The COVID-19 Pandemic, Biogerontology and the Ageing of Humanity

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Abstract

The World Health Organization designated the decade 2020-2030 as the "decade of healthy ageing". It is a tragic irony that the year 2020 should begin with a pandemic that is so lethal for older persons. Not only are older persons the most vulnerable to COVID-19 mortality, but many of the mitigation efforts to slow the spread of the virus have imposed yet further emotional and mental health burdens on the most vulnerable among those over age 70. To help prevent future infectious disease mortality and suffering, as well as the profound health burdens from the chronic diseases associated with ageing, insights from biogerontology must become an integral part of global public health priorities. The timing is ripe for making the public health aspiration of developing an applied gerontological intervention a reality.

Key words: COVID-19, disease, healthy ageing, pandemic, preventative medicine

Introduction

The World Health Organization had designated the decade 2020-2030 as the "decade of healthy ageing".[i] It is a tragic irony that the year 2020 should begin with a pandemic that is so lethal for older persons. By the end of 2020 The World Health Organization estimated the global death toll from COVID-19 to be > 1.8 million deaths.[ii] The Centers for Disease Control and Prevention in the United States estimates that 80% of the deaths that have involved COVID-19 have occurred among persons age 65 and older.[iii] Despite the variation in estimates for the virus' infection mortality rate in different geographical areas, the COVID-19 mortality data to date makes it clear that advanced age (age > 70) is the highest risk factor of COVID-19 mortality. In people age < 70, COVID-19 infection fatality rates have ranged from 0.00% to 0.31% with crude and corrected medians of 0.05%.[iv]

Not only are older persons the most vulnerable to COVID-19 mortality, but many of the mitigation efforts to slow the spread of the virus have imposed yet further emotional and mental health burdens on the most vulnerable among those over age 70.[v vi] Long-term care and assisted living facilities have restricted visits during the pandemic, in an effort to help protect the elderly from COVID-19. But by doing so those who already live in conditions isolated from family and loved ones face further isolation, and the emotional and mental health burdens that can accompany such isolation.

The COVID-19 pandemic reveals many important societal lessons about our (lack of) preparedness to contain or mitigate new infectious diseases- such as the interconnectedness of the health prospects of today's global population, the adverse health effects of prolonged lockdowns, and the logistical challenges of developing safe and effective vaccines. While there will be many important public health lessons we learn from this pandemic, one very significant lesson is already evident but, sadly, often under reported in the media and underappreciated by many medical researchers whose research focuses on treating specific

diseases. And this is the lesson that today's ageing populations face high risks of *multi-morbidity* in late life, risks much more expansive than just COVID-19. And these are not health risks that can be prevented with the public health prescriptions of hand washing, wearing face masks, social distancing or a COVID-19 vaccine.

To help us better address the rise in the chronic diseases of late life this century, and future pandemics like the current one, insights from biogerontology must become an integral part of global public health priorities. The development of an applied gerontological intervention could help make the world's ageing populations more resistant to infectious and chronic disease.

Biogerontology and Humanity's "Biological Warranty Period"

The suggestion that biomedical research should be harnessed to target the ageing process itself was first argued for over 40 years ago, in an edited volume by Bernice Neugarten and Robert Havighurst entitled *Extending the Human Life Span: Social Policy and Social Ethics*. The preface of the book notes that biomedical research can be utilized in one of two strategies to increase the lifespan.

> The first is the continuing effort to conquer disease. The second is the attempt to identify the intrinsic biological processes that are thought to underlie aging… to discover the genetic and biochemical secrets of aging, then to alter the biological clock that is presumably programmed into the human species. The second approach is directed at rate control, rather than disease control.[vii]

Robin Holliday (1932-2014) was one of the first scientists to apply modern molecular medicine to the study of ageing, and he had the following sage insights about ageing 20 years before the current pandemic.

> At the end of this century there is still a strong emphasis on the treatment of age-associated disease, rather than on its prevention. The possibility of prevention depends on research on ageing itself.… Development of preventative measures will certainly lower the costs of health-care for the aged. The overall aim should not be to increase the lifespan, but to increase the healthspan. This approach will not only improve the quality of life for the elderly, but also reduce the costs of medical

treatment, and diminish the burden of the very large number of people who at present care for the elderly and infirm.[viii]

Two decades on and Holliday's aspiration that humanity increase the healthspan, vs simply extending the lifespan by preventing death from specific diseases of ageing, has still not been realized. And a consequence of this is the tragic loss of life we are now witnessing among the elderly living with an extended lifespan and the co-morbidities that put them at high risk of severe COVID-19 illness. Many of the conditions that increase the risk of severe illness from the virus that causes COVID-19, like cancer, chronic kidney disease and type 2 diabetes, increase with advanced age. In humans, the incidence of cancer rises exponentially in the final decades of life.[ix] Loss of nephrons and a decline in glomerular filtration rate (GFR) is a characteristic of normal ageing, called renal senescence.[x] Almost one-third of U.S. adults over the age of 65 years have diabetes.[xi] And immunosenescence and inflammaging occurring in some older adults, could be predisposing conditions that sustain the mechanisms by which the SARS-CoV-2 escape the immune surveillance and leads to serious COVID-19.[xii]

Many prominent ageing researchers have re-iterated the call for targeting the ageing process itself as a form of preventative medicine.[xiii xiv xv xvi xvii] The pandemic has brought into sharper focus the moral imperative of making "healthy ageing" a global health priority. And not just because it could help prevent severe COVID-19 symptoms and mortality, but to also help insulate ageing populations from the pandemic of chronic diseases that kill most humans in the world today, and will continue to be responsible for most human deaths after the current COVID-19 pandemic subsides.

The COVID-19 mortality numbers are only the tip of the iceberg of the health predicaments facing the world's ageing populations this century. Most of the chronic disease deaths in the world, like the 9.6 million[xviii] cancer deaths or 17.9 million deaths from

cardiovascular diseases[xix], also occur primarily in persons over the age of 70. The question of why COVID-19 has been so lethal for those over age 70 will need to be examined in greater detail as we learn more about the virus and its impact on lungs and other organs. But the mortality data already in hand provides ample evidence for championing the cause of developing an applied gerontological intervention to help protect the world's ageing populations from severe COVID-19 illness and other types of infectious (and chronic) diseases.

Why is there Disease?

When explaining why infectious diseases plague human populations, part of a complete answer will entail detailing the plurality of risks *inherent* in our inhospitable world. *SARS-CoV-2* is only one of over 1400 species of infectious organisms that have been identified as causing disease in humans.[xx] Another part of a complete account of our vulnerability to a virus (like SARS-CoV-2) will involve detailing how the specific living circumstances of different populations increase or decrease the rate of spread, and lethality, of the virus.[xxi] People living in dense, populated cities in multi-generational homes, for example, will experience more rapid spread of the virus and its potential lethality may be more severe.

A complete explanation of why certain viruses are more lethal in particular regions than others will also emphasize the public health and medical resources available to prevent and treat specific types of infectious disease. Affluent countries with sophisticated and well funded healthcare systems, for example, can be expected to fare better than impoverished countries with minimal prevention and treatment options to offer their population and patients. However, this pandemic has revealed that this is not always the case. Researchers are puzzled by the lower than estimated COVID-19 mortality in Africa.[xxii] Many factors could be at play in explaining this, such as the amount of testing done to verify the prevalence

of the virus in different populations and the underreporting of deaths. But given Africa's weaker health systems, and the fact that the continent also faces significant challenges with other infectious diseases such as HIV and malaria, one would expect the developed countries to fare much better with respect to COVID-19 mortality than developing countries in Africa. But that has not been the case. While more research is needed to determine the reasons for this surprising result, one obvious factor is the reality that Africa has a much younger population than the developed countries. Africa has a comparatively young population, with a median population age of 19.7 years for the continent versus 38.6 years for the United States.[xxiii]

As the case of Africa's low COVID-19 mortality reveals, focusing only on *proximate* level explanations of infectious disease mortality omits a key insight concerning our vulnerability to different types of disease- and that is the *ultimate* or evolutionary causation of disease (and health). An important part of the story of our vulnerability to infectious (and chronic) disease is the story of our *evolved biology*. Telling that element of the story requires us to invoke the evolutionary explanation of why there is infectious diseases and why they can be so lethal among persons age > 70.

The evolutionary biologist Theodosius Dozhansky famously remarked that "Nothing in biology makes sense except in the light of evolution".[xxiv] Pathogens are arguably the strongest selective pressure to drive the evolution of modern humans.[xxv] Charles Darwin's theory of evolution by natural selection not only helps us understand why certain infectious organisms survive and persist, but it also helps us understand why viruses like SARS-CoV-2 are more lethal for persons over age 70. This is where insights from biogerontology are critical to public health in the 21st century.

The fact that age (especially being over age 70) has clearly emerged as the biggest risk factor for COVID-19 mortality in all countries justifies invoking the likely *evolutionary* (or ultimate) causation of COVID-19 mortality among the elderly. And this evolutionary explanation is the same explanation that helps us make sense of why chronic disease mortalities share a similar age mortality profile as this infectious virus. Namely, that the human species (like other sexually reproducing species) has an evolutionary history that prioritized reproduction over the somatic maintenance needed for indefinite survival. Natural selection acts more weakly to reduce mortality at older ages.

Evolutionary accounts of senescence build on the research and insights of many prominent scientists from the twentieth century, such as Ronald Fisher[xxvi], JBS Haldane[xxvii], Peter Medawar[xxviii], George Williams[xxix], William Hamilton[xxx], and Brian Charlesworth[xxxi]. The two main theories of the evolution of ageing are the *mutation accumulation theory* of ageing suggested by Peter Medawar, and the *antagonistic pleiotropy theory* of ageing suggested by George Williams. A dominant version of the latter explanation is known as the *disposable soma theory*.[xxxii xxxiii] This theory posits that the winning evolutionary strategy for sexually reproducing species, species that have had to find ways to survive the extrinsic risks of the hostile environments of life on this planet, is to prioritize health during the "essential lifespan". The "essential lifespan" of a species is defined as the time required to fulfill the Darwinian purpose of life, that is, successful reproduction and continuation of generations.[xxxiv]

A species' "essential lifespan" determines its *biological warranty period*- biological warranty periods are an inadvertent by product of evolutionary neglect, and genetic programs for growth, development and reproduction.[xxxv] There are compelling sources of evidence for the conjecture that humans have a biological warranty period of approximately 70 years. In their extensive cross-cultural examination of longevity in hunter-gatherers,[xxxvi] Michael

Gurven and Hillard Kaplan conclude that human bodies are designed to function well for about seven decades in the environment in which our species evolved. Within this seven decade period of time humans could, if they escaped the extrinsic threats to their lives, reach sexual maturity, produce and nurture their offspring. And, for at least one-fourth of the adult population living in such conditions (e.g., with no sanitation, immunizations, or medicine, nor a reliable food supply, etc.), they likely lived 15-20 years as grandparents.

Data on longevity among extant hunter-gatherers and forager-horticulturalists, coupled with ample biological evidence[xxxvii] concerning the risks of infertility, disease, frailty, disability and death after age 70 make it clear that the biology of ageing itself ought to be a target of preventative medicine. And the pattern of COVID-19 mortality amplifies the urgency to prioritize this strategy given that the virus is most lethal for persons over age 70.

The late life mortality pattern of COVID-19 is very distinct from the influenza pandemic of 1918, which killed an estimated 50 million people worldwide.[xxxviii] What made the 1918 virus particularly devastating was the fact that nearly half of the influenza-related deaths occurred among young adults (20-40 years of age).[xxxix] This was an outlier in that it is usually the very young or older adults (age > 65) who are most at risk of death from influenza, as these vulnerable persons have less immunity. By reconstructing the 1918 virus, researchers found that particular genes may have played an important role in the virus' ability to obstruct airway cells. HA, NA, and PB1 genes, for example, have been identified as being the genes most optimal for virus replication and virulence.[xl]

Preventative Medicine in an Ageing World

Despite the enormous health and economic costs of the COVID-19 pandemic, there are some positive public health insights the pandemic might highlight to help us recalibrate public health priority initiatives. This pandemic has brought to the fore the importance of traditional

preventative medicine. Tackling obesity and smoking[xli] (both risk factors for COVID-19 mortality), as well as being better prepared for outbreaks of infectious diseases, are all obvious areas for improvement. But the bolder vision of increasing the human *healthspan* by targeting ageing itself, which Holliday encouraged we pursue over two decades ago, has never been more urgent as it would help delay the health vulnerabilities of senescence. This is a radically different way of conceptualizing what the legitimate goals of medicine are. That goal goes further than simply proposing behavioural modifications (like healthy diet and active lifestyle), or promoting basic scientific research into the development of new therapeutics for specific diseases. Biogerontology encourages us to address the *evolutionary* (and not simply proximate) causation of disease, frailty and disability (the traditional concerns of epidemiology), and to aspire to develop safe and effective medical interventions that help us improve the biology we have inherited from evolution by natural selection. Such interventions need to expand the *biological warranty period* of 70 years vs simply preventing death in the post-warranty stage of life. Such an aspiration is both novel and bold.

In a recent editorial in the journal *Ageing and Disease* many prominent ageing researchers noted that the death and economic toll of the COVID-19 pandemic amplified the urgency of the strategy to health research they have been advocating for many years:

> The COVID-19 global emergency has emphasized to vast masses of people the vital need to prevent old-age multimorbidity, protect the elderly and improve their health span. Proponents of geroscience have argued for the importance of such preventive measures for many years. Now we see in front of our own eyes the disastrous consequences of the deficit in such preventive measures, and the portent this gap in our approach represents for the future. We are witnessing how this new infectious disease is wreaking havoc among individuals, the healthcare system and the entire social fabric around the world, while the rapid ageing of the population represents the main risk factor and aggravating condition. Therefore, arguably, one of the most important lessons to be learned from this pandemic, is the need to therapeutically address degenerative ageing processes to prevent ageing-related ill health as a whole.[xlii]

With constant media attention on COVID-19 infections and mortality it is easy to lose sight of the reality that the chronic diseases are responsible for most human deaths in the

world today and will continue to after this pandemic. By prioritizing the study of the biology of ageing, with the goal of developing an applied gerontological intervention, we can better ensure we effectively improve the health of today's ageing populations and all future generations of humans by increasing the human healthspan vs lifespan.

The World Health Organization's aspiration of the "decade of healthy ageing" for 2020-2030 is more important than ever. And this pandemic should not discourage us from realizing this ambition. The rapid speed at which mRNA vaccines for COVID-19 were developed in the year 2020 is reason for optimism. At the same time we should recognize the reality that making this decade a decade of healthy ageing requires scientific innovation that goes much further than developing a vaccine for just one infectious disease. Santesmasses et al. argue that COVID-19 is an emergent disease of ageing, and as such COVID-19, and deadly respiratory diseases in general, may be targeted, in addition to antiviral approaches, by approaches that target the ageing process.[xliii] And Mueller et al. suggest that with advances in the field it may even be possible to reverse the age of cells and tissues so that high-risk older individuals can respond to viral infections as though they were young.[xliv]

The world has never had so many people living beyond our evolved "biological warranty period". To continue to focus primarily on therapeutics for specific diseases of ageing will result in persons living longer with multi-morbidity, making populations more susceptible to death from a virus like SARS-CoV-2. By prioritizing instead the goal of extending the human healthspan we should be better prepared to meet the health predicaments facing the world's ageing populations.

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