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REVIEW

A review of 65 years of human adenovirus seroprevalence

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ABSTRACT

Introduction: Human adenovirus (HAdV)-derived vectors have been used in numerous pre-clinical and clinical trials during the last 40 years. Current research in HAdV-based vaccines focuses on improving transgene immunogenicity and safety. Because pre-existing humoral immunity against HAdV types correlate with reduced vaccine efficacy and safety, many groups are exploring the development of HAdV types vectors with lower seroprevalence. However, global seroepidemiological data are incomplete.

Areas covered: The goal of this review is to centralize 65 years of research on (primarily) HAdV epidemiology. After briefly addressing adenovirus biology, we chronical HAdV seroprevalence studies and highlight major milestones. Finally, we analyze data from about 50 studies with respect to HAdVs types that are currently used in the clinic, or are in the developmental pipeline.

Expert opinion: Vaccination is among the most efficient tools to prevent infectious disease. HAdV-based vaccines have undeniable potential, but optimization is needed and antivector immunity remains a challenge if the same vectors are to be administrated to different populations. Here, we identify gaps in our knowledge and the need for updated worldwide epidemiological data.

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Adenovirus; vaccination; gene therapy; immunology; seroepidemiology

1. Introduction

An increasing interest in human adenoviruses (HAdVs) arises from two major factors: persistent HAdV infections are being increasingly linked to morbidity in immunocompromised adults and children undergoing hematopoietic stem cell transplantation [1]; and HAdV vectors are efficient gene transfer tools and are used for clinical gene transfer (http://www.abedia.com/wiley/vectors.php).

HAdVs were used in clinical trials long before their development as gene transfer vectors in the late 1980s [2,3]. Identified as an oncolytic agent, the 'adenoidal-pharyngeal-conjunctival virus' (now known as adenovirus) was trialed for the treatment of cervical cancer during the late 1950s [2,3]. In addition to their continued use as anti-cancer therapeutics, HAdV-based vectors are used as vaccines. Beyond development of vaccines against tumor antigens, HAdV-based vaccines are currently being tested for various infectious agents such as tuberculosis, HIV, and Ebola virus. The need for vaccination is particularly strong in some developing countries where infectious diseases account for 50% of all deaths. Of note though, geographical distributions of endemic or emerging pathogens are not limited by geopolitical borders and are increasingly associated with climate change, temporal variation, immigration, and animal habitat. Due to improvements along the way, replication-defective HAdV (and nonhuman AdV) vectors have become attractive because they are biochemically stable, readily produced in high titers (>10^{13} physical particle/ml), can induce $CD8^+$ T-cell and B-cell responses, infect multiple nondividing and dividing cell types, and they can carry relatively large expression cassettes (up to 38,000 bp). Moreover, antigen expression can be relatively stable over time and the vector genome poorly integrates into the host genome [4,5].

However, the clinical use of HAdV vectors is not risk free: it could lead to possible recombination with wild type virus, mobilization (i.e. a vector infected cell that becomes infected with a replication competent HAdV, which leads to the amplification and dispersion of the replication-defective vector), hepatic lesions, thrombocytopenia, neutropenia, systemic inflammation, and fever [6]. In addition, pre-existing B and T cell immunity to some HAdV types also creates challenges for their widespread utility [7]. Currently, HAdV species C type 5 is the best characterized vector system, but also has the disadvantage of being one of the most common HAdVs worldwide and therefore pre-existing immunity is nearly ubiquitous. A possible solution to this problem is to use vectors derived

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Supplemental data for the article can be accessed here.

Article highlights

- A human adenovirus (HAdV) were isolated in 1953 by Rowe and colleagues from adenoid tissue.
- HAdVs are nonenveloped particles containing a double-stranded linear DNA genome and belong to the family Adenoviridae and the genus Mastadenovirus, grouped into species A–G and classified in 'types' based on serology and sequence.
- HAdVs cause mild, self-limiting infections in immunocompetent people with an array of clinical manifestations, targeting the lower respiratory, digestive and ocular tracts (depending of the type), predominantly children, and people in close contact situation.
- -HAdV-derived vectors have been explored during the last 40 years and, despite challenges along the way, have become powerful tools for *in vivo* gene transfer.
- HAdV have been used in numerous vaccine trials, including a multitude of tumor-associated antigens and infectious agents.
- The use HAdV vectors is not risk free because pre-existing immunity creates challenges for their widespread utility as vaccines.
- HAdV-C5 is the best characterized vector system, which is also the most common type that infects humans worldwide.
- Clinical use of HAdV-C5 vectors exposed some limitations, drawbacks, and side effect are associated with pre-existing humoral and cellular immunity.
- In 1999, a death in a gene therapy trial remind us the critical need for fundamental research concerning HAdV use.
- In 2008, the HVTN502 vaccine STEP trails was prematurely interrupted due to lack of efficacy and increased risk of HIV acquisition in HAdV-C5 seropositive patients.
- To circumvent pre-existing immunity, vectors derived from 'rare' human or from animal AdVs were progressively developed. However, selective seroprevalence data have been incomplete and misleading.
- By 2018, hundreds of vaccines (and cancer) trials have used, or are using, HAdV-based vectors.
- Many studies and clinical trials are based on results that were generated more than 40 years ago.
- Seroepidemiological data were mostly performed for North America, Western Europe, China and Japan. HAdV seroepidemiology data from South America, Australasia and for most countries from Africa are limited and incomplete
- HAdV-D26 seroprevalence appears relatively high in Africa and Asia and low in North America and Europe and HAdV-B35 seroprevalence is reasonably low worldwide, according to the few studies performed.
- NAbs against some NHP AdVs can be detected in humans. Cross-reactivity is likely the reason.
- Technical procedures performed for seroepidemiologocal investigations contain noteworthy variation between studies, which make sometimes comparisons difficult.
- We encourage worldwide seroepidemiological studies, development of fundamental research on basic vector biology and interactions between HAdV and preexisting host immunity, systematic HIV surveillance in the trial endpoints, standardization of technical procedure for seroepidemiology investigations and improvement of a North-South collaborations.
- Determining HAdV seroprevalence will be challenging mostly due to increasing international travel and immigrations, and because of difficult social, medical, political, and military situations in specific areas.

from adenovirus isolated from animals, or HAdV types that are rarely found in humans.

In this review, we gather and discuss 65 years of HAdV seroprevalence data. We highlight gaps in our knowledge and the need for updated worldwide epidemiological data. In as much, we include unpublished data from HAdV seroprevalence in the Republic of Chad and Burkina Faso. We list the strengths and drawbacks of the techniques that were used for neutralizing Abs (NAbs) titration. We also discuss the impact of the geographical distribution of HAdVs seroprevalence with respect to the development of HAdV-derived vaccines. Finally, we address the possibility that HAdV-derived vaccines could be, in some areas, a long-term risk.

2. Background

2.1. Structure and physiopathology

HAdVs are nonenveloped particles containing a double-stranded linear DNA genome. Structurally, HAdVs are composed of two major elements, the external capsid and the internal core, in which viral genome is enclosed [8]. To date, all AdVs have the same overall capsid architecture, an icosahedral nucleocapsid that consists primarily of three polypeptides, hexon, penton base, and fiber [9] surrounding the viral genome of approximately 34,000–36,000 base pairs. The genome is divided into early (E) and late (L) genes, expressed, respectively, before and after replication of the viral genome. A HAdV was first described in 1953 by Rowe and colleagues while trying to develop adenoid tissue derived cell cultures [10].

HAdVs are ubiquitous pathogens that generally cause mild, self-limiting infections with an array of clinical manifestations [11]. Depending to the type, HAdVs display various tropisms that correlate with clinical manifestations. HAdVs typically infect the respiratory, digestive and ocular tracts. Less frequently, HAdVs can be associated with hepatitis, cystitis, colitis, or meningoencephalitis. Approximately 5% of childhood respiratory tract infections are due to HAdVs. Transmission generally occurs when children are in childcare centers, schools, summer camps, and before 5 years old [12]. Most children have serological evidence of HAdV infection by 10 years of age and, in turn, have robust adaptive immunity. Recent studies identified HAdVs among 6 to 20% of hospitalized children presenting with lower respiratory tract infections [13,14], and from 10 to 23% of children admitted for acute gastroenteritis [15–17].

Severe or lethal HAdV infection occurs typically in persons with immunodeficiency such as transplant recipients or those living with HIV. Children aged from 6 months to 2 years who are in childcare and elderly individuals are more susceptible to severe complications related to HAdV infections. Of note, outbreaks of HAdVs have been reported globally in close communities, especially in young military recruits [18]. Peaks occur in winter and spring, but remain common throughout the year. Transmission involves the airborne route by aerosolized droplets reaching the upper airways and conjunctiva, by fecal-oral spread, close personal contact, or by touching environmental contaminated surfaces. Occasionally, contamination occurs during and solid organ transplantation [19]. The average incubation period is about 5–12 days, but the contagious period can last for weeks to months. Vaccines against HAdVs are currently not available to the general population, but after several years of hiatus, are reuse within the military in the United States [20–22].

The predominant HAdV types can change over time within a region [23] and transmission of new strains across continents appears to be frequent [24–26]. Considering the dynamics of seroprevalence, the global dispersion of HAdVs is particularly important.

2.2. Classification

HAdVs belong to the family Adenoviridae and the genus *Mastadenovirus*. The nomenclature of HAdV 'species' was introduced in 1960 by L. Rosen [27]. Now HAdVs are grouped into species A–G (Figure 1 and Box 1). Individual HAdV "type" nomenclature is currently in flux and has not reached a global consensus within the scientific community. HAdV types were historically defined by antigenic determinants detected by viral neutralization assays, hemagglutination properties, morphological, and pathogenicity criteria [28]. It is accepted that there are about 70 types [29]. Since HAdV-52 [30] new types have been primarily identified based on genomic sequencing analysis [31]. Consequently, 40 genotypes have been proposed (http://hadvwg.gmu.edu/). Sequence of three regions (penton, hexon, and fiber) or of the entire genome have been recommended to provide alternative identification [32–34] (Figures 1 and 2(b)). Currently, no globally accepted nomenclature has been recommended by the International Committee on Taxonomy of Viruses. To be as informative as possible in this review, we are using the format 'human adenovirus dash species, type' (e.g. HAdV-C5) whenever appropriate.

3. The unveiling of HAdVs

In 1953, Rowe and colleagues isolated a transmissible agent from adenoid tissues undergoing a cytopathic effect. The following years focused principally on understanding its natural history (Figure 2(a) highlights some key events). Initially, studies mostly focused on a group of viruses that shared specific viral characteristic and classified as "newly recognized group of common viruses of the respiratory system. In 1956, the name 'adenovirus' was proposed for this new respiratory tract virus [35–38]. Initially, diagnosis was serological and based on complement-fixing antibodies to the HAdV group antigen. Between 1954 and 1956, many outbreaks and sporadic cases of febrile illness of unknown etiology mostly with respiratory or nervous symptoms were registered. In almost all those in which evidence of HAdVs infection was found, respiratory tract symptoms were predominant and touched predominantly young children. In parallel, HAdVs were incriminated as new type of adeno-pharyngeal-conjunctival (APC) virus, responsible for epidemic keratoconjunctivitis [39]. These studies indicated that in children, HAdV-C1, C2, and to a lesser extent C5, were primarily responsible for childhood respiratory infections.

HAdV-B3 was responsible for epidemics in adult civilian populations and children from 4 to 15 years old. HAdV-C6, D8, and D10 were implicated in epidemic conjunctivitis [40,41]. Interestingly, HAdV-E4 and B7 were predominant etiologic agents responsible for acute respiratory disease (ARD) in US military recruits [36]. In addition, HAdV-B14 was the causative agent of an epidemic of ARD in army recruits in the Netherlands [42]. These observations accentuated the degree of HAdV tissue selectivity, raising the conundrum of how a pathogen with similar biological and physical characteristics could cause such diverse clinical pathology. The critical need for anti-HAdV vaccines was naturally raised. By 1957, 14 HAdV types were identified, principally by neutralization test in HeLa cultures using type-specific rabbit sera.

3.1. 1950s and 1960s: HAdVs etiology and pathogenicity

During the late 1950s and early 1960s, studies on HAdV infections and HAdV seroprevalence spread from Europe [43] and North America [44] to Japan, Taiwan, Singapore, China [45], and Russia [46]. Studies in indigenous population of the Eastern Arctic region suggested seroprevalence of 35%, for which 80% had high NAb titers [47]. These studies suggested that HAdV

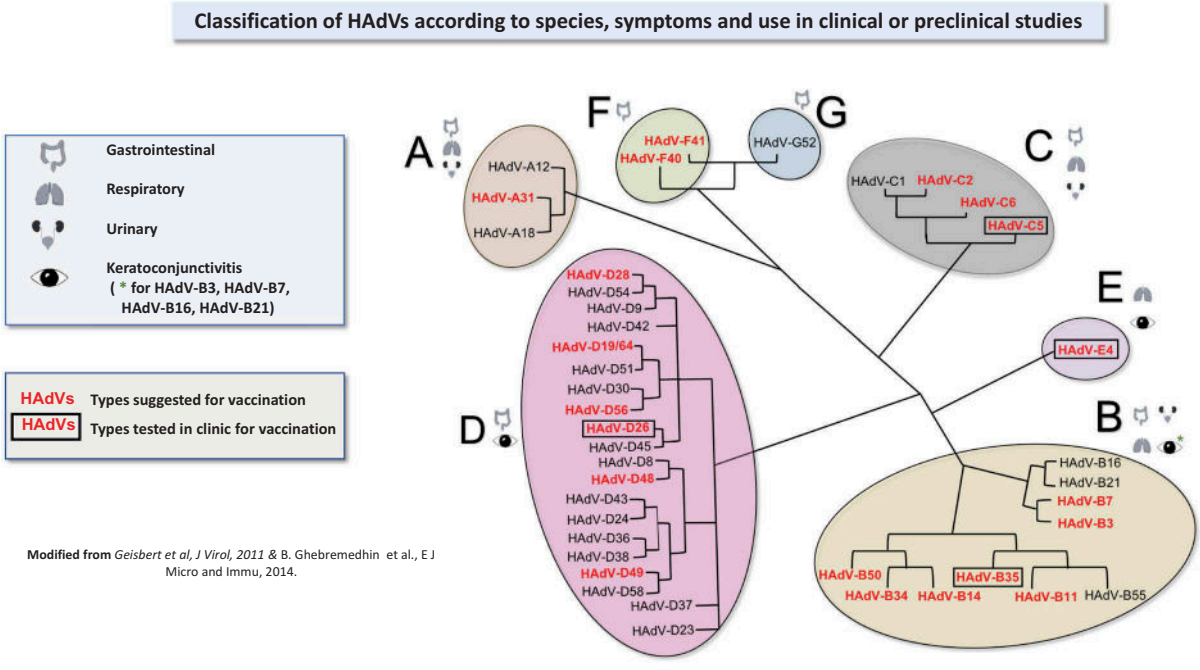

Figure 1. **Adenovirus classification** by species (A-G) and clinical symptoms. Types marked in red are vaccine vector candidates. Framed types have been tested in clinic.

Species A (including types 12, 18, 31)

Members of species A, such as HAdV-A12, have the ability to induce tumors in newborn rodents [54]. To our knowledge, HAdV-A31 is the only A proposed for vaccination strategy, principally because of its ability to escape the host's immune surveillance. Moreover, limited evolution of clinical isolates of HAdV-A31 indicated low probabilities for the emergence of new subtypes in the recent years [173].

Species B (including types 3, 7, 11, 14, 16, 21, 34, 35, 50, 55)

The species B HAdVs (which, as mentioned above are from gorillas) are subdivided into subspecies B1 (types B3, B7, B16, B21 and B50) and B2 (types B11, B14, B34, B35 and B55) based on DNA homology. Most subgroup B1 members cause respiratory infections, while subgroup B2 are mainly associated kidneys and the urinary tract infections [174]. In addition to low seroprevalence, members of the species B use the CD46 or desmoglein (for types B3, B7, B11 and B14) as a primary receptors. Among the species B, type 35 was intensively characterized and launch for pre/clinical trials against HIV, Ebola, malaria, tuberculosis or the respiratory syncytial virus [175,176]. Historically, HAdV-B7 vector was the first species B to be developed [177,59], later type B11 [178], B3 [164], B14 [165], B50 [95] and B34 [166,167] were proposed as alternative candidate for vaccine platforms (Figure 1).

Species C (including types 1, 2, 5, 6, 57)

The five species C (C1, C2, C5, C6 and C57) are the most common types reported in most populations. Members of this species cause a significant proportion of acute respiratory tract infections in children [179,180]. Despite widespread pre-existing immunity, HAdV-C5 vectors are currently being used as vaccine platforms in many countries, principally against HIV [181,182], malaria [183,184,185], Ebola virus [186,187,188,189,190], influenza virus [191], tuberculosis [192,193], or in pre-clinical studies that are targeting Zika virus [194,195], Clostridium botulinum [196], type O foot-and-mouth disease virus [197], Middle East respiratory syndrome coronavirus [198,199], rabies virus [200,201], or Dengue virus [202]. In mice and NHPs, HAdV-C2 delivered antigens protected against Ebola virus [203]. Because the other species C types likely have biological characteristic similar to C5, C6 is being proposed as candidate for vaccination and because of its lower seroprevalence [204,205,206].

Species D (including, but not limited to types 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 51, 53, 54, 56)

This is the largest of the seven species with 44 out of the 70 recognized types. Except for a few types that cause epidemic keratoconjunctivitis (Figure 1), most of the types from the species D are associated with moderate or asymptomatic diseases. The majority of HAdVs from this group have been isolated or detected in HIV-positive patients, suggesting an opportunistic pathogenicity profile [29,207]. However, knowledge about their pathogenicity is still limited and very few of these HAdVs have been exploited as candidates for vaccination. CD46 seems to be used as primary receptor and integrins and/or CAR as alternative primary receptors. However, some members of this species also use sialic acid-modified surface moieties [208,209]. HAdV-D26 is frequently being advertised as a lower seroprevalent platform and consequently is the best characterized from this group. Additionally, D26 is the only member from the species D being evaluated in large-scale human vaccination trials against HIV and Ebola virus [210,211]. Among other candidate from this group, type D24 [212], D28 [142,213], D43 [214], D48 [215,216], D49 [120,217], and most recently D56 [130] or D19 [218] (recently renamed D64 [219]) were also suggested or tested for pre-clinical vaccination studies.

Species E (type 4)

HAdV-E4 is the only member from this species and is frequently implicated in outbreaks of ARD in military training camps [220]. Phylogenetically, HAdV-E4 falls with the simian AdVs, and therefore likely jumped the species barrier several decades ago. Vectors derived from type E4 were designed to optimize systemic and mucosal antibody responses and were clinically tested as Ag delivery system against influenza virus (including the bird flu H5N1 strain) [221,222,223], but also more recently against HIV (https://clinicaltrials.gov/ct2/show/NCT03408262). HAdV-E4 has been tested as vaccine vector candidate for other infectious diseases such as Hepatitis B [170] and respiratory syncytial virus [171], supporting future exploration of HAdV-E4 as vaccine vectors against alternative pathogens [59].

Species F (types 40, 41)

HAdV-F40 and F41 are associated with gastrointestinal disease exclusively [224]. HAdVs from the F groups have thus the potential to be excellent candidates for oral vaccination or gene therapy targeting gastrointestinal or mucosal tract [168,169,225]. These types were thus proposed as oral delivery vector candidate for vaccination against HIV [172] middle East respiratory syndrome coronavirus [199] or for the induction of allergen-specific intestinal mucosal tolerance [225]. In addition, levels of NAb to this groups seems relatively low in children and elderly.

Species G (type 52)

HAdV-G52 - Polysialic acid is the cellular receptor for type G52 [226].

infections were likely pandemic. At that period, seroprevalence against HAdV-C1, C2, and C5 was more frequent than HAdV-B3, C6, and B7. HAdV-E4 and B7 seroprevalence was generally low or nonexistent [48]. However, some notable exceptions where found: in the Tokyo area HAdV-E4 seroprevalence was very low, while 73% in Okayama were seropositive. Similarly, among adult women in Washington, D.C., 71% had ant-HAdV-4 seroprevalence antibody while for the other studies in the United States, the range in adults was between 12 and 29% [43,45]. In retrospect, the seroprevalence of HAdV-E4 in Washington, D.C. (and possibly Okayama) is not surprising, given that the city has high US military personnel. These pioneering investigations highlighted variability of HAdV seroprevalence around the world and also underlined the first observations of the temporal variation of HAdV type infections among a given population. In the early 1960s studies were also performed to understand HAdV-D26, which was not associated with specific illness. The study, using intentional infection of male inmates of an American correctional institution, revealed that HAdV-D26 caused an acute conjunctivitis and an asymptomatic enteric infection that could persist for weeks. Moreover, >50% of the 'volunteers' from correctional institutions from seven different American states had NAbs against HAdV-D26 [49]. By 1961, 19 different types of HAdVs had been identified, based on serology.

During the late 1960s, HAdV seroprevalence was surveyed in many parts of the world [50] including populations such as military camps or children and adults in small closed communities [51,52]. Most of these studies did not identify the HAdV type, and the studies that did, focused on HAdV-C1 to B7 (the low number types). Yet, the frequency with which HAdV infection occurred was unclear because these studies mostly concerned small numbers of hospitalized patients or local outbreaks. In 1969, Brandt and colleagues investigated 18,000 infants in a study lasting 10 years. The study concluded that HAdVs infections were predominantly in children with low socioeconomic status, and that many infections may be asymptomatic. HAdV-C2 (34%), HAdV-C1 (26%), HAdV-C5 (11%), and HAdV-B3 (10%) were isolated from approximately 10% of the children. Of note, this study provided critical information about the incidence of HAdV infection (vs. seroprevalence) according to the type, and was the first long-term investigation on a large,

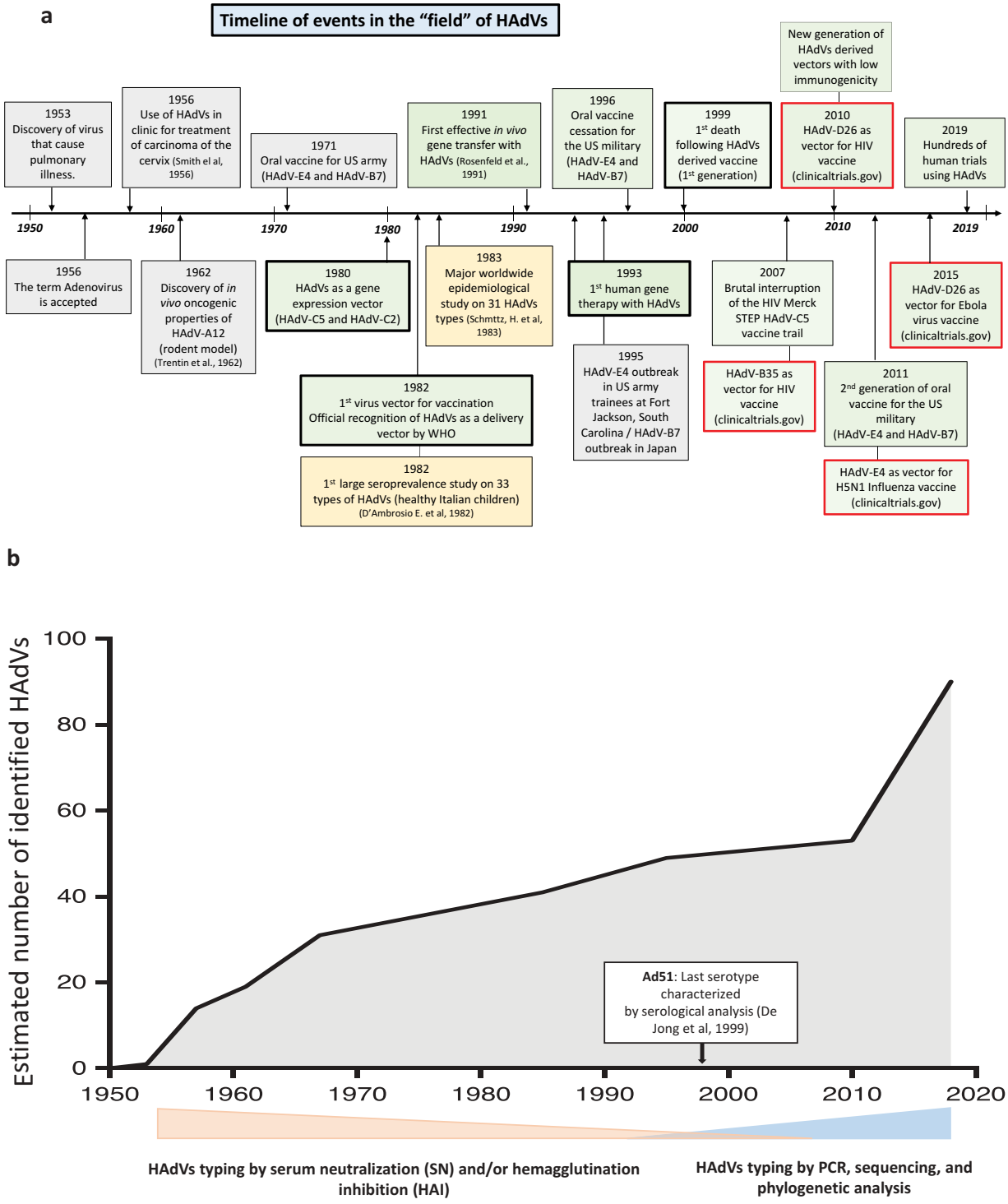

Figure 2. **(a) Key events in the adenovirus "field"**. The gray boxes indicate major findings on the etiology and pathogenicity. Green boxes indicate notable events involving adenovirus-derived vectors. The yellow boxes indicate the major epidemiological studies. The bold borders indicate important events or discoveries. The red bold borders indicate the initiation of some clinical trials involving vectors derived from "alternative or rare" adenovirus types. **(b) Chronology of adenovirus type reporting**. Adenovirus types were historically defined according to their antigenic determinants and ability to agglutinate red blood cells. Since HAdV type 52, identification has been primarily based on genomic sequencing analysis (https://hadvwg.gmu.edu/). However, no globally accepted nomenclature has been currently recommended by the International Committee on Taxonomy of Viruses. To date, there are ~70 recognized types and ~40 additional types based exclusively on sequence data.

random cohort [53]. By 1967, 31 HAdV types had been identified. During this period, Trentin et al. reported in 1962 that injection of HAdV-A12 of into newborn Syrian hamsters led to the induction of sarcomas at the site of administration [54] HAdVs subsequently became a model of choice for molecular biologists to study DNA replication, RNA transcription and splicing, and the molecular basis of cell transformation.

In the late 1960s, the US army initiated a program for ARD surveillance. Initially started during World War II [55], the first epidemiological studies of respiratory illnesses in soldiers at

Fort Bragg, North Carolina and Fort Dix, New Jersey, found that ARD syndrome caused large outbreaks, with a high-risk period during the initial 5 weeks of training [56,57]. Previous epidemiological surveys showed a direct correlation of HAdV-E4 and B7-related ARD rates with crowding. Infection rates approached 70% and were primarily limited to the military population. Approximately 20% of the infected individuals required hospitalization [58]. During the 1970s, HAdVs infections were largely studied in the military recruits, principally because of the unusual pathogenicity and selectivity of HAdV-E4 and B7. Consequently, in 1971 the US began routine administration of a lyophilized HAdV-E4 and B7 oral vaccine [59], which significantly reduced respiratory morbidity at training centers. The benefits of immunization were significant in term of both, ARD hospitalizations and cost-benefit [60].

3.2. The 1970s and 1980s: breaking down HAdVs biology and global epidemiology

The 1970s was the period where persistence of HAdV infection was reported, principally within adenoid vegetation of asymptomatic hosts. Persistant HAdVs were thought to promote high NAb levels that did not, counterintuitively, clear HAdVs from the host. HAdV persistence may be one of the causes responsible for its pandemic nature [61]. The late 1970s was also marked by a better understanding of the HAdV structure, cell cycle, and mechanism of DNA replication [62]. Historically, the 1980s was a crucial period for the development of molecular biology. Control of HAdV gene expression was better characterized as well as the structure of the virus components. In addition, HAdV-C2 and C5 were developed into gene transfer vectors [63].

During the 1980s the seroprevalence of other HAdV types was explored. Epidemiological data suggested that some HAdV types are common in all age groups and populations, while other types infected later in life. Furthermore, about half of the HAdV infections were asymptomatic, meaning that physicians were not detecting infections of nonpathogenic HAdVs. Thus, epidemiological studies on HAdVs generally focused on types 1 through 8, and type B21, which were those most frequently associated with the symptomatic disease.

One of the largest (n = 338 individuals) studies on HAdV seroprevalence was performed on Italian children using microneutralization tests. This study showed that ~75% of the children were positive for at least one HAdV type among the 33 tested. The highest seroprevalence was for HAdV-C2 (41,5%) and HAdV-C5 (33%), followed in decreasing order by HAdV-C1, B3, C6, D31, and D18. NAbs against other serotypes were present in less than 10% of the children or never found, including HAdV-D9, D20, D26, and D32 [64]. This study was consistent with the seroprevalence described in the United States, with a higher frequency found for types 1 through 7, but also highlighted the presence of less common and less virulent types. Moreover, this study challenged early conclusions concerning the common global distribution of HAdVs [65] and highlighted the substantial differences. In 1983, Schmitz and colleagues addressed the epidemiology of 31 HAdV types, based on approximately 25,000 reports to the WHO from 1967 to 1976. They found an absolute frequency of HAdV-C2, C1, B7, B3, C5, C6, E4, and D8 in decreasing order (with a large gap between HAdV-C5 and C6). The southern hemisphere showed a higher incidence of HAdV-E4 and species B (without HAdV-B3 and B7), and a lower incidence of HAdV-C6, whereas HAdV-D8, D13, D19, and species A were rarely found. For species B, many differences were found between countries and ages, principally concerning HAdV-B3 and B7 [66].

Initially found by electron microscopy in stools from children with diarrhea, HAdV-F40 and F41 were linked to enteric infections [67,68]. HAdV-F40 and F41 genomes were notably different from the 39 previously described types and were resistant to numerous attempts of *in vitro* culture [69]. HAdV-F40 and F41 could not be distinguished from each other by classical hemagglutination-inhibition tests, indicating a close antigenic relationship. Of note, HAdV-F40 and F41 have the shortest of all HAdV hexon hypervariable regions, which may play a role in their stability at low pH. The early 1980s was also marked by the development of restriction enzyme analysis of HAdV genomes, which became a valuable epidemiological tool in studying the geographic and temporal occurrence of different HAdV types. Analysis by DNA restriction profile allowed differentiation between HAdV-F40 and F41. Later, monoclonal antibodies were used to differentiate them by neutralization assay [70]. According to the first epidemiological studies using neutralization assays, HAdV-F40 and F41 were likely pandemic. Sera from healthy children from Hong Kong, New Zealand, Gambia, Kuwait, and the United Kingdom were 40%–50% seropositive. Surprisingly, the 16 samples from Guatemala were negative [71,72]. A study performed among children in Thailand demonstrate a relatively low prevalence for HAdV-F40 and F41 (2%), suggesting that among the spectrum of diarrheal etiologies, they may be proportionately less prevalent in a tropical climate than they are in countries with temperate climates [73].

The 1980s were a critical period for epidemiologic studies on HAdV-B7. Previous data from the United States and Europe suggested that HAdV-B7 was frequently associated with severe illness that caused fatal lower respiratory disease and outbreaks in schools, hospitals, and military facilities [74,75]. The highest seroprevalence against HAdV-B7 was detected in Taiwan during the 1960s, where about 30% of children were positive. However, in that study, HAdV-B7 was the only type for which adults (vs. children) were more likely to have NAbs [45]. In comparison to Japan and the US, HAdV-B7 infections were also more frequent and occurred at an earlier age in Taiwan. In contrast to Australia, Brazil, China, Sweden, the United States, the United Kingdom, Germany, and Belgium, HAdV-B7 was rarely isolated in Japan. The low frequency of HAdV-B7 isolation in Japan during the 1980s (before the outbreak in 1995) and its particularly high frequency in US and European military recruits was a unique characteristic [76]. By 1985, ~41 HAdVs types were identified.

Taken together, studies from the 1980s highlighted major advances in HAdVs seroprevalence: (i) global HAdV serology was associated with greater variability (ii) there was significant variations of temporal epidemiological patterns of HAdVs infection for a given region, and (iii) the existence of frequent asymptomatic HAdV infections making epidemiology unpredictable and therefore a need for permanent surveys.

3.3. The 1990s: a renaissance of Ad biology, vaccination, and gene therapy

During the late 1980s and early 1990s, HAdV seroepidemiological studies took place during difficult sanitary and health context in developing nations, where the need for the prevention of childhood pneumonia or diarrhea was imperative. In 1990, the WHO estimated that 14.6 million children <5 years old died each year in developing countries. Of note, studies from that time indicated that HAdVs were not of significant health risks (with the exception of HAdV-E4 and HAdV-B7 in military training centers).

3.4. HAdVs and immunodeficiency

The 1990s was also a dynamic period for the HAdVs scientific community because of the impact of HAdV-related diseases linked to HIV infection. By the end of 1990, between 8 and 10 million peoples were thought to be living with HIV [77], with HAdV infections more virulent and frequently in HIV-positive individuals [78]. Along with rotavirus, HAdVs were frequently incriminated in HIV-positive individuals with diarrhea [79], encephalitis [80], hepatitis [81], pneumonitis [82], and gastrointestinal infections [83]. In addition, HAdV infections were reported in pharmacologically-induced immunocompromised individuals undergoing cell or organ transplantation [84]. In 1995, ~ 49 HAdVs types were identified.

3.5. A better understanding of HAdV molecular biology: medical hopes and disappointments

During the 1990s, advances in molecular and cellular biology were used to improve our understanding of the mechanisms by which HAdVs counteract antiviral immune defenses [85]. As a result, this period saw the successful demonstrations of replication-defective HAdV vector expression of open reading frames/cDNA in animals. Quickly, HAdV vectors became a popular gene transfer tool for mammalian cells [86,87]. HAdV-C2 and C5 dominated the gene transfer field because they could be readily propagated to high titers. In 1991, the first effective *in vivo* gene transfer with HAdVs was performed [88]. In 1993, the first human gene therapy trial used a recombinant HAdV-C5 vector at the Clinical Center, NIH, on a 23-year-old cystic fibrosis patient. Other clinical studies on various disease, using HAdV-C2- or C5-based vectors followed [89–91]. 25 years on, HAdVs are still the most common vectors used in clinical trials worldwide [92].

The use of a viral vector for the delivery of antigens in vaccination was first described by in 1982 and the WHO recognized the potential value of such a delivery system [93]. Replication-defective HAdV vectors (typically deleted in the E1 region) were particularly promising because they were relatively cheap to produce, stable, and provided long-term immunity [94]. In preclinical trials HAdV-based vaccine induced strong humoral response and T-cell specific immunity [95]. Many thought that HAdV-C5-based vaccines would be extremely efficient to induce protection against human pathogens.

3.6. The limits of HAdV-C5 for clinical application

Clinical use of HAdV-C5 vectors exposed some limitation, drawbacks and side effects [96]. During preclinical testing in immunologically naïve animals, HAdV-C5 vectors induced robust responses [97]. Not surprisingly, pre-existing immunity to HAdVs, which concerned the majority of the world's population, precluded robust responses against the encoded antigens. In some populations the pre-existing immunity against HAdV-C5 was >90% by 2 years of age [98]. HAdV-specific T cells, NK cells and cytokines also contribute to the fading efficacy of HAdV-based vaccines in individuals with pre-existing immunity [99].

HAdV-based vaccination may also include other adverse effects as illustrated by STEP, an HIV Vaccine Trial Network 425 (HVTN502 STEP) [100]. HVTN is the world's largest publicly-funded international collaboration for the development of vaccines against HIV. HVTN502 STEP was an international, randomized, double blind, placebo-controlled Phase II test-of-concept clinical trial. This trial enrolled 3,000 HIV-negative volunteers from diverse populations at high risk of HIV infection, including men who have sex with men and female sex workers. HVTN502 STEP was prematurely interrupted due to lack of efficacy and also because vaccinees who had high NAb titers against HAdV-C5 had a statistically significant increased risk of HIV acquisition during the first 18 months post-vaccination [101,102]. Ten years later, the mechanisms by which these side effect occurred are still not fully understand and certainly complex. HIV acquisition occurred in uncircumcised men who have higher levels of mucosal inflammation and HIV susceptibility in general. Growing evidence suggest also that specific generation of immune complexes with HAdV-C5 and NAb can be captured by antigen-presenting cells that present conserved HAdV-C5 epitopes via the MHC II pathway and thus create an acute local proinflammatory response [103]. In individuals with high levels of HAd-C5 NAbs that inflammatory environment could lead to the proliferation of HAdV-specific CD4 T cells (IL-17^{+}), which have preferentially mucosal tropism [104] and are particularly susceptible to HIV infection (through a mechanism linked to CCR5 and α4β7 expression) in comparison to other virus-specific CD4 T cells [105]. Of note, the epitopes recognized by memory T cells against HAdVs are broadly shared among human and nonhuman AdVs [106,107]. Thus, higher levels of mucosal inflammation added to recurrent stimulation and mucosal trafficking of HAd-C5 specific memory CD4 T cells during vaccination might lead to this adverse effect. These data shed light on the complex cellular events that could rise from the interactions between host pre-existing immunity and, theoretically, other HAdV derived vectors [102,108].

In addition, the late 1990s witnessed the first death of a volunteer in a gene therapy trial. An 18-year-old who had ornithine transcarbamoylase (OTC) deficiency was administered 6×10^{11} viral particles/kg of an HAdV-C5 vector containing the OTC cDNA. The man died 4 days later from multiple organ failure [109]. In addition to ethical and technical issues (mostly concerning the controversial aspects of eligibility criteria for participation and explanation of the risks and benefits of the clinical experiment), these events remind us the critical need for further fundamental research concerning administration of HAdVs and their complex interactions with the host's pre-existing immunity.

3.7. Alternatives to HAdV-C5 vectors

To circumvent pre-existing immunity, vectors derived from 'rare' human or from animal AdVs were progressively developed. Canine type 2 (CADV-2 or better known as CAV-2) was the first nonhuman adenovirus vector [110]. The HAdV types were selected according to their supposedly low seroprevalence [111,112]. The NHP AdVs were selected primarily for production characteristics as all could be propagated and produced in GMP-certified human cell lines. The human and nonhuman AdVs are generally stable, and easily produced, but in some cases their biology still needs to be better characterized.

In principal, the rare HAdVs and NHP AdVs should be unaffected by pre-existing anti-HAdV humoral immunity. However, seroprevalence against chimpanzee, simian and rare HAdV types exists in human populations [113]. For example, some rare HAdV types were chosen for their low seroprevalence in North America and Europe (e.g. HAdV-D26) – only to be significantly more prevalent in some African countries. One study demonstrated that the original host of species B HAdVs are gorillas, and that HAdV-B's jumped the species barrier a handful of times starting ~100,000 years ago and have now affected human health for most of our species lifetime [114]. Even though many people are not exposed to NHP AdVs, they may have pre-existing immunity that cross-reacts against NHP-AdVs. Take for example a study using a chimpanzee AdV (ChAd-3) as an Ebola vaccine vector. Twenty volunteers from the Washington, D.C. metropolitan area were enrolled in a clinical trial. More than 40% of those volunteers had significant levels of anti-ChAd-3 antibodies and no evidence of the source of exposure was described [115]. The other conclusion from this interesting study is that species D HAdVs are the quintessential HAdVs. HAdV-E4 is another clear example of a NHP AdV that jumped the species barrier. Other studies showed that NHP types carry the potential for cross-species transmission between monkeys and humans [116]. Moreover, if selection of alternative HAdV types has been largely driven by the absence of NAbs in North Americans, very little attention has been given to cross-reactive AdV T cells [107,7]. It is clear that global AdV seroepidemiology is incomplete, especially concerning African countries that are often primary targets for vaccination campaigns.

4. HAdV-based vaccines: results from the last 20 years

This section focuses on HAdVs that have been chosen for vaccine development, mainly because of their theoretical low seroprevalence compared to HAdV-C5. Potential HAdV candidates will be first presented by species. Based on HAdV seroprevalence in the clinical setting, only half of the known HAdV types cause morbidity. Hence, HAdVs infection can be clinically silent and thus only seroepidemiology investigations can evaluate the incidence within a given population. Technically, HAdV seroprevalence is characterized as one in which exhibits limited cross-reaction with others. The definition is nevertheless difficult to apply because some cross-reactivity can occur, especially among HAdVs from the same species. This is particularly problematic concerning the recently identified species D HAdVs that have been generated by recombination [117].

4.1. Preclinical and clinical trails

By 2018, hundreds of vaccine (and cancer) trials have used, or are using, HAdV-based vectors (https://clinicaltrials.gov/ct2/home and Box 1). Today, many HAdV-based vectors are modified versions of HAdV-C5 [94,118], but its use is becoming more restricted to limited cohort of cancer patient and/or single gene transfer. In regard to vaccination strategies that may very well involve millions of random people anywhere on earth, the clinical use of HAdV-C5 may be limited.

4.2. Seroprevalence of principals HAdV vaccine candidates

Many studies from the last 20 years, that contain data from healthy individuals (if not, pathology will be outlined) in a specific area, are discussed (**Supplementary Tables 1–4**). We recently assayed sera collected in Burkina Faso and the Republic of Chad (West and Central Africa, respectively). Data are included here (organized by species and continents). A caveat due to technical conditions and thresholds at which samples are considered positive are indicated, as well as number of samples, location and year(s) of the studies (when available). Only HAdV types that are suggested or tested for preclinical or clinical studies are included in the **Supplementary Tables 1–4**, and only HAdV types that are tested in clinic are displayed in Figure 3.

4.3. Moving forward

Gathering data from about 50 studies, it is first notable that the majority has been performed using cohorts from North America, Europe, Africa, or China. Cohorts in South America, the Middle East, Asia (except China and Japan) and Oceania, are poorly represented **(Supplementary Tables 1–4** and Figure 3). In Africa, Europe, and Asia, only a handful of countries where investigated for HAdV seroprevalence. In Africa, except for a handful of exceptions, most of the data have been generated from scattered sub-Saharan populations. In Europe, studies where performed primarily in Western Europe, and in Asia, 80% of the investigations took place in China. Data gathered here outlines that members of species C, D, and B were principally investigated.

Among the species C, HAdV-C5 seroprevalence is the most widely reported, either as principal target of the studies or for comparison with other human or nonhuman AdVs. HAdV-C5 is clearly pandemic, but the proportion of seropositive people in North America is globally lower compared to Europe, Asia, and Africa (100% of seroprevalence detected in some sub-Saharan countries) [119]. HAdV-C2 global seroprevalence is relatively high (36–92%) and ≥ HAdV-C5 [120,121]. HAdV-C6 was presented as a low prevalence type by one study in the United States (8.5% adult and 2% children [122] and reach 12% in of healthy adult in China [123]), while others studies show a seroprevalence rate fluctuating between 78% in Thailand and Cameroon; 73% in South Africa and 71% in Malawi [124].

For the types belonging to species D, HAdV-D26 and to a lesser extent D48 and D28, infections are globally more frequent in Africa. HAdV-D26 NAbs were detected in 88% of the

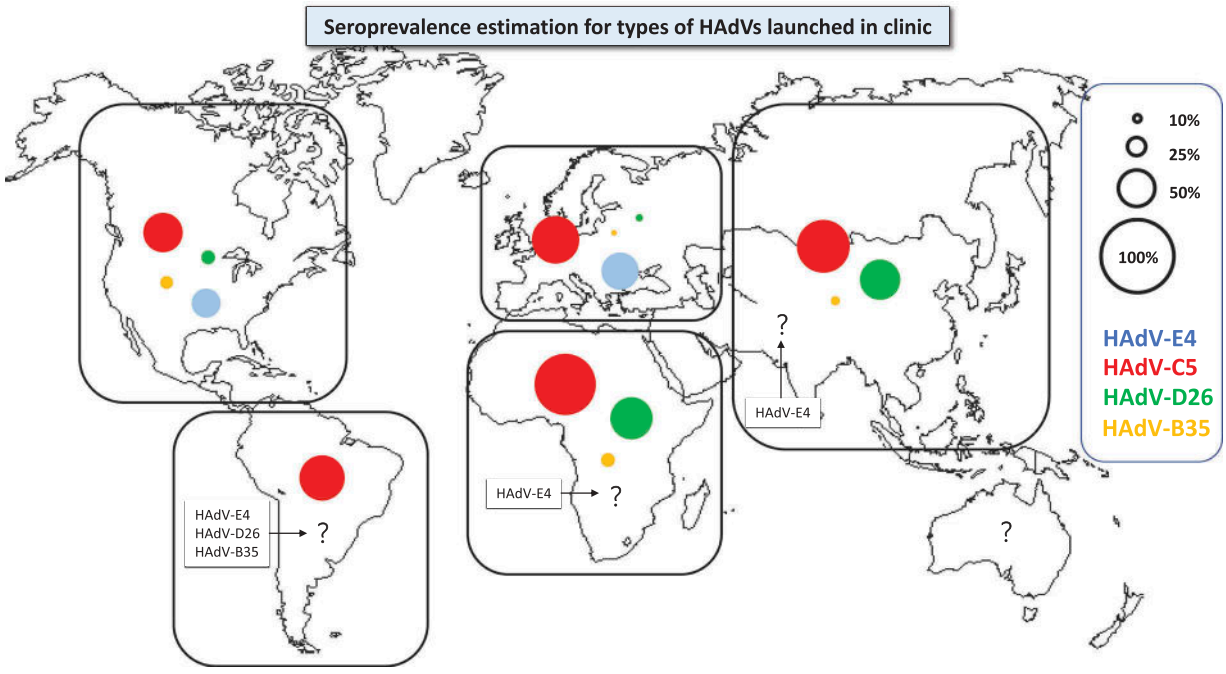

Figure 3. Seroprevalence for adenovirus types used in clinic. Calculated according to the results of about 30 studies from the last 20 years, this figure estimates by continent the serology of HAd-E4, C5, D26, and B35.

serum tested from Cameroun [124], and ~70% in the Republic of Chad and for some areas of Burkina Faso (unpublished data). By contrast, seroprevalence was always ≤12% in the United States and Europe among all the studies listed in this review. In China and Thailand, seroprevalence for HAdV-D26 is 35–60% [124–126]. Studies that targeted HAdV-D48 or HAdV-D28 are consistent with a lower seroprevalence compared to HAdV-D26, including for Africa.

For species B types, global seroprevalence for HAdV-B7, HAdV-B11, and HAdV-B35 are relatively low. Similarly to others species, seroprevalence appears to be slightly higher in Africa, reaching 20% for B35 [126–128], and around 30% for B11 [129] [98,127]. However, the results fluctuate between countries. In Europe and North America, the prevalence for B35 and B11 NAbs were <10%, with the exception of Haiti (22% and 30%, respectively [127]) and one study performed on United States healthy adults older than 50 years (22% for B35 [130]). In Asia, results are similar to Europe and North America, with the exception of Thailand, where B35 seroprevalence reached around 17% for a healthy group of adults associated with high HIV risks. [126].

Studies from Japan suggested a higher rate of B11 seroprevalence (18–30%) compared to Europe and North America. Moreover, HAdV-B11 seroprevalence rate in Japan was globally higher than B35 [129,131]. Of note, only limited studies were performed in Asia for these types. On the other hand, the seroprevalence for HAdV-B7 was largely explored during last 20 years in Japan. Indeed, HAdV-B7 was rarely isolated in Japan before 1995 when a nationwide outbreak suddenly occurred [132,133]. Despite the epidemic, HAdV-B7 seroprevalence remained relatively low in Japan (2–13%) [133–135] compared to China (13–85%) [123,136], the United States (27–78%) [122,137], and Belgium (38%) [131].

For species, A, E, and F, the seroprevalence for the type HAdV-E4 was evaluated in healthy adults in the United States and Europe (17–46%) [123,132]. Not surprisingly, seroprevalence in United States army recruits was notable (71%) [137]. The arguments used for HAdV-E4-based vaccines were its biological properties and respiratory tropism. HAdV-F41 showed high seroprevalence worldwide according to the handful of studies performed on US, European, and Asian samples, reaching a maximum of 95% for healthy children from south China [138]. It is also clear that reporting HAdVs seroprevalence in populations from vast and diversified countries (in terms of climates, populations and densities) such as the United States, China, or Brazil can poorly reflect the likely diversity. For example, Kahl and colleagues showed substantial HAdV-C5 seroprevalence variations within healthy adult populations across the United States, fluctuating from 35% for Northeast region to 71% for Upper Midwest region [139]. More recently, Wang et al. found significant variation between healthy adults from coastal regions vs. inland regions in China [140].

Given the overlapping epidemiology of HAdVs, it is clear that understanding host immunity remains a challenge, especially because HAdV vectors could be used for different populations [141]. Most HAdV epidemiology studies also found that seroconversion against the vast majority of HAdV types is an age-dependent process. Clearly, some types are pandemic (C5, C2, F40, and F41) independently of the sanitary condition of the country. Other types such as HAdV-B35, B11, D26, D48, D56, and D58, are globally less frequent, but their seroprevalence fluctuates considerably. In addition, and compared to Europe or North America, the average seroprevalence of these types is higher in Africa and for some regions of Asia. Of note, many of the studies listed here also investigated the proportion of sera that exhibited low, medium or high NAb titers,

indicating that these 'rare' types have generally low NAb titers. Consequently, as vectors, they might be less problematic when used as population-based vaccines. Nevertheless, at least 10% of the samples from the Republic of Chad (N'Djamena) and Burkina Faso (Ouagadougou) had anti-HAdV-D26 NAb titers above 1000 (unpublished data).

Understanding how alternative AdV vectors are affected by pre-existing humoral immunity constitutes a challenge. Yet, pre-existing immunity is not the only criterion that will influence HAdV vector efficacy. As indicated above, HAdVs species and types have different receptors, tropism, transduction, longevity, and immunogenicity profiles. For instance, mice do not have ubiquitous or homologous expression of CD46 (or desmoglein 2) and combined with the fact that these HAdVs do not replicate in mice, substantially limits preclinical studies of HAdV derived from species D and B in small animals. Thus, identification of functionally relevant immune responses is an essential element that needs to be determined to design potent vaccines. Of note, HAdV vectors based on B35 or D26 have lower immunogenicity compared to HAdV-C5 [98]. Moreover, in contrast to injection, oral administration can elicit mucosal immune responses and greatly circumvent the pre-existing antivector immunity [142]. These issues shed light on the complexities between the species and types, and strongly indicates that more research is required to identify the mechanisms that play a key role in the induction of protective immunity induced by HAdV derived vaccines.

5. Technical procedure for type-specific seroprevalence assays

Supplementary Tables 1–4 contain noteworthy variation between values from studies performed on similar populations. These variations can be due to differences in the numbers of samples, technical conditions, and thresholds at which samples are considered positive. These technical disparities can make comparisons among different studies particularly difficult. Historically, the first methods used to determine antibody titers in human sera were complement-fixation [143] and hemagglutination-inhibition tests [56]. We now know that species C HAdVs agglutinated erythrocytes from some animals and not others because of the differential expression of the CAR on their membrane [144].

Today, the use of neutralization assay using transgene expression are more sensitive, and less demanding in terms of amounts of virus, cells, and sera [145]. Transgenes cloned into the vectors for these assay are either GFP (green fluorescent protein) [146], luciferase [126], β-galactosidase [147], or secreted alkaline phosphatase (SEAP) [148]. The type of cell line used is critical, especially for studies that compared HAdV types because of the variability in infection efficacy. Cells lines used in the studies listed here are mainly the A549 (human adenocarcinomic alveolar epithelial cell), HEK 293 (human embryonic kidney cells), Hep2 (HeLa derivative/human cervix carcinoma cells), 911 (human embryonic retinoblasts cells), or PER C6 (human embryonic retinal cells) cell line, because they are permissive to infection by a large range of HAdV types. In addition to the ability of the virus to infect the cell line, the $TCID_{50}$ (the number of physical viral particles needed to infect 50% of the cells) between of HAdV types needs to be similar to be able to compare respective NAb titers. Studies presented here also displayed a different threshold for which the sera are considered positive. Most studies used serum titer >16 or dilution >1:4 to define a threshold, but substantial variations can be found ranging from 8 to 100 for sera titer and 1:2–1:32 for sera dilution. In addition, NAb titers were determined either by the dilution at which 50% (EC_{50}) or 90% (EC_{90}) of cell viability or transgene expression was observed. These variations make comparison between studies nebulous. A low threshold might lead to excessive false positive samples. In addition, distortions in the neutralization curves of samples at high serum concentrations are often observed, possibly resulting from nonspecific interactions. By contrast, a high threshold might fail on low titers samples and include them as negative, especially for HAdV types that generally displayed weak NAb titers. Standardizing the parameters will reduce the variability in sera titer values and make easier and more accurate comparison between studies.

6. Conclusion

The use of HAdVs with low seroprevalence as antigen delivery platforms was one of the main strategies to circumvent pre-existing HAdV humoral immunity. Arguments in favor of these vectors often underlined their potential abilities to overcome HAdV-C5-specific NAb [131,149], and enhance immune responses in populations with a high prevalence of HAdV-C5 immunity. But at least one question remains: in a situation where seroprevalence against rare types is high, what are the risks of using a vaccine derived from this type? The results from HIV STEP trial should not be underestimated. HAdV-C5 vector administration increased HIV acquisition in participants with high pre-existing HAd5 immunity. Will this situation also hold true for other HAdV vectors expressing different antigens? HIV acquisition will not be an endpoint that most vaccine trial organizers will include/promote. Furthermore, quantifying the human and economic costs of increased HIV infections versus reduced vaccine target is not straightforward. We therefore recommend systematic monitoring of HIV acquisition when any kind of HAdV vector is used in the clinic [102,150]. Others strategies have been established to overcome HAdVs pre-existing immunity such as the development of nonprimate-AdV vectors. Most of these vectors are derived from canine, bovine, porcine, ovine, and fowl and are currently in preclinical stages of development. NHP-AdV vectors from monkey origins are the most advanced and have reach clinical trials against Ebola, Malaria, HIV, tuberculosis, HCV and influenza principally [115,151–154]. Animals-derived vectors share some appropriate characteristics of the well characterized HAdV-C5, but with seemingly negligible seroprevalence among human population [7,107,155]. However, while NAb titers against a ChAdVs in healthy volunteers were 2% in the United States [119], substantial NAbs titers were detected in the sub-Saharan Africa [156], Brazil [157], and China [125].

We believe that developing seroepidemiological research on rare HAdVs need be amplified to generate an accurate global mapping of HAdV seroprevalence and consequently improve the safety and the efficacy of these vectors. Too many studies are based on results that were generated more

than 40 years ago. But, determining HAdV seroprevalence will be challenging. International travel and increasing immigration foster pathogen spreading from previously isolated areas. Sample collection can be problematic due to social, medical, political, and military situations in a specific area. Shipping biological samples from Africa to outside of the continent can be particularly costly, administratively demanding, and time consuming. For this reason, we encourage development of local serological studies to update the database. Thus, it is imperative to develop, standardize, and adapt technical procedures to countries with limited technical resources to perform accurate, robust, and reproducible data at minimum cost. This is all the more important because low income countries are usually the ones that need most to improve vaccination coverage and to be most susceptible to support vast vaccination campaigns. In addition, HAdVs are constantly undergoing recombination [117]. Increasing urbanization and globalization of poor sanitary developing countries, coupled with insufficient resources for control, are combinatorial factors that are greatly increasing probabilities of generating new types and consequently periodic outbreaks of HAdV infections [158].

We also encourage fundamental research on interaction between the pre-existing immunity, AdV and antigen-presenting cells. A better understanding of cellular and molecular interactions between host immunity and AdVs would inevitably improve the next generations of vaccine platforms, possibly allowing one to safely target specific population or individuals according to their unique serology profile. This challenging task will require a concerted effort between countries, research facilities, medical staff, and political authorities.

7. Expert opinion

After access to potable water, vaccination is the most efficient tools to prevent disease. AdV-based vaccines have undeniable potential. Nevertheless, optimizing is needed, especially against complex diseases such as HIV or malaria. Anti-vector immunity remains a challenge if the same vectors are to be administrated to different populations because most of us likely been infected with at least five different HAdV. The ideal scenario would take in consideration the HAdV sero-epidemiology of targeted areas for vaccination campaigns, associated to a systematic survey of HIV acquisition following clinical trials.

Fundamental research addressing virus-host interactions are essential. Relationship between pre-existing humoral and cellular immunity [159–161]. Studies on interactions of the host with pre-existing T cells, anti-microbial peptides, and natural occurring immunoglobulins need also to be developed and clarified, especially concerning the 'rare' HAd types. The variability of the host immune response, in particular during preclinical trials in animals, has to be taken in consideration. It is also possible that the limitations imposed by vector-host interactions could be overcome if postpurification modifications of the capsid are included [162]. Other approaches include genetically fusing epitopes to capsid proteins and/or single-round replicating vaccines that increase the transgene-directed immune response and allow a lower inoculation dose. Restricted replication in targeted cells or tissues may increase safety and potentially immune focus on the transgene.

8. Five-year view

Remarkable efforts have been made to improve HAdV-derived vector efficacy, safety, and to sidestep pre-existing immunity. Vaccine candidates against malaria, Ebola, or HIV may reach the market in the near future (Box 1). In the context of our review, one key issue is whether the HIV surveillance will be incorporated into vaccine trial endpoints in regions where infection rates are high. In these regions, will governments and NGOs recommend the used of AdV-based vaccines? Hopefully, seroprevalence will be characterized before performing vaccination campaigns. Another key issue is the paucity of data on seroprevalence for areas where future 'rare' Ad-based vaccines could be used. This task could be challenging due to cultural, social, and governmental issues. There are potential strategies to complement to serology-based assays: with the advent of next generation sequencing, pathogens will be more easily detected in blood samples. This will clarify the issues of AdV prevalence [163].

Finally, success will depend on better understanding the biology of each AdV type. Undoubtedly, fundamental research in term of cell attachment, and intracellular trafficking will enhance AdV vectors efficacy and safety for gene transfer and vaccination.

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