

Title

When chronic diseases meet infectious diseases, a proposal toward healthy aging: lessons from
COVID-19 outbreak

Authors

¹ Gómez-Verjan JC, Departamento de Investigación, Instituto Nacional de Geriátría (INGER), Mexico City, Mexico.

² García-Peña C, Instituto Nacional de Geriátría (INGER), Mexico City, Mexico

^{1*} Rivero-Segura NA, Departamento de Investigación Básica, Instituto Nacional de Geriátría (INGER), Mexico City, Mexico.

Corresponding Author: *NA Rivero-Segura, PhD *Affiliation:* Departamento de Investigación Básica, Instituto Nacional de Geriátría, INGER. Anillo Periférico 2767, Magdalena Contreras, San Jerónimo Lidice, 10200 Mexico City, Mexico. Tel. +52-(1)-55-5573-8601 ext. 54521. *E-mail:* nrivero@inger.gob.mx

ABSTRACT

As the novel COVID-19 disease spreads around the world, the most affected population are those who suffer from the most common chronic diseases, such as obesity, hypertension, and type 2 diabetes, which are quite associated with the so-called age-related diseases. On the other hand, since the Spanish influenza outbreak, humanity has not experienced an infectious disease that synergizes so quickly with chronic diseases, making it mortal for those individuals with comorbidities. In this context, COVID-19 is challenging for health systems all around the world due to the high prevalence of chronic diseases. Nowadays, we are facing the beginning of a new era in which health infectious and chronic diseases meet. Therefore, epidemiologic and biomedical researchers must work together to solve further contingencies, and politicians should direct science-centered decisions on public health. In the present paper, we make an urgent call to learn from the COVID-19 lessons in order to mitigate the chronic diseases prevalence and to address the influence of the infectious diseases on the aging process; since we are about to begin the Decade of Healthy Aging.

Keywords: COVID-19, Chronic diseases, Aging, Immune response, Public health, Healthy Aging

1 INTRODUCTION

1.1 The rise of chronic and viral diseases

In the last 30 years, there have been several viral outbreaks that impact human health and influence our way of living since its acquisition depends on sexual practices (HIV, HPV, Herpes virus, HAV), food intake (SARS-CoV, MERS, Ebola), seasonal climate (Influenza, rhinoviruses, metapneumovirus, mainly), travel or living in tropical areas (Zika, Dengue, Chikungunya), to poor water and sanitation (HAV, Ebola, Dengue, Zika, among others), and more recently to anti-vaccine practices (Measles). Among the most representative viral outbreaks stand out those that have been extraordinarily contagious or lethal. For instance, since HIV emerged in the 1980s, it has accumulated 32 million deaths and 75 million infections worldwide (WHO 2019). Moreover, according to the Center CDC data from 2017-2018, influenza infected 9,3 - 45 million people, causing 810,000 hospitalizations and 61,000 of deaths in the USA alone (CDC 2020).

1.2 Chronic diseases become the individual vulnerable to infectious diseases.

Chronic diseases, also known as noncommunicable diseases have been defined by Centers for Disease Control and Prevention (CDC) as “conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both”. Additionally, this cluster of diseases experienced a severe increase of its prevalence over the last years, due to the poor nutrition (high-fat and carbohydrate enriched diets), the sedentary lifestyle and to the increase of life expectancy and increased longevity over the last years (aging) (Black et al. 2012).

The World Health Organization (WHO) reports five chronic diseases (cardiovascular diseases, diabetes, cancer, obesity, and chronic respiratory disease) which represent the primary concern in public health worldwide, since they are partially responsible of both disability and early death (‘WHO | Integrated chronic disease prevention and control’, 2010). Additionally, as Table 1 describes, chronic diseases impaired the immune system due to the sustained chronic inflammation representative of this cluster of diseases.

On the other hand, the prevalence of chronic diseases is quite common during aging, and in several cases they are closely related to the development of the so-called age-related diseases and the enhanced immunosenescence (Barzilai et al. 2018; Tchkonina and Kirkland 2018).

Table 1. Mechanisms associated with the immune system disruption induced by the main Chronic diseases.

Chronic Diseases	Mechanisms that become organisms more vulnerable to infectious diseases	Refs
Cardiovascular diseases	T cells senescence and increased inflammatory response.	(Meng et al. 2016)
Type 2 Diabetes	Impaired immune responses due to elevated glucose, increased production of advanced glycation end products (AGEs), and constant inflammation. Monocyte/macrophage impaired phagocytosis became organisms susceptible to infection.	(Ferlita et al. 2019)
Hypertension	T-cell infiltration in perivascular tissue, oxidative stress, impairment in endothelial-dependent vasodilation, and expression of TNF- α . Increased expression of proinflammatory interleukins (IL-1a, IL-2, IL-8, VEGF, IFN-g, TNF-a, and MCP-1). Expression of autoimmune phenotype driven by vascular damage. Induce activation of Th17 cells that are involved in inflammatory reactions via IL-6, TGF-b, IL21, and IL-23.	(Rodriguez-Iturbe et al. 2017)

	Induction of proinflammatory cytokines and cells of both innate and adaptive systems.	
Cancer	Impaired immune response due to chemotherapy with purine analogs or with immunosuppressants in bone marrow transplants and hematopoietic stem cell transplant recipients. Natural killer cells dysfunction and T cell exhaustion.	(Debes et al. 2017)
Obesity	Impact negatively on immunity and pathogen defense, including the disruption of lymphoid tissue integrity and architecture, induces pro-inflammatory leukocyte phenotypes, affects the distribution of leukocyte populations among organs and tissues, impaired T cell-mediated immune surveillance. Increased risk of vaccine failure for hepatitis B, tetanus, and influenza.	(Andersen et al. 2016)
Chronic respiratory diseases (Chronic obstructive pulmonary disease and asthma, among others)	Compromised mucociliary and barrier function that allow virus entry into epithelial cells. Increased disproportionate cytokine expression. Inadequate activation of innate and adaptive.	(Allie and Randall 2017)

1.3 Immunosenescence, chronic diseases and aging: the evil triad

As mentioned by several authors, aging is a complex and heterogeneous process characterized by the decline of many physical and cognitive functions. In this sense, during aging the immune system becomes immunosenescent, meaning a gradual deterioration in the immune response (Pawelec 2018). Moreover, it is well established that chronic diseases such as cardiovascular diseases, hypertension, and type 2 diabetes mellitus, may accelerate the immunosenescence (Bagatini et al. 2017). Thus the mix of chronic diseases, the immunosenescence and the aging, that we term as *the evil triad*, synergize and work together to become more vulnerable to the individual to acquire infectious diseases (Zhavoronkov 2020; Tam et al. 2020).

This hypothesis may be supported by the Fig 1, in which accordingly with data from the Institute of Health and Metrics (IHME) at first sight both groups of diseases show no apparent relationship between them (Fig 1A); however, when correlated (Fig 1B) both seem to be more associated than expected.



Fig 1. The relation between chronic and viral infections. (A) Normalized prevalence comparison between chronic diseases and viral infections. (B) Pearson correlation between chronic and viral infections. Data obtained from the Institute of Health and Metrics (IHME) (Date 01-04-2020): Other non-communicable diseases (ONCD), Diabetes and kidney disease (DBKD), Neurological diseases (NEUD), Chronic respiratory diseases (CRDS), Cardiovascular diseases (CVDS), Cancer, Chronic liver disease (CLDS), Zika, HIV/AIDS, Dengue, Ebola, Hepatitis

(HAVD), Measles, Varicella and *Herpes zoster* (VAR-HV), Respiratory infections and Tuberculosis (RITB), Viral skin disease (VSD).

As mentioned above, most of the chronic diseases are related to aging, highlighting the relevance of immunosenescence and the molecular pillars of aging. Therefore, it is crucial to reconsider opening a new epidemiological panorama where infectious diseases meet chronic conditions, in order to develop effective approaches to address its impact on the elderly population. Otherwise, the *evil triad* will increase mortality abruptly as occurs in frailty HIV positive individuals due to the immune exhaustion, accelerated aging and precipitated immunosenescence (Álvarez et al. 2020); or as occurs nowadays in the novel COVID-19 outbreak in which the main victims are those with hypertension, obesity, and diabetes.

1.4 COVID-19 outbreak

Coronaviruses are members of the family Coronaviridae; only alphacoronaviruses and betacoronaviruses infect mammals, humans particularly. Both cause respiratory illness and gastrointestinal diseases such as porcine enteric diarrhea virus (PEDV) or the swine acute diarrhea syndrome coronavirus (SADS-CoV). Betacoronaviruses are the most dangerous, developing severe acute respiratory syndrome (SARS-CoV), middle east respiratory syndrome (MERS-CoV), and the novel COVID-19 outbreak (SARS-CoV-2) (Liu et al. 2020; Zhu et al. 2020). As we write this paper there are about 217,813 deaths associated with COVID-19, this disease has been reported to be in approximately 200 countries and two international cruises, confirming 3,136,543 cases (April 28th, 2020). The outbreak has been called a public health high alert as the infection spreads all over the world, and several countries have called for a quarantine affecting millions of lives and the global economy. Today the most affected countries are USA (59,266 deaths), Spain (23,822 deaths), France (23,660) Italy (27,359 deaths) and the UK (21,678 deaths) (April 28, 2020, Worldometers.info(coronavirus/). COVID-19 is challenging for most health systems all over the world, most of which have suffered in the last years reforms and restructuring (cuts in their budgets or infrastructures) as commonly said: "*politics is a public health and public health is politics.*"

BOX 1. A clinical perspective: Lessons learned from COVID-19 outbreak in the pursuit of healthy aging

Lesson 1. The prevalent situation highlights the need for longitudinal studies in the aging population to analyze the links between aging, immunosenescence and chronic conditions

Lesson 2. New strategies of disease prevention and effective immunity are needed in older populations

Lesson 3. The process of aging represents major public health challenges, associated with the incredible burden of chronic diseases but also COVID-19 has shown the vulnerability of aging populations to new diseases

2. Conclusions

COVID-19 is giving us painful lessons at different levels about healthcare and science systems performance around the world. In this context, the consequences of sustaining both sedentary and poor nutritional lifestyles (for many years) lead to the development of chronic diseases that later impact negatively on the immunological system, and in the impaired immune response during aging. The first lesson should be considered for the politicians, and the health professionals since our public health care systems need to be improved, to guarantee access to medical services for the population. To achieve this goal is necessary to strengthen the public health systems and to avoid budget reductions; this will help be prepared to attend any contingency. Another lesson is that we urgently need scientists, physicians, and public health professionals to work together with both pharmaceutical and food-processing industries to develop new strategies which target the etiological agents responsible for chronic diseases, efficiently. Finally, we encourage the government and politicians to follow scientific evidence and establish interdisciplinary networks of specialists to lead and find alternatives to counteract against COVID-19 or further contingencies; we urgently need science-centered policies for public health. Since it will certainly not be

the last pandemic and we could face similar outbreaks such as Dengue, Measles, or antibiotic resistant bacteria that could re-emerge.

3 Conflict of Interest

None

4 References

- Allie SR, Randall TD (2017) Pulmonary immunity to viruses. *Clin Sci* 131:1737–1762
- Álvarez S, Brañas F, Sánchez-Conde M, et al (2020) Frailty, markers of immune activation and oxidative stress in HIV infected elderly. *PLoS One* 15:e0230339
- Andersen CJ, Murphy KE, Fernandez ML (2016) Impact of Obesity and Metabolic Syndrome on Immunity. *Adv Nutr* 7:66–75
- Bagatini MD, Cardoso AM, Dos Santos AA, Carvalho FB (2017) Immune System and Chronic Diseases. *J Immunol Res* 2017:4284327
- Barzilai N, Cuervo AM, Austad S (2018) Aging as a Biological Target for Prevention and Therapy. *JAMA* 320:1321–1322
- Black D, O’Loughlin K, Kendig H, Wilson L (2012) Cities, environmental stressors, ageing and chronic disease. *Australasian Journal on Ageing* 31:147–151
- CDC (2020) Flu Activity & Surveillance. In: Centers for Disease Control and Prevention. <https://www.cdc.gov/flu/weekly/fluactivitysurv.htm>. Accessed 2 Apr 2020
- Debes JD, de Knecht RJ, Boonstra A (2017) The Path to Cancer and Back: Immune Modulation During Hepatitis C Virus Infection, Progression to Fibrosis and Cancer, and Unexpected Roles of New Antivirals. *Transplantation* 101:910–915
- Ferlita S, Yegiazaryan A, Noori N, et al (2019) Type 2 Diabetes Mellitus and Altered Immune System Leading to Susceptibility to Pathogens, Especially. *J Clin Med Res* 8.: <https://doi.org/10.3390/jcm8122219>
- Liu C, Zhou Q, Li Y, et al (2020) Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Central Science*
- Meng X, Yang J, Dong M, et al (2016) Regulatory T cells in cardiovascular diseases. *Nat Rev Cardiol* 13:167–179
- Pawelec G (2018) Age and immunity: What is “immunosenescence”? *Exp Gerontol* 105:4–9
- Rodriguez-Iturbe B, Pons H, Johnson RJ (2017) Role of the Immune System in Hypertension. *Physiol Rev* 97:1127–1164
- Tam BT, Morais JA, Santosa S (2020) Obesity and ageing: Two sides of the same coin. *Obes Rev* 21:e12991
- Tchkonian T, Kirkland JL (2018) Aging, Cell Senescence, and Chronic Disease: Emerging Therapeutic Strategies. *JAMA* 320:1319–1320
- Zhavoronkov A (2020) Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. *Aging* 12.: <https://doi.org/10.18632/aging.102988>
- Zhu N, Zhang D, Wang W, et al (2020) A Novel Coronavirus from Patients with Pneumonia in China,

2019. New England Journal of Medicine 382:727–733

(2019) WHO | HIV/AIDS