Pollution, Inflammation, and Vaccines

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Different environmental pollutants can have different effects on the immune system, which can then promote complex pathologies, such as autoimmune disorders and cancer. The interaction with the microbiota also further helps to determine the consequences of contamination on wellbeing. The pollution can affect vaccination efficacy, given the widespread effects of vaccination on immunity. At the same time, some vaccinations also can exert protective effects against some forms of pollution.

Keywords: pollution ; vaccination ; inflammation ; immunity ; microbiota

1. The Interaction between Humans and the Environment, a Focus on Health

The importance of the environment on human health is a well-known fact. It is speculated that certain cultures would not have been born if it were not for the favorable environmental conditions. Modern technology allows most developed countries to modify the surrounding environment to their advantage. Those same societies are the ones which create the most pollution, a key factor in modifying the environment. Yet, the dramatic climate changes, for instance, have a massive toll, mostly on those who live in less developed countries.

Pollution is defined as an unfavorable alteration of the environment as a result of human activity. It is possible to classify pollution into three main classes—air, water, and land. Human activities can cause also other forms of pollution, such as noise and light pollution [1].

Alongside the more evident consequences of massive natural catastrophes, climate change and pollution have had a serious, yet less evident, impact on human health [2]. In this review, we will concentrate mostly on the three main forms of pollution, but it is worth noting that other forms of pollution also have an impact on human health, even though the underlying mechanisms are not always completely clear.

For instance, it has been observed that there is a significant relationship between light pollution, which is caused by anthropogenic and artificial electric light in the night environment, and cancer [3]. The cause of such apparently strange association of events, probably roots back to the important consequences of light pollution on metabolism, which in turn is caused by disruption of circadian rhythm, as seen, in particular, in murine models [4]. Interestingly, a conscious sleep disruption is not necessary to determine alterations of the circadian rhythm [5]. Similar results have been observed in humans, whose alteration of circadian rhythm is also linked to metabolic shifts and a tendency to lose muscle mass and gain weight [6][7].

The importance of air, water, and land pollutants on human health is undeniable and has been identified as one of the primal drivers in health inequality even in the developed world [8]. An example is the water crisis in Flint, which has led to serious consequences, particularly in children [9]. Contamination of food and drinking water is a consequence of water and land pollution, and typically affects the most delicate parts of the population. The effects are often mediated by the gut microbiota and intestinal niche immunity, and range from neurological disorders to cancer, and endocrine disruption [10]. The underlying mechanisms and the long-term consequences are not yet completely clear; thus, the effects might be even more serious than expected.

In Table 1, a summary of the different forms of pollution, possible impact on human health, and main references is shown.

Table 1. Types of pollution and possible impact on human health.

Type of Pollution	Description	Health Consequences	References
Air	Presence of gases, biological molecules, and particulate matter in the atmosphere.	Air pollution significantly impacts health. Ozone and particulate matter are two of the most important components and determine a high number of hospitalizations yearly.	[11]
Water	Contamination of water bodies with different kinds of pollutants.	Sewerage, pesticide, and industrial water pollution affect a large part of the population, leading to diarrhea, bowel inflammation and other.	[12]
Soil contamination	Degradation of land and soil, caused by pollutant contamination.	Industrial and pesticide contamination of the soil have been linked to adverse health outcomes, particularly if in agricultural sites.	[13]
Noise	Unpleasant and disturbing sounds that disturb the equilibrium of that environment.	Noise pollution has been linked to hearing loss and alterations. Other pathologies, such as psychiatric and cardiovascular disorders have also been linked to this form of pollution	[14][15]
Plastic	Plastic accumulation in the environment.	Plastic is dangerous for human health on different levels, in particular, in its micro- and nanoparticles, which can be ingested and determine direct effects on the organism.	[16]
Radioactive contamination	Presence of radioactive material.	Radioactive contamination of the environment can have immediate and long-term consequences. In particular, cancer and cardiovascular disorders are common among those chronically exposed to radiation	[17]
Light	Anthropogenic light disrupting nocturnal environment.	Light pollution has been linked to disruption of circadian rhythms with various consequences on hormonal cycles, which can in turn determine stress related conditions, cardiovascular and endocrine disorders.	[5][6][18]
Thermal	Induced change in water temperatures.	Thermal pollution is often a consequence of industrial efforts. It can directly impact the water, altering the species living in it, and promoting water pollution, and also impact the quality of air, raising temperatures, further enhancing the negative effects of air pollution.	[19]

Type of Pollution	Description	Health Consequences	References
Visual	Presence of barriers disrupting the surrounding environment.	Visual pollution is usually associated to the construction of buildings and infrastructures, were there were none before. While it is difficult to state whether it has a direct impact on human health, it is associated to other forms of pollution.	[20]
Littering	Human waste not properly disposed of.	The presence of litter in the environment is, in itself, another form of pollution. Usually, it is caused mostly by the presence of microplastics in the litter, which can then contaminate the soil and water.	[21]

2. Consequences of Pollution on the Immune System

For the first time ever, in 2020 air pollution was recognized as a cause of death: the victim, a young girl suffering from asthma, died after a particularly severe asthma attack after being exposed to air pollutants [22]. The decision highlighted the importance of pollution on human health, not only through environmental changes but also through direct effects.

Pollution impacts human health on many levels, but the public tends to underestimate its consequences, which impact politics and behaviors [23].

Pollutants can stimulate and interact with the immune system through different paths, one of them is stimulating inflammation: Chen et al. have studied the effects of particulate matter on elderly persons, both with and without chronic obstructive pulmonary disease. Interestingly, the patients who were most affected were those who did not suffer from other inflammatory pulmonary diseases [24].

Air pollution appears to be capable of determining widespread inflammatory responses, which can, in turn, determine a wide variety of diseases, through chronic inflammation [25][26][27].

Not only particulate matter has the capacity to trigger inflammation: something similar can be observed with pollutants more typical of water and land, such as microplastics; studies on animals show that ingestion of this material can cause bowel inflammation and microbiota disruption, which translates to more widespread disorders [28]. Even though the thought of finding petrol in everyday drinking water and food is not appealing, this is also another kind of pollutant that has important consequences on human health, particularly in terms of inflammation [29][30][31].

Exposure to particulate matter and microplastics activates different inflammatory pathways. Oxidative stress is probably a key mechanism: generating reactive oxygen species (ROS), many different inflammatory pathways are activated, depending on the damaged tissue. While at low doses, ROS actually exert a positive function, when at high levels, they can damage different cell components, leading to an inflammatory response [32].

In the lung, which is one of the most directly targeted tissues, interleukin (IL)-1, IL-6 [33], and tumor necrosis factor (TNF) are secreted by T-lymphocytes upon damage. The activation of this pathway also determines the production of C-reactive protein (CRP) and serum amyloid A (SAA), while also determining a more localized inflammation, through polymorphonuclear leukocytes [34]. It is worth noting that the relationship between pollutants and oxidative stress is not directly proportional but also depends on its components, particularly metals and soluble substances [35].

IL-1β and TNF-α are key players also in cerebral inflammation following exposure to pollution: when exposed to air pollution, the microglia starts producing higher quantities of inflammatory cytokines, which can chronically lead to disequilibrium in the central nervous system, and to the development of neurodegenerative disorders [36], given that pollution exposure leads not only to a change in cytokine profile but also alters the expression of other key mediators for vascular and cellular health, such as inducible nitric oxide synthase (iNOS) [37]. Microglia plays a very important role in the inflammatory response that takes place when the central nervous system is exposed to pollution. For instance, a study con-ducted in Mexico City demonstrated that exposure to diesel exhaust particles (DEP) in animals drives neuroinflammation, activating the Mac1-NOX2 (NADPH oxidase) pathway [38].

Another activated inflammatory pathway is the Aryl hydrocarbon receptor (AHR) pathway. The activation of AHR leads to a series of consequences, particularly involving Th17 lymphocyte differentiation. Indeed, regulation of Th17 by IL-2 is reduced, and so are Signal Transducer and Activator of Transcription (STAT)-1 and -5. At the same time, immunosuppression is also stimulated through the activation of c-MAF or STAT-3 [39].

Inflammation is also driven by other mechanisms: in the case of the gut, fibroblasts and epithelial cells are the activators of the immune system after exposure to pollution, through direct production of inflammatory cytokines (particularly TGF-β, IL-10, IL-17), but also changing the expression of toll-like receptors (TLRs) and surface proteins [40]. Petrol, which interestingly is a key pollutant for the gut, is also known to activate directly IL-17, TNF, and other cytokines, similarly to pesticides [41].

The inflammatory response to environmental pollutants is also driven by more complex mechanisms, such as micro-RNAs, which can involve different genes and processes [42] and DNA alterations. In particular, the exposure to particulate matter leads to anti-ICAM, IL-1β, and TNF-α activation, following DNA damage [43]

In some cases, the inflammatory effects of different pollutants can act in a synergic fashion: for instance, ozone can react with carbon black, producing a fulvic acid-like substance, which has a high inflammatory potential [44].

The impact of pollution on the immune system goes beyond inflammation, as some substances can directly act on it: Perfluorinated Alkyl Substances (PFASs) directly influence Th1 and Th2 pathways, also leading to higher immunoglobulin (Ig)-E levels [45]. PFASs seem to impact more specifically cytokine production by Th1 and Th2 lymphocytes, stimulating the latter (IL-4 and IL-5), while inhibiting the former (interferon (IFN)-γ, IL-2) [46]. PFASs can determine their effects in particularly delicate populations, such as newborn babies; as seen in a Canadian study, exposure to PFASs and bisphenol A can lead to alterations in the levels of IgE, IL33, and thymic stromal lymphopoietin (TSLP) [47]. Nuclear factor-κB (NFκB)–inhibitor of κB kinase, c-Jun N-terminal kinase and activator protein-1 (JNK-AP1), and inflammasomes are other key immune components in determining the interactions between the body and PFASs [48]. In some cases, the synergic effect takes place between pollutants and pathogens, which can determine direct cellular damage, resulting in altered immune responses. During the current COVID-19 pandemic, this mechanism has been used to explain the higher prevalence of the disease in more polluted areas [49].

Overall, it appears clear that the immune system is the first to react to pollutants, but it is not left unshattered by the interaction. Below we will discuss the possible effects of the interaction between the immune system and pollution, focusing on three main areas, also linked to vaccination response, summarized in Table 2.

Table 2. Effects of pollution on health and vaccination.

Diseases	Effect of Pollution	References
Autoimmune diseases	Triggered by different types of pollutants, creating low-grade chronic inflammation, possibly impairing response to vaccination.	[50]
Cancer	Different pollutants are involved in the development of different forms of cancer, dysregulating immunity and triggering inflammation.	[51][52]
Gut microbiota	Microbiota acts as an immunomodulator and is also involved in the response that our organism gives to vaccination: different types of bacteria inhibited by PFASs, for instance, are also linked to better immune response to vaccination and overall longevity	[53]

3. Vaccination and Immune System

Vaccination is a safe and effective measure against a great number of diseases and has been deemed responsible for cutting down child mortality [54]. Yet, many people are still skeptical about their effectiveness and suggest that they may cause different diseases, including autism [55]. The underlying reason is probably the way vaccinations are administered, given that the general public often sees them as the inoculation of the diseases they should prevent. The fact that they are administered, in particular, to a delicate population, such as children, further explains the suspicion they can raise [56].

In the past, the vaccination process was indeed based on the idea to administer low or weakened doses of the pathogen, to avoid severe infections, as done by Jenner in the case of smallpox [57] and then by Pasteur for rabies [58]. Over time vaccine technology has evolved and is now more refined, safe, and effective [59][60].

A recent example of this is the design of the vaccine against Sars-CoV-2, the pathogen responsible for COVID-19 disease [61]. While different methods have been used to try to produce vaccines, the most interesting is the one based on mRNA technology, in which the host interacts with the inoculated mRNA and produces antibodies without having to be exposed to even the smallest viral particle. While some express concern for those suffering from autoimmune conditions, this type of vaccination is safe and effective [62].

A vaccination is effective if it determines an adequate immune response, obviously, an adequate immune response also depends on the conditions of the vaccinated individual. Age, sex, and immune status are all linked to different responses to vaccinations [53][63]. It has even been suggested that baseline immunity should be studied in order to design personalized vaccination strategies, to maximize the immune responses of each individual [64].

Environmental factors also play a significant role. Firstly, in developing countries, especially in rural areas, malnutrition is the more frequent pathological condition that severely affects functions of T and B cells with consequent impairment of antibody production; it may decrease complement and phagocyte activity [65]. These impaired functions have a key role not only in favoring infectious diseases but also in the impairment of vaccine response. Corrections of low levels of vitamins, iron deficiency, and protein intake could improve the immune-regulatory system [66]. Moreover, it has well been demonstrated that the area of residence with the associated microbial environment may play a role in the development of immune responses. The 'hygiene hypothesis' links a minor exposure to infections during childhood to a minor regulation of Th1, Th2, and Th17 inflammatory responses. However, some authors have observed that children living in urban areas of the tropics had significantly increased levels of IL-10 [67]. Moreover, it has been observed that children living in the countryside have an increased response to vaccinations when compared to children living in cities. The difference is based on differences in the activated immune pathway: when living in rural areas vaccination activates a Th1-skewed response (IL-5 production) while in an urban context it activates a Th2-skewed response (IFN-γ production) [68].

The importance of the Th1 immune response in enhancing vaccination efficacy is proven by the fact that in populations who tend to have defects in this immune response, vaccinations are not as effective.

An example of this is the lower immune response that elderly people exhibit to vaccination [69]: indeed, an imbalance towards Th17 pathway expression, which penalizes Th1, is a key factor lowering the efficacy of vaccines in this group [70].

Other immune pathways are involved in the vaccination process, depending on the pathogen. Cytotoxic lymphocytes CD8+, for instance, need to be activated for pathogens entering cells, and cancer [71], while delayed hypersensitivity, involving CD4+ lymphocytes and monocytes, is fundamental in tuberculosis, leprosy, syphilis, and fungal infections [72].

Another interesting aspect is that, while the immune system impacts the way we react to vaccination, vaccinations also have the potential to shape our immunity. Studies have concentrated on different populations, particularly those with a higher risk of not being immune-competent. Neonates, for instance, are at a particular risk of infections, which may carry serious consequences. On the one hand, there are specific vaccines against specific pathogens, on the other, it is not possible to vaccinate against all potential pathogens. A possible alternative strategy is to administer immune boosting vaccinations, which should stimulate immune response overall [73]. Immune boosting vaccination strategies include homologous and heterologous prime boosting approaches, which have been tested in pre- and clinical trials [74].

Vaccinations boosting immunity have also been a staple in other populations, particularly cancer patients. In this case, vaccinations are designed to activate immunity against cancer-specific antigens or to stimulate the patient's immune system to attack the cancerous cells [75].

While some interactions between the immune system and vaccinations are desirable, some others are not: for instance, in some persons, vaccination has been identified as a trigger for autoimmune disorders, and there still is not a consensus around vaccinations in people who are suffering from these diseases. The underlying mechanisms in this interaction are complicated: adjuvants, for instance, can trigger immune activation, similarly to what happens with some pollutants; antigens can also trigger immune activation which, combined with molecular mimicry, can determine autoimmune disorders; finally, other components of the vaccination, can determine allergic reactions, activating, once again, the immune system [76]. Interestingly, inadequate immune activation of the immune system caused by pollutants has also been observed and will be discussed below.

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