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Review article

Original antigenic sin: A comprehensive review

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ABSTRACT

The concept of "original antigenic sin" was first proposed by Thomas Francis, Jr. in 1960. This phenomenon has the potential to rewrite what we understand about how the immune system responds to infections and its mechanistic implications on how vaccines should be designed. Antigenic sin has been demonstrated to occur in several infectious diseases in both animals and humans, including human influenza infection and dengue fever. The basis of "original antigenic sin" requires immunological memory, and our immune system ability to autocorrect. In the context of viral infections, it is expected that if we are exposed to a native strain of a pathogen, we should be able to mount a secondary immune response on subsequent exposure to the same pathogen. "Original antigenic sin" will not contradict this well-established immunological process, as long as the subsequent infectious antigen is identical to the original one. But "original antigenic sin" implies that when the epitope varies slightly, then the immune system relies on memory of the earlier infection, rather than mount another primary or secondary response to the new epitope which would allow faster and stronger responses. The result is that the immunological response may be inadequate against the new strain, because the immune system does not adapt and instead relies on its memory to mount a response. In the case of vaccines, if we only immunize to a single strain or epitope, and if that strain/epitope changes over time, then the immune system is unable to mount an accurate secondary response. In addition, depending of the first viral exposure the secondary immune response can result in an antibody-dependent enhancement of the disease or at the opposite, it could induce anergy. Both of them triggering loss of pathogen control and inducing aberrant clinical consequences.

Contents

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1. Introduction

The concept of "original antigenic sin" was first proposed by Thomas Francis Jr., in his treatise "On the Doctrine of Original Antigenic Sin" and has been advocated to explain a number of immunological phenomena. In the 1940s the concept of "original antigenic sin" was used to explain the way by which the immune system contributed to the requirement for yearly influenza vaccines. As early as 1958, there was evidence that the clinical pandemics of influenza in the early 20th century depended on interaction between immunological patterns of the human host and viral characteristics [1]. "Original antigenic sin" is not limited to humans [2–4], this was demonstrated in a study in rabbits primed with beef myoglobulin, and thence boosted with myoglobulin from other species including sheep, chicken, pig and sperm whale, that mounted an increased antibody response to the original beef myoglobulin [5].

With many viruses, the clinical presentation of an infection can be quite different depending on the original virus or first serotype to which the individual was exposed. For example, human Bocavirus 1 (HBoV1) infects the respiratory tract, causes lower respiratory infections including pneumonia with high prevalence in children [6]. However, the serotype HBoV2, affects the gastrointestinal tract causing gastroenteritis. At first sight, the topic of evolving serotypes should not be a problem, as the immune system, in theory, should be able to combat each subsequent serotype effectively. However, as we delve deeper, a strange phenomenon emerges. After prior exposure to a virus, the immune system has an ineffective to no response to a subsequent exposure of a different serotype of the virus [6]. This observation can be explained with the concept of "original antigenic sin".

Although simple, the concept has extreme implications. It can be explained in the following way. A body contacts a hypothetical first virus, since the body has no prior exposure to this virus; it must establish a primary response, a slow and intricate process of identifying an antigen of a virus and develop the classic immune response through innate and adaptive components with the aim to activate both cellular and humoral defenses to combat the virus. Subsequent exposure to the virus elicits a secondary amplified response, in which the body responds much quicker against the signal of a familiar antigen. Normally, classical understanding of the mammalian immune system would suggest that exposure to a closely related form of the virus, should trigger a secondary response. If the virus is significantly different, the body should recognize this as a completely new infection and undergoes a primary response (Fig. 1).

But according to "original antigenic sin", reality is somewhere in between, and it is indeed this hole that can trigger immune evasion by the pathogen. In "original antigenic sin", if an individual is exposed to a serotype very similar to the pioneer virus, the immune system can mistakenly identify the secondary virus antigens as antigens from the first virus encountered, and progress to a classical memory response producing virus1-specific antibodies, which may be ineffective towards the second virus. Another way of looking at this is that the immune system is unable to differentiate between the two serotypes (Fig. 1) [7], and makes a misdirection error [8]. Actual clinical events that illustrate the effects of "original antigenic sin" include the influenza epidemics, as it was observed that people born prior to 1956 had a worse outcome than young people exposed to influenza virus for the first time. This effect was modeled in rats in a study by Angelova and Schvartzman in 1982 [9]. "Original antigenic sin" can affect a varied array of microbials, including RNA viruses, bacteria and parasites [10]. In this manuscript we will describe the mechanism of "original antigenic sin" and its relevance in different human pathogens and clinical outcomes.

2. Mechanism

The cellular mechanism of "original antigenic sin" has been discussed in a triad of papers by Deutsch et al. in the 1970s [11–13]. The pathophysiologic mechanism of "original antigenic sin" includes two immunological components, the innate and adaptive immune systems, which influence the way by which the body mounts a secondary response on re-exposure to an antigen. Normally, on first exposure to a pathogenic antigen, the initial response involves the innate immune system, which recognize the antigen as being "new", foreign and/or dangerous and prime the antigen presenting cells (APCs) to further mount an adaptive immune response. APCs process and present the antigens to naïve T lymphocytes through the major histocompatibility complex (MHC) activating this way antigenic-specific lymphocytes. This leads to effector B-cells, effector T-cells, memory B-cells, and memory T-cells being produced en masse in a process called clonal expansion. The activated B-cells, or plasma cells, then proceed to produce specific antibodies to identify, flag, and "catch" the pathogenic antigens, which are then engulfed by phagocytes and destroyed, thus protecting the body from the harmful effects of the infection. The adaptive immune response to the first exposure of the antigen takes time to occur, and has to go through the steps of recognition, amplification and response. This whole process is known as the primary response, which occurs after exposure to a completely new pathogen, and takes approximately two weeks to run its course.

Upon a second exposure to the same pathogen, the response occurs in a similar fashion but at a much faster pace due to the B and T-cells having already seen the antigen of the pathogen and being able to recognize it much quicker. The subsequent steps are much faster and antibodies are produced more rapidly as well. This secondary response allows for rapid clearance of the pathogen, and is the basis for the mechanism of vaccines. The function of vaccines is to provide a less harmful exposure to a pathogen so that if in future the body is re-exposed to the wild type virus, the body can respond much quicker. However, it is during this secondary response that the problem of "original antigenic sin" can worsen the pathogenicity of the infection.

The mechanism of "original antigen sin" occurs when the body is re-exposed to a slightly evolved or different pathogen during a subsequent exposure. In this case, due to the prior exposure of the first antigen, memory lymphocytes do not respond to the variant antigen itself, but instead use their memory, interprets the second antigen as the original antigen and proceeds with a secondary response to the original antigen. At first glance, this may seem like a favorable phenomenon. The immune system is thus able to more quickly respond to the intrusion. However, the problem arises

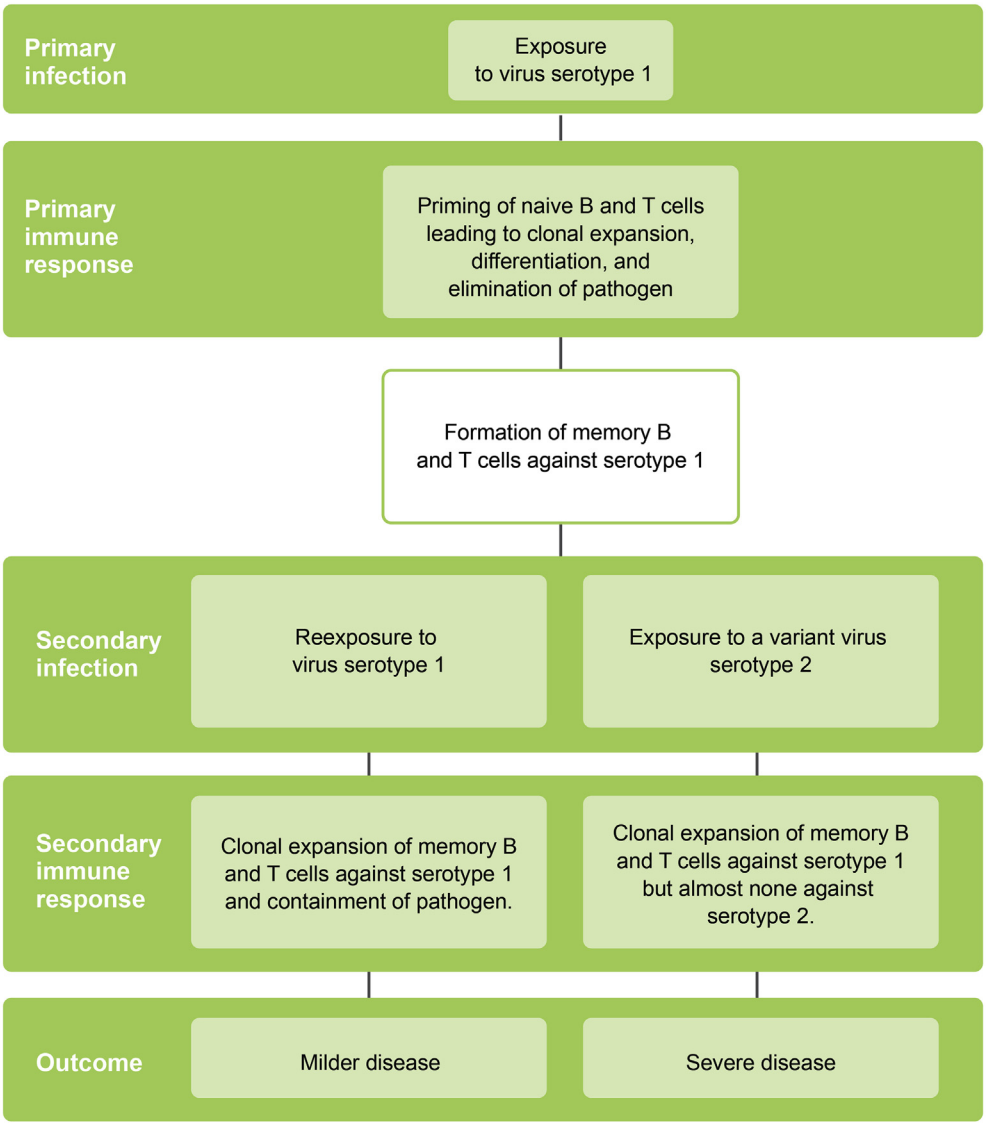

Fig. 1. Mechanistic path of "original antigenic sin" response against a hypothetical virus, detailing the effects of the abnormal clonal expansion of B and T lymphocytes after exposure to a variant virus serotype 2.

when the second antigen is sufficiently different from the original antigen, and the response to the second antigen is not quite precise, leading to a less-effective response and possibly failure to clear the pathogen. In a more extreme example, the immune systems recognition of the pathogen is compromised, with a failure of the immune response to even identify or flag the offending secondary antigen, leading to a complete evasion of the pathogen from the immune system, a situation which clearly could have deadly implications (Fig. 2).

Antibody production plays an important role in controlling virus infection through four major ways: 1) neutralization, antibodies strongly bind to the virus and avoid viral activity; 2) opsonization, complex of antibodies and virus promotes phagocytosis via Fc receptor expressed on phagocytes cells membrane; 3) complement activation, complex of antibodies and virus are recognized by proteins of the complement, which activates complement system leading to the lysis of the pathogen, and 4) antibody-dependent cell-mediated cytotoxicity, natural killer cells recognize antibodies binding to infected cells and degranulate perforin and granzymes, which trigger infected cells lysis.

After secondary infection, there is a more rapid and elevated antibody response compared to the primary response. This increased in immune response is motived by the stimulation of memory lymphocytes B from the primary infection. The first antibodies that appear following a secondary infection are able to neutralize the original virus in a timely manner. However, in a new infection with a slightly similar virus "original antigenic sin" leads to the production of cross-reactive antibodies efficiently able to control the original virus but unable to neutralize the new one. Moreover, binding of such antibodies to the new virus could trigger the internalization of the virus into Fc and complement receptor-bearing cells such as macrophages or dendritic cells (DCs), enhancing the entry of virus. In a classical scenario, neutralized virus will enter into the cell guide to the lysosome and destroyed but if the neutralization is not sufficient then opsonization can lead to increase viral replication, which will augment the severity of the infection. This phenomenon is known as antibody-dependent enhancement (ADE) and has been described in dengue virus (DENV) and human immunodeficiency virus (HIV) infection [14,15]. ADE related to "original antigenic sin" is theoretically possible for

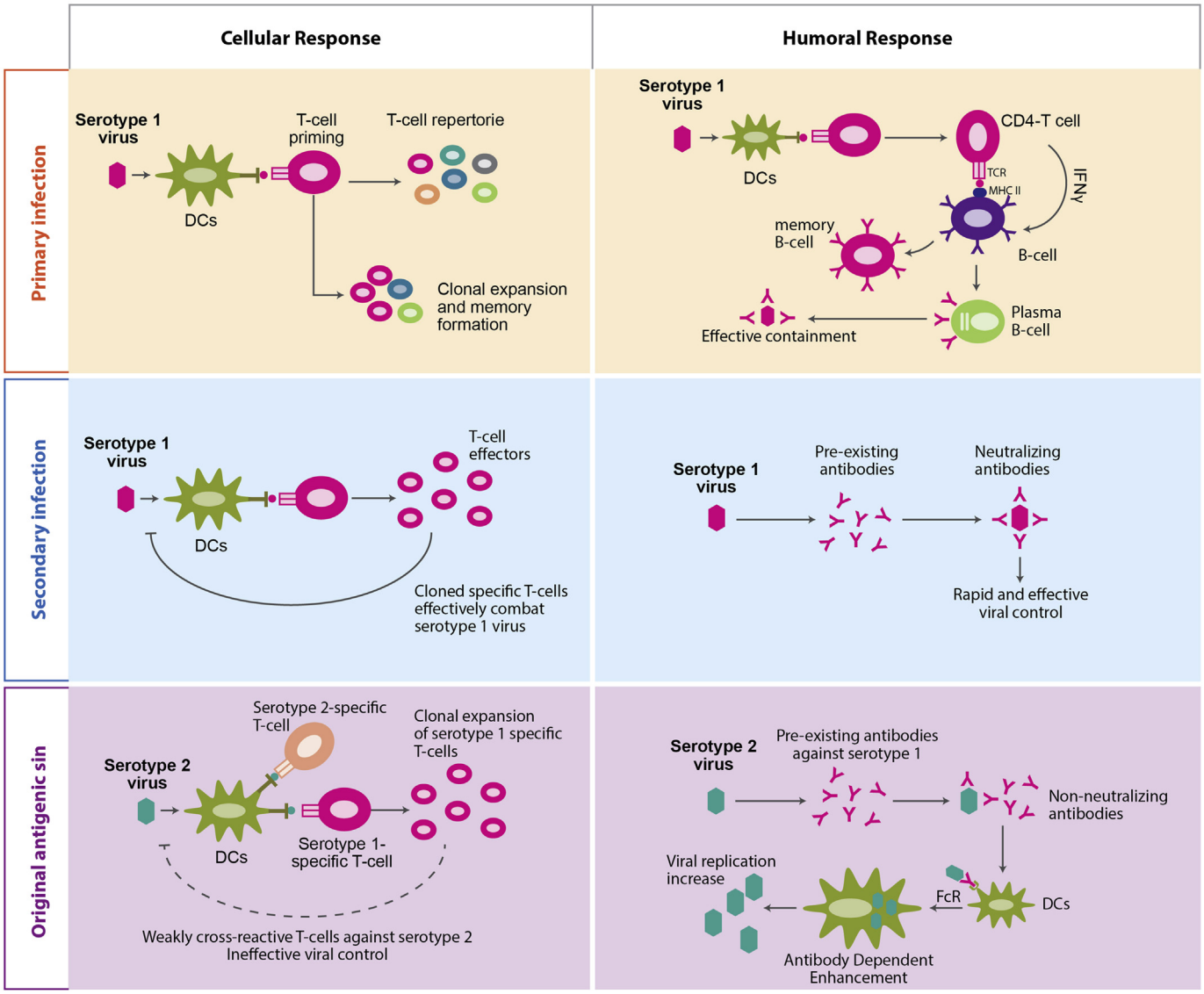

Fig. 2. Conceptual mechanism of "original antigenic sin". Response to exposure to two similar serotypes virus. Serotype 1 antigen is processed and presented by the antigen presenting cells (i.e., dendritic cells -DCs-), leading to the priming of the B and T lymphocytes, and subsequent clonal expansion of serotype 1 specific lymphocytes. This clonal expansion is cross-reactive, and occurs even upon exposure to serotype 2, rendering an ineffective response against the serotype 2.

any pathogen that can productively infect Fc and complement receptor-bearing cells resulting in infection of a higher number of target cells, which may lead to higher viral production (Fig. 2).

Although initially described in the humoral response against influenza virus and its different serotypes, "original antigenic sin" can occur at the cellular immune response against other viruses. During a first infection, virus-specific cytotoxic T lymphocytes (CTL) are prime by APCs via epitope-MHC-II complex recognized by specific T-cell receptor. This interaction generates memory T-cells and effectors CTL able to lyse infected cells through secretion of cytokines and lytic enzymes. If a second infection by a somewhat different virus occurs, pre-existing memory CTL will lead the immune response over the naïve response. This may occur because memory T-cell express more adhesion proteins and cytokines receptors and are prone to rapidly reacts against antigen at low doses. Such peptides variants resulting from the new virus strain may be of lesser avidity for the T-cell receptor triggering a qualitatively different immune response. In some cases this leads to an exacerbated immune response such as a "cytokine storm" and immunopathogenesis as described in DENV [16], and in others cases leading to CTL anergy and loss of viral control [17,18] as described for HIV and lymphochoriomeningitis virus [19].

The most drastic consequence of pathogens inducing "original antigenic sin" is that it is much worse than not recognizing it at all. The immune system completely ignore the antigen as a new microorganism, and incorrectly identifies it as something else triggering detrimental clinical outcomes after a secondary infection.

3. Clinical implications in specific infections

3.1. Human Bocavirus (HBoV)

The lapse in the capability of the immune system to mount a proper response to a pathogen through the mechanism of "original antigenic sin" can obviously lead to dire consequences within clinical practice. An example of this occurred with HBoV, a recently identified human-pathogenic parvovirus. HBoV has several similar

serotypes that affect the human body in vastly different ways. HBoV1 infection is relatively common among children. It causes lower respiratory tract infections including pneumonia. On the other hand, HBoV2 infection primarily largely affects the gastrointestinal tract and is linked to gastroenteritis and diarrhea. HBoV3 and HBoV4 also infect the gastrointestinal tract, but tend to cause asymptomatic infections. In a 2011 study, Kantola et al. [20] found that healthy children who had pre-existing immunity to HBoV2 due to prior infection tended to show extensive symptoms of wheezing upon exposure to HBoV1. This was thought to be due to an ineffective response caused by the minimum or non-existent production of HBoV1-specific antibodies, spite of a previous infection with HBoV2, leading to the clinical manifestations of HBoV1 infection. It is suggested that children with no previous history of HBoV2 infection are able to efficiently respond and clear an infection by HBoV1 [6,20].

In order to further study the effects of "original antigenic sin", Li et al. [6] used rabbits heterologously vaccinated with a combination of 2 HBoV1-4 antigens, while others were vaccinated against only a single HBoV1-4 antigen. They have shown than among the 10 rabbits vaccinated with heterologous antigen combinations, five of them indicated "original antigenic sin". Authors argued that if the human immune system acts in a similar fashion with other pathogens, "original antigen sin" can theoretically be responsible for 1) increased severity of endemic infections, especially in places with limited public healthcare resources, 2) increased spread of disease, and 3) an unexpected detrimental effect of vaccines programs against a specific serotype, leading to potentially higher morbidity and mortality [6].

Paradoxically, if "original antigenic sin" scenario would occur with each secondary infection, it would be more dangerous to have been heterologously inoculated than not to be inoculated at all which would argue against vaccination principle. However, it is important to remember that "original antigenic sin" has only be described in few infections of highly homologous microbes. In addition, "original antigenic sin" is not always associated with a bad outcome; in some cases, it can be associated with a beneficial response during re-exposure to the same microorganism but a different strain. For instance, in a recent study, sera antibodies specific for PR8-influenza strain were passively transferred to mice without prior exposure to any influenza strain, then mice were challenged with a different influenza strain (S12a). Authors demonstrated that PR8-specific antibodies were able to protect mice from S12a strain as efficiently as S12-specific antibodies [21].

3.2. Dengue virus (DENV)

DENV, a mosquito-borne flavivirus, is a single stranded RNA virus of the family *Flaviviridae*, genus Flavivirus. DENV has four main serotypes (1–4) and causes a wide range of diseases in humans, from a self-limited dengue fever to a life-threatening syndrome called dengue hemorrhagic fever or dengue shock syndrome [16]. "Original antigenic sin" was evidenced in a 1983 study in which sequential blood samples of eight Thai children with dengue shock syndrome were examined [22]. Authors found that the children appeared to be able to mount a secondary response to exposure to DENV [23]. Instead of developing limited infection that would be expected by prior exposure, these children developed a prior secondary response to DENV-1, -3, or -4, but not against DENV-2 infection. Original antigenic sin would explain this by virtue of cross-reactive DENV-1, -3, and -4 antibodies occupying the majority of the immune response as a result of immunological memory, thus preventing the development of a primary or secondary response to DENV-2. The result was therefore not limited infection, but instead severe disease leading to dengue shock syndrome and hospitalization [23].

As described above, dengue hemorrhagic fever has been largely explained through the "original antigenic sin" and its serotypes cross-reactivity. Nevertheless, this a very simplistic model and other immune hallmarks have to be considered to explain the disease outcome such as the relationship between the HLA haplotype and the lymphocytes T specificity. Thus the complexity of parameters influencing the severity of the immune response depends not only on the "original antigenic sin" as it has been believed before, but of other possible mechanisms including host genetics and virus variants [23]. For instance, HLA-B7 restricted tetramer-positive T-cells correlated with disease severity only in individuals HLA-A11 negative [24]. In addition, cross-reactive response against DENV is not always detrimental for fighting against a secondary infection. It would depend of the variant epitopes encountered in the secondary heterologous DENV infection, in some cases T-cell responses can contribute to either protection or inmunopathogenesis [23,25]. Also, ability of epitope-specific T-cells to secrete cytokines influence the disease outcome. For example, Th1-biased memory T-cell ruled by IFN-γ is associated with less severe secondary DENV infection [26–28]. Instead, a TNF-α skewed T-cell response was associated with a more severe infection [27]. As pointed out by Rothman et al. [16] it is true than vaccines should seek to avoid "original antigenic sin" but deeper studies are necessary to predict the function phenotypes of T-cells elicit by multi-serotypes vaccines.

3.3. Zika virus (ZIKV)

Infection by ZIKV, an arbovirus of the *Flaviviridae* family, is transmitted by the female *Aedes* mosquito genus. The response to infection normally varies between completely asymptomatic individuals to those with mild and self-limiting disease [29]. In such individuals, the typical symptoms include rash, fever, arthralgia, and conjunctivitis. Nevertheless, in some severe cases, ZIKV may cause congenital [30] and neurological syndromes [31].

ZIKV shares a high degree of genetic and amino acid sequence similarity with other members of *Flaviviridae* family. Specifically, ZIKV envelope protein bears more than 50% homology with DENV, resulting in immunological cross-reactivity. As described above, primary infection with DENV typically results in a production of neutralizing antibodies toward this virus. However, a secondary infection with other DENV serotypes can lead to "original antigenic sin" due to high similarity between both serotypes [32]. According to the original antigenic sin model, it has been hypothesized that this phenomenon can be replicated during ZIKV infection due to its high similarity with DENV. It is probable that in previously DENV-infected individuals ZIKV infection will trigger the production of non-neutralizing antibodies or T-cell responses specifically directed to DENV and unable to control the current ZIKV infection. Moreover, these cross-reactive non-neutralizing antibodies against ZIKV are responsible for ADE phenomenon; their binding to ZIKV mediates endocytosis via Fc receptor into DCs, monocytes or macrophages and leads to intracellular viral replication and higher viral load [33,34]. In this context, ZIKV infection has been associated with autoimmune disease development such as Guillain-Barré syndrome (GBS), however relationship between ADE phenomenon and autoimmunity remains to be further investigated. Indeed, in a recent study we observed an association between previous infection with *Mycoplasma Pneumoniae*, and GBS in patients with ZIKV disease [31]. Whether this observation is related to ADE phenomenon remains to be evaluated.

These studies are revealing because they illustrate the problem when microbials having high homology develop altered antigenic determinants. Classical theories of how vaccines work and how

they are developed must now be re-visited. According to the concept of "original antigenic sin", it can actually be detrimental to vaccinate people against a microbial if there exists or in future may evolve alternate serotypes or similar viruses with closely related but not identical microbial antigens. Thus, it now becomes important in the case of multiple serotypes, that we vaccinate to all the serotypes known, or at least those known to be pathogenic and causative of severe disease. This has critical implications in the development of the influenza vaccine, because influenza is a virus known to have multiple subtypes, and mutate quickly. Each year brings new strains. Immunological responses to the 2009 H1N1 epidemic suggest a role of "original antigenic sin" [35].

3.4. Influenza virus

"Original antigenic sin" plays a role in influenza virus infections [36] and impacts the development of vaccines against it. During the 2009 Swine Flu (H1N1) pandemic, researchers found decreased antibody production in patients who had been vaccinated against the seasonal A/Brisbane/59/2007 influenza (H1N1) in the previous three months due to the cross-reactivity of the previously developed monotypic antibodies [16]. Nachbagauer et al. [37] found that immune responses that are generated by natural infection are superior in quality, duration and quantity than those elicited by immunization with influenza vaccines. More importantly, the responses to vaccines were dependent upon exposure to influenza virus strains during childhood. The authors found that young subjects who were exposed to H1N1 and H3N2 as children when these two viruses co-circulated demonstrated high immune responses to these subtypes, whereas there was limited cross-reactivity. But older, middle aged subjects who were exposed only to H3N2 as children had high titers only to H3 and low titers to H1. In addition, those subjects initially exposed to H1N1 or H2N2 had very high levels of antibodies to H1 and H2, as well as H5. These observations supported the concept that it is the first hemagglutinin subtype encountered by a subject that leaves a defining immunological memory, and this significantly impacts the antibody cross-reactome which the individual eventually develops, which is an illustration of "original antigenic sin" [37].

The actual chemical differences that result in a failure to adapt to new epitopes are not known, but one study of H1N1 proposed that it was glycosylation that shielded the viruses from detection, leading to the immune systems inability to recognize the mutated species, leaving it with only immunological memory to depend on. This theory proposes that the mismatch would be more severe in progressively younger individuals, producing a susceptibility gradation based on age distribution [38]. A study performed by Nachbagauer et al. [37] proposed the role of glycoproteins in "original antigenic sin". On the other hand, a separate study found no evidence of "original antigenic sin" in humans and ferrets who were previously infected with H1N1, then subsequently infected with the 2009 pandemic H1N1 influenza virus [39]. Another study on CTLs recall responses demonstrated that "original antigenic sin" is not universally applicable to all heterologous infections [40].

3.5. Human immunodeficiency virus (HIV)

The trapping of an immune system into a certain response through its own memory has implications for vaccine development in general. Attempts to produce a vaccine for HIV, a sexually transmitted disease that affects more than 1.2 million people in the United States alone, have been ongoing for the past 40–50 years. However, since the virus itself frequently mutates (the mutation rate of DNA viruses is 0.1 per genome, and RNA viruses mutate 10 times faster), scientists have not yet found a way to form a secondary response that will adequately attack the virus [10,19]. In addition, the formation of a vaccine that would trap an individual's response to the inoculation generates a secondary response, which is ineffective in combating the viruses [10,19].

3.6. Enterovirus (EV)

EV is part of the *Picornaviridae* family which includes members as poliovirus, coxsackievirus, and echovirus. They are transmitted by either respiratory or fecal-oral route and are commonly encountered in infants and children. These viruses are responsible for numerous clinical manifestations, including encephalitis, aseptic meningitis, herpangina, hand foot and mouth disease and pleurodynia. A study by Tsuchiya et al. [41] in Japanese children with EV meningitis showed heterotypic and homotypic responses. Indeed neutralizing antibodies produced after EV infection were usually type-specific. However, if a child had immunological memory of another EV infection, the child produced together neutralizing specific-antibodies to the first and the second infection [41]. In a recent murine study by Elmastour et al. [42], animals inoculated with Coxsackievirus B4 and subsequently challenged with encephalomyocarditis virus (another member of the family *Picornaviridae*) presented enhanced infection as compared with the non-previously inoculated control. This was explained by the "original antigenic sin" followed by ADE phenomenon [42,43].

3.7. Chlamydia trachomatis

Besides evidence of "original antigenic sin" in HBoV, DENV and Influenza, this phenomenon has been observed with other microbials as well. The antibody response to *Chlamydia trachomatis* serves as an example of differential priming effects to various serovars. The response to the major outer membrane protein varied in an experiment that involved priming with serovar C and then boosting with either the homologous serovar or heterologous serovars A, B, H or K. The antigenic sin response is demonstrated by the fact that boosting with heterologous serovars led to an antibody response to serovar C. The authors traced this response to the variable domain 1 peptide of the major outer membrane protein of serovar C, consistent with a typical "original antigenic sin" response [44].

3.8. Leptospirosis

A case of leptospirosis was described in which a patient had an initial primary infection, then re-infection twice within 3 months. According to the organism isolated, the patient was first infected by *Leptospirosis Bulgarica*, then *Leptospirosis Celledoni*, and finally with *Leptospirosis Zanoni*. However, the antibody response after the third infection was primary to indicate an increase in antibody titer response to *Celledoni* from 100 to 200 and a decrease in response to *Bulgarica* from 1600 to 200. This is consistent with "original antigenic sin", because the primary memory response to *Bulgarica* may have diluted the response to *Celledoni*. The patient was lost to follow up during the third infection, so subsequent antibodies titers to the three species could not be obtained [45].

3.9. Plasmodium

In addition, parasites such as *Plasmodium* have also been described to trigger sub-optimal immune response due to "original antigenic sin". Malaria is a mosquito borne disease caused by parasite from the *Plasmodium* type; five species of *Plasmodium* are responsible to cause Malaria: *P. falciparum*, *P.* vivax, *P. ovale*, *P. malariae* and *P. knowlesi*. Parasites are delivered to bloodstream

via mosquito saliva and migrate to the liver where it infects hepatocytes and reproduces asexually. Multiplication of these parasites on the cells triggers hepatocytes burst out and delivering to the blood able to infect erythrocytes. Disease results from the host responses to this infection and the increased destruction of both infected and uninfected erythrocytes. In 1992, Currier et al. [46] demonstrated that CD4 T-cells clones from individuals who were not previously exposed to malaria were able to proliferate and respond against *Plasmodium* stimulation. It has been stipulated that this preexistent immune response to others microorganism might skewed anti- *Plasmodium* specific T-cell repertoire to a non-specific and non-protective response against this parasite [46].

Table 1 summarizes all of these microorganisms mentioned above, which trigger "original antigenic sin" and its clinical implications [6,10,14,16,19,20,22,25,32,33,35–39,41–59].

4. Mitigating the effects of "original antigenic sin"

From the standpoint of vaccine strategies, the development of newer vaccines against the same organisms with an increased number of serotypes is one method of counteracting "original antigenic sin" [60]. In the development of vaccines against viruses with common antigenic determinants, all virus that could reasonably be encountered must be inoculated concurrently and prior to any infection in order to stem off the effects of "original antigenic sin". This is what is being attempted with the newly developed universal DENV vaccine. However, this would seem an almost impossible task, since we cannot vaccinate against a serotype or strain which has not yet emerged.

Because of this, other strategies to counter the effects of "original antigen sin" have been developed. One method is the use of adjuvants [61]. A study by Kim et al. [62] found that the use of dendritic cell-activating adjuvants such as *Bordetella pertussis* toxin, CpG oligodeoxynucleotides or squalene based oil in water nanoemulsions were able to prevent "original antigenic sin" when given during the first influenza immunization in mice, whether or not this technique was employed in subsequent vaccinations. They also found an alternative way of combating "original antigenic sin" using repeated immunizations of the second viral strain. There are two known mechanisms to abrogate "original antigen sin" based on the DCs activation during the viral challenge. First, DCs can be activating with the adjuvants during the initial stimulation with the original virus; thus will trigger production of multiple cross-reactive B and T-cells against the first virus from which some will efficiently cross-react with the second virus. In the other hand, adjuvant-stimulation of DCs during the second infection with the new virus will induce a large production of B and T-cells specific from the second virus but also from the original virus triggering neutralizing antibodies and control of the infection [62].

Another method of potential mitigation of "original antigen sin" is to use recombinant technology. We already have recombinant vaccines, such as the Hepatitis B vaccine. In a trial conducted in 2015, Villar et al. [63] recombined antigens from multiple DENV serotypes and attached them to a yellow fever virus, another flavivirus that is similar enough to host the antigens, to form a vaccine that would not trigger cross-reactivity. This vaccine was then given to a sample subgroup of around 2000 Latin American children, with 79.4% of them having a seropositive status for one of more DENV serotypes. For the group that had not been exposed prior to a DENV serotype, there was a vaccine efficacy against hospitalization of 60.8%. For the group that had prior exposure to one or more serotypes, there was a surprising increase in efficacy of 80.3% [63]. Anderson et al. [64] compared immunization with a single peptide epitope with a cocktail of multiple peptide that are closely related to the epitope, and found that the latter results in a more highly reactive and durable T-cell response [64].

Recombination of vaccines can circumvent the problems surrounding issues with vaccinations with prior exposure to a serotype or new serotypes appearing post vaccinations, but it cannot yet be applied to all viruses as a host virus such as yellow fever is not readily available. The struggle to find a suitable host virus is something that must be done for each individual virus and must be a forefront of research to come (Table 2).

5. Discussion and perspectives

The concept of "original antigenic sin" can be employed to explain the failure of the immune system to generate an immune response against microbials that are closely related to a strain to which the host had been either infected with or vaccinated against. While this phenomenon has been recognized since the 1960s, recognition or appreciation of the clinical implications have been rather muted [65]. The concept of vaccination is based on generated efficient production of memory B and T-cells responses against the pathogen. Nevertheless, those pathogens are frequently changing or are present as different strains, which stances a problem for

Table 1
Pathogens with high degree of genetic variability within its own species inducing "original antigenic sin" described in the literature. Abbreviations: HBoV: Human bocavirus, DENV: Dengue virus, ZIKV: Zika virus, HIV: Human immunodeficiency virus, EV: Enterovirus.

Pathogen	Description	Original antigenic sin implication	References
HboV	Single-stranded DNA virus of the family *Parvoviridae*.	Respiratory complication upon infection by HBoV1 in previously HBoV2 infected children	[6,20,58]
DENV	Single-stranded RNA virus from the *Flaviviridae* family.	Hyper-reactivity of T-cell and B-cell and "cytokines storm" after a re-infection with DENV by a different serotype	[14,16,22,25,56,57]
ZIKV	Single-stranded RNA virus from the *Flaviviridae* family.	Antigenic sin trigger by DENV induce ADE phenomenon increasing the pathology	[32,33]
Influenza	Single-stranded RNA virus from the family of the *Orthomyxoviridae*.	Difficulty to induce an efficient vaccine due to sequential mutations of the virus inducing sub-optimal memory response due to original antigenic sin	[35–39,47–54,59]
HIV	Double-stranded RNA virus of the family *Retroviridae*.	High rate of HIV mutations results in viral evasion of the immune response due to original antigenic sin resulting in high viral load	[10,19]
EV	Single-stranded RNA virus from the family of the *Picornaviridae*..	ADE phenomenon trigger by subsequently infection with members of the family *Picornaviridae*	[41–43]
Chlamydia trachomatis	Gram-negative bacterium from the *Chlamydiaceae* family.	Cross-reactive antibody response to the *Chlamydia trachomatis* provide protection between different serotypes via Original antigenic sin	[44]
Leptospirosis	Bacterium from the *Leptospiraceae* family.	Case report about Leptospirosis Bulgarica infection followed by Leptospirosis Celledoni demonstrating a defective control during the second infection	[45]
Plasmodium	Parasite from the *Plasmodiidae* family.	Broad cross-reactive response against environmental pathogen induce poor anti-malaria response	[46,55]

Table 2
Possible methods to circumvent the "original antigenic sin" phenomenon induced by vaccines.

Methods to avoid Original antigenic Sin	Rational	Problems	References
Inclusion of different serotypes in the same vaccine	First exposure to virus will target all serotypes at once	Impossibility to predict emergence of new serotypes	[60]
Vaccine delivery Dendritic cell-activating adjuvants at the first immunization	Increase the possibility to generate effective cross-reactive B-cells an T-cells to multiple serotypes	Decrease the possibility of "Original antigenic Sin" but do not exclude it completely	[61]
Vaccine delivery Dendritic cell-activating adjuvants at the second boosting with a new serotype	Generation of the novo-response against the second serotypes	Only effective against already known serotypes of the same microbe.	[62]
Recombinant Vaccines	In a single viral recombinant vector, different serotypes can be added	Optimization of the safety of viral vectors need to be addressed	[63,64]

Table 3
Animal models used for "original antigenic sin" studies.

Animal model	Advantages	Disadvantages	References
Guinea Pig	Suitable model for Dengue virus infection and serotypes cross-reactivity	Broad immune cross-reactivity with different DENV serotypes. Do not recapitulate second exposure in humans	[4,37]
Rabbit	Established laboratory model for infectious disease	Do not fully recapitulate immune cross-reactivity in humans	[6]
Mouse	Established laboratory model for infectious disease	Do not fully recapitulate immune cross-reactivity in humans	[17,19,21,37,42,44]
Ferret	Immune cross-reactive response similar to the human one	Lack of tools for it study	[37,39,49,67]
Non-Human Primate	Closely recapitulate human immune response	Infection diseases outcome and symptoms differs from the human	[69,70]
Humanized Mouse	Recapitulates human immune response	Optimization of the system is required.	[68]

vaccination design. Vaccination are generated against immunodominant epitopes and do not take into account the different antigenic variation of the pathogens. In general, this issue is unnoticed because immune response can generate efficiently cross-reactive response recognizing the different variant of the microorganisms. However, in some cases "original antigenic sin" is an important problem in terms of vaccine development due to the generation of sub-optimal or not entirely cross-reactive immune response. This has been largely described in the seasonal influenza virus vaccination strategy, which can induce non-protective immune response against appearance of variant strains [10]. Yet, this concept can be the reason why classical vaccinations strategies may not afford adequate protection, and may signify a need for novel methods for preventative vaccines. Moreover, the immune "blind spots" that can be caused by "original antigenic sin" can be responsible for patterns of exceptionally high severity of influenza epidemics seen throughout history [66].

Further studies of "original antigenic sin" implications are of vital importance as drug developers make improved versions of already available vaccines in order to protect against more strains of the same pathogen. For instance, the new Human Papilloma Virus vaccine (Gardasil 9) is designed to protect against five added viral strains, and there are not studies about "original antigenic sin" that could be generated by the previous vaccine. It is not known if this vaccine could be used as a vaccine booster for young people already vaccinated [60].

Another harmful immune response elicits by "original antigenic sin" is the ADE phenomenon allowing the virus to gain entry into the host cells and increase viral replication. This phenomenon has been described in DENV successive infections resulting in hemorrhagic fever disease. In addition, it has been proved that ZIKV pathogenesis can be exacerbated by ADE phenomenon induced by previous DENV infections. More studies are necessary to understand and dissect ADE phenomenon between different virus sharing homologies. Especially in the context of new vaccines trials against endemic virus such as DENV, ZIKV, Chykungunya and others, which can trigger cross-reactive immune response that are not predictable yet.

In this context, animal models should be improved, as mouse model do not recapitulate "original antigenic sin" in humans. Ferrets seem to be a better model for "original antigenic sin" [67] since in some studies their recapitulate better than mouse the secondary response in human as shown by O'Donnell et al. [39]. Unfortunately, we do not have the necessary tools to study this system. Another promising model in this area are the humanized-mouse in which epitopes recognized by different HLA can be replicated, although such a model need improvement in order to recapitulate human infection accurately [68]. Optimization of these models will provide better understanding on how the first immunization will influence futures immune responses (Table 3). This new knowledge on "original antigenic sin" will be vital in the design and implementation of vaccinations with respect of exposure history.

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