are many diseases for which no vaccine is available. Rejuvenation of the immune system requires more knowledge about the aging process as well as the identification of biomarkers that reliably show the effects of aging on the immune system, as the aging process varies widely among individuals. Several methods of immune regeneration are in discussion. One of these is caloric restriction, i.e. a 30–50% decrease in dietary intake of calories; however, little is known about the health effects of caloric restriction in humans, and it is questionable whether the probable minor benefits warrant such extreme self-denial. Rejuvenation of the involuted thymus through treatment with cytokines and hormones is also being discussed, but while increased thymus size and a stimulated peripheral immune response have been reported in humans, little is known about side effects.

While it is clear that aging is more complex than the sum of up- and down-regulated immune mechanisms, there is hope that as the processes involved in immune senescence are deciphered, the growing number of those lucky enough to celebrate their 80-some and 90-some birthdays can increasingly enjoy not only length but also quality of life. And probably it is just the daily glass of red wine that makes the difference to a healthy immune system.



"The man who with constant longing awaits with joy each new springtime ... does not perceive that he is longing for his own destruction." Leonardo da Vinci (drawing and notebook)

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