Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

The under-reported role of toxic substance exposures in the COVID-19 pandemic

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ABSTRACT

Coronavirus disease 2019 (COVID-19) and previous pandemics have been viewed almost exclusively as virology problems, with toxicology problems mostly being ignored. This perspective is not supported by the evolution of COVID-19, where the impact of real-life exposures to multiple toxic stressors degrading the immune system is followed by the SARS-CoV-2 virus exploiting the degraded immune system to trigger a chain of events ultimately leading to COVID-19. This immune system degradation from multiple toxic stressors (chemical, physical, biological, psychosocial stressors) means that attribution of serious consequences from COVID-19 should be made to the virus-toxic stressors nexus, not to any of the nexus constituents in isolation. The leading toxic stressors (identified in this study as contributing to COVID-19) are pervasive, contributing to myriad chronic diseases as well as immune system degradation. They increase the likelihood for comorbidities and mortality associated with COVID-19.

For the short-term, tactical/reactive virology-focused treatments are of higher priority than strategic/proactive toxicology-focused treatments, although both could be implemented in parallel to reinforce each other. However, for long-term pandemic prevention, toxicology-based approaches should be given higher priority than virology-based approaches. Since current COVID-19 treatments globally ignore the toxicology component almost completely, only limited benefits can be expected from these treatments.

1. The human virome

We live in a "sea" of viruses known as the human virome (Lecuit and Eloit, 2013). Viruses are integral to life itself; they are nature's way of ensuring "survival of the fittest". They constantly probe the immune system defenses of the body. If the immune system is healthy, the viruses are neutralized. If the immune system is degraded/dysfunctional, pathogenic viruses can invade the cells, replicate, and trigger a chain of events leading to clinically manifested infectious disease.

Wylie et al., (2014) analyzed DNA viruses from up to five significant body habitats (nose, skin, mouth, vagina, and stool) of 102 subjects (generally healthy adults; not symptomatic for acute infections; not diagnosed with HPV infection within the last two years; females had not had any active genital herpes infection within the last two months). They detected an average of 5.5 viral genera in each individual. These included herpesviruses, papillomaviruses, polyomaviruses, adenoviruses, anelloviruses, parvoviruses, and circoviruses.

In a later study, Wylie (2017) identified common viruses detected in the respiratory tract virome, including picornaviruses, paramyxoviruses, orthomyxoviruses, coronaviruses, adenoviruses, parvoviruses, herpesviruses, anelloviruses, papillomaviruses, and polyomaviruses. Thus, the viral distribution of the above experiments depended largely on the body

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sampling site.

2. Beneficial versus pathogenic effects of viruses

Viruses are parasites of host organisms, and produce beneficial or pathogenic effects. The latter include infectious diseases to humans, animals, and other living organisms. Emerging evidence suggests that some viruses could have beneficial effects, including host protection against second virus, protection against non-infectious diseases by childhood virus infection, regulation of gut microbiota, and host protection by endogenous retroviruses (Watanabe and Kawaoka, 2020).

There is a large diversity of viruses; currently, approximately 263 viruses from 25 viral families can infect humans. Most emerging infectious diseases are zoonotic, caused by viruses that originate in wild animals (e.g., primates, rodents and bats). The PREDICT program (https://ohi.vetmed.ucdavis.edu/programs-projects/predict-project) has identified over 1100 viruses in animals and humans. According to the Global Virome Project (http://www.globalviromeproject.org), ~1.67 million yet-to-be-discovered viral species from key zoonotic viral families may exist in mammal and avian hosts, with 631,000–827,000 of them having zoonotic potential (Watanabe and Kawaoka, 2020).

The mammalian virome includes diverse commensal and pathogenic viruses that evoke a broad range of immune responses from the host. A subset of the virome (in particular, zoonotic viruses that appear to be pathogenic in humans) challenges the immune system continually. This process appears to be a dual-edged sword. Healthy immune systems respond optimally to viral challenges and are further strengthened by the continual challenges, offering additional protection against other viral challenges. Degraded/dysfunctional immune systems over-respond or under-respond to viral challenges, and are thus unable to prevent the occurrence of a life-threatening clinical course.

3. Role of SARS-CoV-2 in emergence of COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the zoonotic virus most closely associated with coronavirus disease 2019 (COVID-19). There are strong misconceptions about the role played by SARS-CoV-2 in the emergence of COVID-19, especially the severity of COVID-19 in selected demographic groups. These misconceptions result in treatments focused on virology without any consideration of toxicology: containing/attenuating SARS-CoV-2 exposure/viral loads rather than intrinsically strengthening the immune system. These virology-based actions do not address the underlying toxicology-based problems that must be addressed properly in order to decrease human vulnerability to infectious diseases, including COVID-19. Short-term, reactive virology-based measures (e.g., quarantines, repurposed drugs, etc.) are required to contain the present SARS-CoV-2 outbreak (Farsalinos et al., 2020; Nitulescu et al., 2020; Zhang et al., 2020; Bhagavathula et al., 2020; Skalny et al., 2020; Torequl Islam et al., 2020). However, the long-term, proactive toxicology-based measures required to intrinsically strengthen the immune system and prevent such future outbreaks have not been addressed. This article attempts to clarify these misconceptions and to propose strategic approaches aimed at intrinsically strengthening the immune system. If such a strategy had been followed consistently in the past, it could have prevented/minimized the incidence and outcome of COVID-19. Still, this strategy is essential to prevent/minimize the adverse effects of the inevitable future pandemics.

4. Immune system health is central to infectious disease resistance

The current COVID-19 pandemic, the SARS pandemic of 2002–2003, and the annual influenza pandemics share some strong commonalities. A small fraction of those who are exposed to the respective viruses become symptomatic; then, a small fraction of those who are symptomatic succumb. Most of these infectious disease deaths result from pneumonia and further acute respiratory distress syndrome (ARDS).

A vast majority of the deaths are among the elderly with important comorbidities and degraded/dysfunctional immune systems (Huang et al., 2020; Liu et al., 2020; Mo et al., 2020; Qian et al., 2020; Qin et al., 2020; Tian et al., 2020; Han et al., 2020; Yun et al., 2020; Medetalibeyoglu et al., 2020; Guo et al., 2020; Docea et al., 2020; Petrakis et al., 2020), and some deaths among younger people with degraded/dysfunctional immune systems. While there is some decline in the immune system with age, comorbidity is a more reliable predictor of impaired immunity than chronological age in older adults (Castle et al., 2005; Castle et al., 2007; Kalula and Ross, 2008; Kostoff, 2010; Gradinaru et al., 2018; Gradinaru et al., 2017; Petrakis et al., 2017). Underlying health conditions among patients with COVID-19 admitted to Intensive Care Units include hypertension, diabetes, cardiovascular disease, chronic respiratory disease, immune compromised status, cancer and obesity (ECDC, 2020). Metabolic stress also contributes significantly to the dysfunctional immune response and, thus, to the increased risk associated with viral exposure (Petrakis et al., 2020; Margina et al., 2020).

These chronic diseases have been linked to toxic stressor exposures (chemical, physical, biological, or psychosocial stressors) that disrupt the immune system and lead to an increased risk of death in COVID-19 patients (Sears and Genius, 2012; Kostoff, 2015, 2019; Tsatsakis et al., 2020). Additionally, the risk of dying can also increase when the baseline inflammatory state that occurs with chronic diseases is challenged by exposure to an infectious agent, such as SARS-CoV-2. The most severe consequences from COVID-19 and influenza stem from a degraded/dysfunctional immune system, and the exploitation of the degraded immune system by the virus. For a healthy immune system, the virus would be unable to overcome its strong defenses, and would be neutralized.

What are the contributing factors to a degraded/dysfunctional immune system? Some immune systems are intrinsically dysfunctional due to genetic/hereditary/congenital factors (Goumenou et al., 2020). However, for most people, other factors may play a much stronger role in determining the health of the immune system.

5. Contributing factors to a degraded immune system

A recent study examined the adverse impacts of toxic lifestyle, iatrogenic, biotoxic, environmental/occupational, and psychosocial/socioeconomic factors on the health of the immune system directly or indirectly (Kostoff et al., 2020). Depending on how one aggregated the results, there were anywhere from 1000–2000+ factors that contributed to immune system degradation, and that number was viewed as a gross under-estimate. Some of the factors in this recent study that were shown repeatedly to degrade the immune system include:

- Lifestyle (e.g., sedentary lifestyle, tobacco smoking, alcohol intake, drugs of abuse, Western-pattern diet (high-fat diet, ultraprocessed food, sugar and refined grains), chronic sleep deprivation, etc.);
- Iatrogenic (e.g., immunosuppressants, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol), surgical stress, anesthesia, psychotropic drugs (antidepressants, antiepileptic and antipsychotic drugs), antibiotics, nanomedicine products, adjuvanted vaccines, ionizing radiation therapy, etc.);
- Biotoxins/Biomaterials (e.g., aflatoxin, ochratoxin, T-2 toxin, anatoxin-A, mycotoxins, microcystin-LR, toxic dietary cyanobacteria, yessotoxin, scorpion venom, Streptomyces californicus, *Pseudomonas aeruginosa*, Rhinovirus, respiratory syncytial virus, etc.);
- Occupational/Environmental (e.g., endocrine-disrupting chemicals, microplastics, heavy metals, pesticides, nanoparticles, perfluorooctanoic acid (PFOA), polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), perfluorooctanesulfonate (PFOS), fine particulate matter, air pollution, acrylamide, aromatic

halogenated disinfection byproducts, benzene, benzo(a)pyrene, crude oil, corexit, sodium fluoride, ultraviolet (UV) radiation, cell or mobile phones and other wireless transmitting devices (WTDs) including cordless phones, cell towers, and Wi-Fi, etc.);
- PsychoSocial/SocioEconomic (e.g., depression, chronic stress, restraint stress, social isolation, stressful life events, childhood adversity, etc.).

Many of the above factors that contribute to a degraded/dysfunctional immune system are pervasive; they contribute to myriad (especially chronic) diseases (Kostoff, 2015, 2019). Thus, people with immune systems degraded by the above contributing factors also have an increased likelihood of having significant comorbidities, such as the demographic most vulnerable to succumbing from COVID-19.

6. The primacy of toxic stressors' effects

Given the wide diversity and prevalence of contributing factors shown above, the public is exposed continually to myriad toxic stressors, with each individual being exposed to a distinct combination of toxic stressors over his/her lifetime (Tsatsakis et al., 2016; Hernández et al., 2020). As several studies have shown (Kostoff et al., 2018; Laetz et al., 2009; Chen et al., 2015; Hernandez et al., 2013; Vardavas et al., 2016; Docea et al., 2017, 2018; Kalogeraki et al., 2017), the broader the combination of toxic stressors and the higher the concentrations of its constituents, the higher the likelihood of adverse combined effects. For infectious diseases, the effect of the combination of toxic stressors will determine the degradation/dysfunction of the immune system, and therefore the severity of the consequences of viral exposure. Different people will be exposed to distinct toxic stressors combinations, and will respond differently according to the composition of the toxic stressors combinations and a person's genetic makeup and overall level of health. There can be substantial synergies among the constituents of a given toxic stressors combination and, depending on the concentration and toxicity profile of the constituents, can result in enhanced adverse effects from the combination (Docea et al., 2019; Kostoff et al., 2018; Ginzburg et al., 2018; Schulz et al., 2018; Zmyslony et al., 2000; Borman et al., 2017; Tsatsakis et al., 2019a,b,c,d; Tsiaoussis et al., 2019; Sergievich et al., 2020; Margina et al., 2019). The key concept here is that the ***virus-toxic stressors combination nexus*** is determining the ultimate health outcome, not necessarily any one of the constituents in isolation.

The response of governments worldwide to COVID-19 has been virology-based, disregarding toxicological issues. That response consisted of: (1) imposing a quarantine on the public (residents, travelers) that will restrict exposure to only one constituent of the virus-toxic stressors combination nexus (SARS-CoV-2) that may be triggering the toxic stressors combination-enabled chain of events leading to COVID-19; (2) conducting searches for, and trials of, mainly repurposed antiviral treatments; and (3) accelerating SARS-CoV-2 vaccine development. The following example highlights the very limited nature of, and flaws inherent in, this virology-centric approach.

Assume hypothetically that a combination of four hazardous elements (including SARS-CoV-2) is required for a lethal bout of pneumonia to occur (see Fig. 1). Three of these elements are toxic stressors in the ordinary sense: pesticides, high-fat-diet, wireless radiation. The fourth is SARS-CoV-2.

Assume that any combination of three of the four hazardous elements would not be sufficient to result in pneumonia, and would result in no symptoms. Assume further that four experiments are conducted to identify the marginal impact of each constituent: each experiment starts with three of the four elements, and the fourth is added. In each of the four experiments, the final result using all four elements will be fatal pneumonia. One could conclude (when assigning responsibility/causation for the death to a single entity) that the marginal impact of adding the fourth element was fatal pneumonia.

In Fig. 1, the four experiments are reflected by the four mixtures shown. In all four cases, the element shown at the top of the mixture is the fourth element added in the experiment. So, for the first experiment (reflected by mixture M_a), where C4 (SARS-CoV-2) was the final element added to the mixture, one could conclude that SARS-CoV-2 was the cause of death, since its addition enabled the emergence of fatal COVID-19. Test kits would show the presence of SARS-CoV-2 in biological samples, and that could be used as confirmation.

For the second experiment (reflected by mixture M_b), where C3 (pesticides) was the final element added to the mixture, one could conclude that pesticides were the cause of death, since their addition enabled the emergence of fatal COVID-19. Test kits would show the presence of pesticides in biological samples, and that could be used as confirmation.

This procedure would be repeated for all four elements, and show that if one chose to select a single element for cause of death, *it could be any of the four based on the marginal impact*. So, once the choice of variables is switched from the combination of constituents as a single element to each constituent of the combination as a single element (in the present case, where the switch was made from one variable (combination of constituents) to four variables (each combination constituent)), cause for death could be assigned to *any* of the four elements. The process is quite arbitrary: the assignment of death to any single entity could be considered a political act, done for political (and financial) reasons, and not for scientific reasons!

Why has this single element (SARS-CoV-2) causation assignment approach been taken? SARS-CoV-2 is one of the few constituents of the

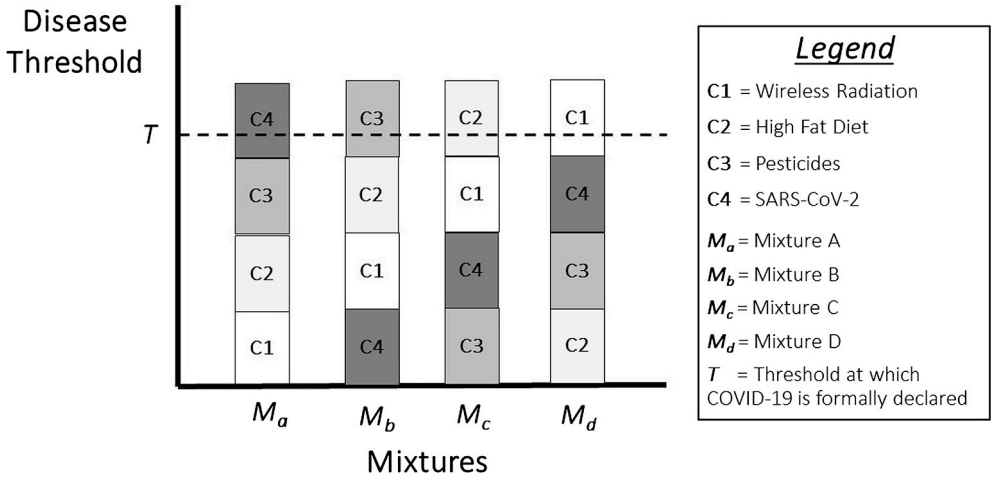

Fig. 1. Arbitrary attribution of death for multi-component mixture.

virus-toxic stressors combination nexus that cannot be related to a technology offshoot, or to a technology that has production and/or consumption stakeholder backing (e.g., pesticides, industrial chemicals, radiation sources, etc.).

Thus, the present quarantine eliminates/reduces exposure to (and the treatment/vaccine development will attenuate viral load of) only one of the many constituents of the virus-toxic stressors combination nexus; it is a constituent that does not have strong production and/or consumption stakeholder backing!

If responsibility for the pandemic can be assigned to the only (or main) constituent of the virus-toxic stressors combination nexus with no backing from the aforementioned powerful stakeholders, then these production and/or consumption stakeholders are protected from responsibility for (and ensuing legal consequences from) the deaths that occurred and were attributed to SARS-CoV-2/COVID-19 and the trillions of dollars of lost revenue in the global economy that resulted from the lockdown. Assigning responsibility for the pandemic to Mother Nature rather than to those who bear the major responsibility for laying the pandemic groundwork ensures that these harmful practices and their associated pandemics (including the annual deaths of the most vulnerable demographic related to the so-called influenza epidemics/pandemics) will continue unabated.

Why are not any of the other constituents of the virus-toxic stressors combination nexus being placed under effective 'quarantine' from the public? Why are not smoking, or air pollution, or excess alcohol, or wireless radiation, or agrochemicals, or industrial chemicals, being placed under quarantine? There is no lack of evidence of linkages between these environmental pollutants and immune-related diseases (Tsatsakis et al., 2020; Kostoff et al., 2020).

7. Demonstration of effective "quasi-vaccine"

It is clear from the SARS results and the present COVID-19 results that exposure to the coronavirus for most people (except the relatively small number in the most vulnerable demographic) results in relatively mild symptoms (or, in many cases, no symptoms). In other words, the vast majority of the public is metaphorically being protected presently by an extremely effective "quasi-vaccine"; namely, following practices that, while they certainly degrade the immune system to some extent because of exposure to toxic stressors, do not degrade the immune system excessively. Promoting healthy lifestyle habits (including healthy diet, regular aerobic exercise, and appropriate responses to adverse life events) and an ambitious regulation of toxic stressors (chemicals, radiations, etc.) are cornerstones to reducing the risk of developing most chronic diseases. These healthy habits represent a "quasi-vaccine" as they are capable of eliminating those factors that contribute to degrading the immune system and adding those factors that contribute to strengthening the immune system. For most of the public, this "quasi-vaccine" has proven to be effective, and further elimination of immune-degrading contributing factors will improve the immune system further and afford even greater protection from infectious diseases.

Thus, a more protective quarantine (for the current pandemic and against future pandemics) would be to impose effective 'quarantines' for the public against the intrinsically toxic constituents of the virus-toxic stressors combination nexus (e.g., pesticides, PFOS, PCBs, nerve agents, wireless radiation, etc.). Whether they would have the same very-short-term benefits as the present quarantine/lockdown is questionable, given the lag times before these preventive measures become effective. From the long-term perspective, the broader quarantine on the constituents of the combination of toxic stressors would be very protective against future viral attacks on the most vulnerable demographic, including protection against the annual influenza infections.

To be fully protected in the present pandemic and against future pandemics, both tactical/reactive responses to survive the immediate threat and strategic/proactive responses to prevent the problem and damage from re-occurring are required. Examples of such tactical and strategic responses have been identified in recent studies (Kostoff, 2020; Kostoff et al., 2020; Calina et al., 2020; Iddir et al., 2020; Nilashi et al., 2020; Lima et al., 2020; Calder et al., 2020).

8. Conclusions

The underlying causes of the present pandemic have been both misrepresented and camouflaged. Causes that are mainly toxicology-based have been ignored relative to virology-based causes. This has resulted in treatments and 'protective' measures that address virology issues to the exclusion of toxicology issues, are of questionable effectiveness, and do little (if anything) to prevent future pandemics. They have produced disastrous effects on the global economy that have worsened social and economic conditions of many people and contributed to a deterioration of their physical and mental health. To correct this situation, and offer intrinsic protection against future pandemics, both tactical/reactive responses to survive the immediate threat and strategic/proactive responses to prevent the problem and damage from re-occurring are required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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