Emerging Microbes & Infections
2025, VOL. 14, 2475831 (11 pages)
https://doi.org/10.1080/22221751.2025.2475831

REVIEW ARTICLE

OPEN ACCESS Check for updates

The seroprevalence of adenoviruses since 2000[1]

Lingling Hong[a*], Jiashun Li[a*], Weikai Zeng[a*], Yuhua Li[c], Changfa Yu[d], Shutao Zhao[a], Ling Chen[b,d] and Ying Feng[b,d]

[a]Department of Respiratory and Critical Care Medicine, Huadu District People's Hospital of Guangzhou, South China Medical University, Guangzhou, People's Republic of China; [b]Guangzhou National Laboratory, Guangzhou, People's Republic of China; [c]Department of Arboviruse vaccine, National Institutes for Food and Drug Control, Beijing, People's Republic of China; [d]Center for Infection and Immunity, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, People's Republic of China

ABSTRACT

Human adenoviruses (Ad) are increasingly used as vaccine vectors, especially after Ad5, Ad26, and ChAdY25 (ChAdOx1) were employed as vectors for SARS-CoV-2 vaccines. So far, more than 116 adenovirus genotypes have been identified, divided into 7 species (A-G). Most adenoviruses do not cause diseases or are mildly pathogenic, with only species B and E leading to acute respiratory infections or conjunctival inflammation and species F causing gastrointestinal infections. Previous studies have shown that the seroprevalence of neutralizing antibodies against adenoviruses can be limiting when applying adenoviral vectors. On the other hand, for highly pathogenic adenoviruses, neutralizing antibodies is beneficial for preventing the diseases caused by these adenoviruses. Here, we summarized the studies on the seroprevalence of adenoviruses, especially adenoviruses that may be utilized as vectors for vaccine and gene therapy. We also analysed possible factors associated with the seroprevalence and neutralizing titres. Given the trend of increasing adenoviral vector application, it is necessary to continue the investigation of the seroprevalence of neutralizing antibodies against adenoviruses in different geographic locations and populations.

ARTICLE HISTORY Received 15 October 2024; Revised 27 January 2025; Accepted 2 March 2025

KEYWORDS Adenovirus; seroprevalence; neutralizing antibody titres; adenovirus vector; pre-existing antibodies

Introduction

Adenovirus and adenoviral vectors

The adenovirus was firstly isolated from human adenoids in 1953. To date, more than 116 adenovirus genotypes have been identified, divided into seven species (A-G) (http://hadvwg.gmu.edu/). Different types of adenoviruses have unique characteristics due to their tissue tropism. Species A, such Ad12, Ad31, mainly causes gastrointestinal infections [1]. Species B, including Ad3, Ad7, Ad14, and Ad55, mainly cause respiratory infections and can lead to severe bronchial inflammation and pneumonia that can be life-threatening [2,3]. Species C, such as Ad1 and Ad2, mainly cause respiratory and gastrointestinal infections and do not cause severe diseases. Species D and E, such as Ad8 and Ad4, can lead to ocular conjunctivitis [4–6]. Species F, such as Ad40 and Ad41, and species G, such as Ad52, can cause inflammation of the gastrointestinal tract. In addition, a few adenoviruses, such as Ad7 and Ad12, have been reported to be associated with cancers [7].

Since the 1980s, several adenoviruses have been developed as gene expression vectors, such as Ad2 and Ad5 [8]. Genetically engineered replication-incompetent adenoviruses have advantages such as high safety, efficient expression of inserted genes, induction of strong antibodies and cellular immunity, and large-scale production. Therefore, many serotypes of adenoviruses, including Ad1, Ad2, Ad3, Ad4, Ad5, Ad6, Ad7, Ad11, Ad24, Ad26, Ad28, Ad35, Ad40, Ad43, Ad48, Ad49, Ad50, have been developed as vaccine and gene therapy vectors to deliver antigens. Adenoviruses commonly used as vaccine vectors include replication-competent and replication-incompetent adenoviruses. Replication-competent adenoviral vectors generally only delete the E3 region that encodes proteins with inhibitory functions on the host immune response. This viral vector shows good immunogenicity and is easy to amplify, but there are concerns about its safety. In addition, no more than 3.5 kb foreign genes can be inserted into its E3 region, so the capacity of such vectors is limited. Replication-incompetent adenoviral vectors usually have E1 or both E1 and E3

CONTACT Ying Feng feng_ying@gzlab.ac.cn; Ling Chen chen_ling@gibh.ac.cn
[1] Supplemental data for this article can be accessed online at https://doi.org/10.1080/22221751.2025.2475831.
*These authors contributed equally to this work.

regions deleted. The protein encoded by the E1 region is necessary for viral replication. Therefore, E1-deficient adenoviruses can only be produced in a cell line that expresses the E1 proteins in trans, such as HEK293. However, this vector showed good safety, and E1 deletion further increased the vector capacity to 7 kb.

Adenovirus neutralizing antibodies

Many studies have shown that serum-neutralizing antibodies against an adenovirus can affect the effectiveness of an adenovirus vectored vaccine or gene delivery [9]. Most anti-adenovirus neutralizing antibodies recognize the major surface protein hexon and the fiber that interacts with the receptor [10,11]. It is generally believed that anti-fibre antibodies can inhibit adenovirus infection by inhibiting the binding of adenovirus fiber knob with the target cell surface receptors [12]. Hexon is not involved in the binding of adenovirus with cell surface receptors. Therefore, it is unlikely that the neutralizing effect of anti-hexon antibodies involves classical blocking of infection. Studies indicated that anti-hexon antibodies may inhibit viral release from endosomes [13] or block the microtubule-depezong'zndent intracellular transport [14].

Since 1969, a large-scale epidemiological investigation has been conducted on various adenoviruses. The pathogenic characteristics and respiratory infection symptoms caused by different adenovirus serotypes were recognized [15,16]. Subsequently, many studies have been conducted on the seroprevalence of several adenoviruses [17,18]. One study used a neutralization assay to analyse 33 adenoviruses, including Ad1 to Ad33. It was found that 74.6% of the population were positive for at least one adenovirus. The highest seroprevalence was Ad2, 41.5%, followed by Ad5, lower than 35%[19]. However, studies performed in recent years showed that the seroprevalence of Ad2 and Ad5 is much higher, ranging from 62.0% to 73.0% [20–22]. Preexisting immunity against adenoviruses includes humoral, cellular, and innate immune responses, such as neutralizing antibodies (nAbs), specific T cells, and type I IFN-activated NK cells [23]. Preexisting antibodies against adenoviruses are generally believed to be the most important factor affecting infection. Common serotypes such as Ad2, Ad5, and Ad6 typically have higher preexisting antibodies than the rare serotypes Ad26 and Ad35 and species B adenoviruses such as Ad7, Ad14, and Ad55 [24]. This article summarizes the seroprevalence of human adenoviruses and simian adenoviruses reported in the literature since 2000 to provide a comprehensive overview to support the application of adenovirus vectors.

The seroprevalence of adenoviruses

The seroprevalence of common serotype adenoviruses

Several adenoviruses have been widely employed as vaccines and gene therapy vectors. Currently, Ad2 [21,25], Ad4 [26], Ad5 [27], Ad26 [28], Ad35 [29], chimpanzee adenovirus type 7 [30], type 68 [31] and chimpanzee adenovirus type Y25 (ChAdOx1) [32] have been exploited as vectors, and some of them have even been used as COVID-19 vaccines in several hundred million people[33].

To support the development and application of adenovirus vectors, researchers have investigated the seroprevalence of several adenoviruses in the past 20 years. Ad5 is the most mature and widely used adenovirus, and its seroprevalence is the most extensively studied. In the study of Ad5 seroprevalence, the survey area included many countries in Africa, America, Asia, Europe, and other regions [34,35]. The survey population included children, teenagers, adults, the elderly, healthy people, HIV patients, hepatitis B patients, cancer patients, and so on [36,37]. By summarizing the Ad5 seroprevalence reported in the literature since 2000, we found that the median Ad5 seroprevalence is generally high, reaching 69.3% (interquartile range, IQR 54.9–84.5%) (Table 1) around the world, and most of the research results

Table 1. The median seroprevalence of different types of human and Chimpanzee adenoviruses worldwide. (IQR: interquartile range).

Adenovirus	median seroprevalence (%)	interquartile range (%)
Ad1	55.0	35.1–65.0
Ad2	61.0	52.0–75.5
Ad3	61.5	39.1–79.0
Ad4	50.2	25.5–61.3
Ad5	69.3	54.9–84.5
Ad6	44.0	20.0–66.7
Ad7	26.0	13.1–44.0
Ad8	26.4	26.4–26.4
Ad11	18.0	6.3–26.0
Ad14	24.8	17.0–48.0
Ad24	10.0	10.0–10.0
Ad26	44.0	18.0–65.4
Ad28	17.0	6.0–58.0
Ad31	73.0	73.0–73.0
Ad34	2.0	2.0–2.0
Ad35	8.4	3.3–17.1
Ad36	34.7	24.7–63.0
Ad41	94.0	73.5–94.7
Ad43	4.0	4.0–4.0
Ad48	10.8	6.3–16.4
Ad49	9.0	7.5–21.2
Ad50	10.8	7.4–14.9
Ad55	19.8	13.2–28.2
Ad56	56.0	56.0–56.0
Ad58	0.0	0.0–0.0
ChAd1	4.0	2.5–7.4
ChAd6	11.8	8.1–20.4
ChAd7	13.1	12.9–17.2
ChAd24	45.0	45.0–45.0
ChAd63	22.1	20.0–24.3
ChAd68	10.2	5.2–22.7
ChAdY25	4.5	2.3–6.8

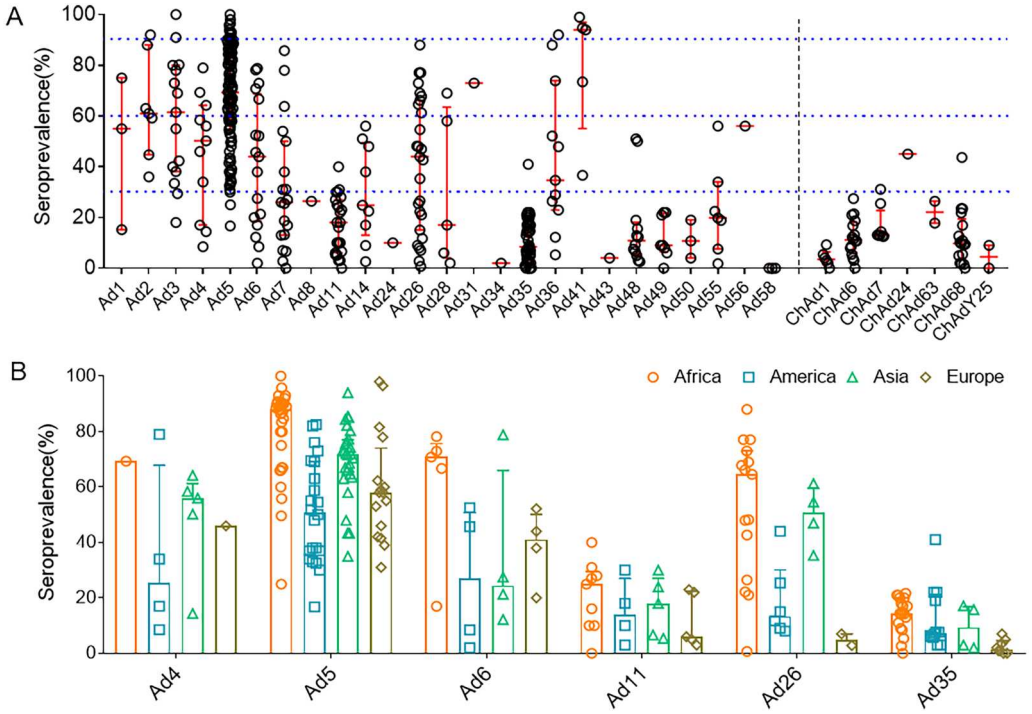

Figure 1. Seroprevalence of adenoviruses. (A) Seroprevalence of 25 human adenoviruses and 7 chimpanzee adenoviruses. We collected and summarized the results of adenovirus seroprevalence surveys in the human population reported since 2000. Each dot represents adenovirus seroprevalence within a survey. (B) Seroprevalence of 6 adenoviruses in different regions.

were between 58% to 92%. Serum samples obtained from infants aged 0–3 years showed Ad5 seroprevalence of less than 50%. There are few studies on the seroprevalence of Ad2 and Ad6 [21,24], which also belong to the species C. We analysed the epidemiological data published since 2000 and found that the median seroprevalence to Ad2 was 61.0% (IQR: 52.0–75.5%), slightly lower than Ad5 (Table 1). The median seroprevalence of Ad6 is 44.0% (IQR 20.0–66.7%), which was lower than Ad2 and Ad5 (Figure 1(A)). The seroprevalence of adenovirus in species C, commonly used as vaccine and gene therapy vectors, is higher than that of other species.

We conducted a statistical analysis to provide a reference for the use of adenovirus vectors in different regions. We found that the median seroprevalence of Ad5 in Africa is the highest (Figure 1(B)), reaching 87.9% (IQR 73.0–90.0%), followed by Asia, reaching 71.8% (IQR 64.5–76.7%) (Table 2), while the median seroprevalence of Ad5 is 50.9% (IQR 37.0–67.6%) and 58.0% (IQR 45.0–66.2%) in America and Europe, respectively. The seroprevalence of Ad5 in developing countries is significantly higher than in developed countries [24,34,38].

Serum-neutralizing antibodies are the main factor affecting the use of adenoviruses as vectors. Therefore, determining neutralizing antibody titres (NATs) is particularly important. Our analysis found that Ad5 NATs were more evenly distributed among the low-, mid-, and high-titres (titres <200, 200–1000, and >1000) in the populations (Figure 2(A, B)). Although Ad5 NATs were detected at all ranges of dilutions, the median seropositivity in the mid-and high-titre range (titres 201–1000 and >1000) was 27.2% (IQR 16.8–37.79%) and 26.2% (IQR 14.6–37.8%) (Table 3), respectively. The Ad5 NATs in the low titres (titres: 18–200) was 20.3% (IQR 14.0–26.9%). It has been considered that in the middle and high NATs populations, adenoviral vectors could be less effective. Interestingly, Ad6, which belongs to the species C, is quite different. There were few people with NATs in the high titres of >1000, accounting for only 4.1% (IQR 0–6.3%), which was significantly less than that of Ad5 (Figure 2(A,B), Table 3). The proportion of Ad6 NATs population in the low titres (titres: 18–200) accounted for the vast majority, suggesting that Ad6 may be able to serve as an alternative vector for other species C adenoviruses such as Ad2 and Ad5.

The seroprevalence of rare serotype adenoviruses

Due to the high prevalence of preexisting antibodies against commonly used adenoviral vectors such as Ad2 and Ad5, rare serotype adenoviruses have been attempted to develop as vectors since the 1990s. Meanwhile, the seroprevalence of rare serotype adenoviruses has also been studied. Among them, Ad26 and Ad35 are the most well-studied [24,34,38–42]. We summarized all analyses of seroprevalence across South America, North America, Europe, Asia, and Africa. The result showed that the median

Table 2. The median seroprevalence of multiple types of human adenoviruses in different continents. (IQR: interquartile range).

Adenovirus	Seroprevalence	America	Europe	Asia	Africa
Ad4	median(%)	25.5	46	56	69.3
	IQR(%)	14.9–45.3	46.0–46.0	50.2–58.4	69.3–69.3
Ad5	median(%)	50.9	58	71.8	87.9
	IQR(%)	37.0–67.6	45.0–66.2	64.5–76.7	73.0–90.0
Ad6	median(%)	27.1	41	24.4	70.8
	IQR(%)	6.8–47.4	33.5–46.1	19.0–40.3	66.7–79.2
Ad11	median(%)	14.0	6.0	18.0	25.0
	IQR(%)	8.3–21.0	5.1–22.0	6.6–24.0	10.0–28.0
Ad26	median(%)	13.35	4.9	50.8	64.6
	IQR(%)	9.7–22.8	3.9–6.0	44.1–56.3	34.6–71.0
Ad35	median(%)	7.3	1.5	9.4	14.4
	IQR(%)	5.9–19.9	0.7–3.9	2.8–16.1	10.0–19.0

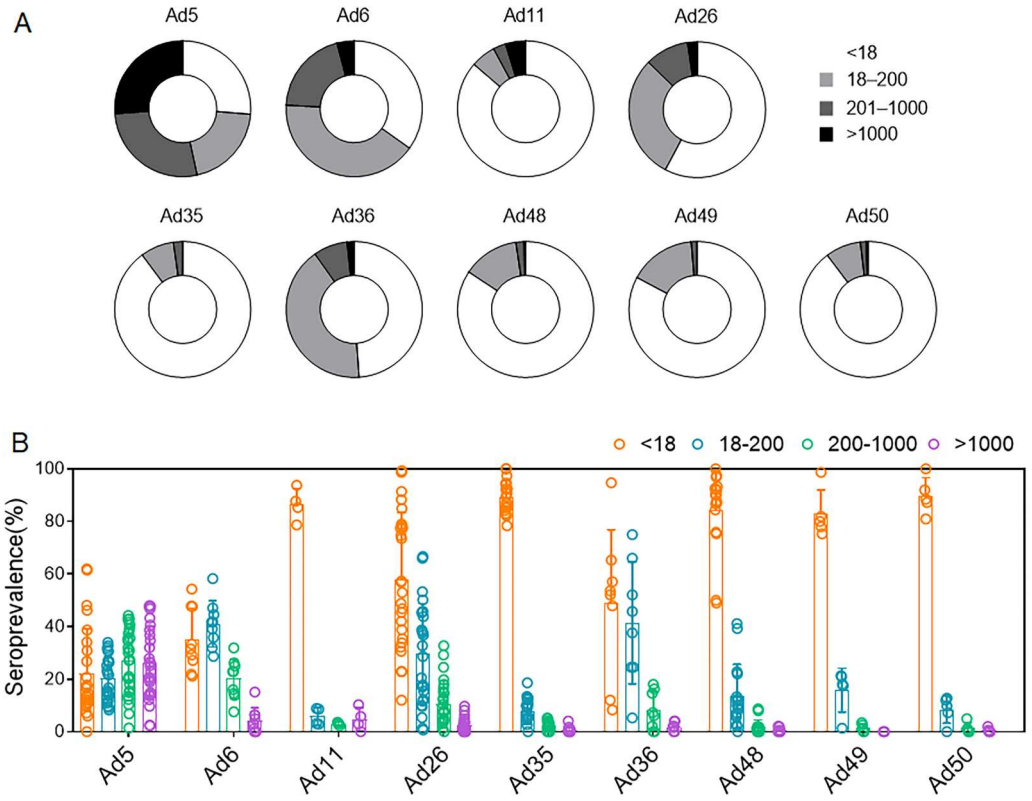

Figure 2. Contribution of different adenovirus neutralizing antibody titres (NATs). (A, B) Serum NATs distribution of adenovirus vectors of different serotypes in the population. The distribution of serum NATs of 9 human adenoviruses reported since 2000 were summarized. NATs ranged are: negative (<18), low (18–200), moderate (200–1000) and high (>1000).

Table 3. Serum neutralizing antibody titres distribution of different types adenovirus vectors in the population. Mean seroprevalence %.

Adenovirus	<18	18–200	201–1000	>1000
Ad5	26.3	20.3	27.2	26.2
Ad6	34.9	41.0	20.1	4.1
Ad11	86.4	5.9	3.0	4.8
Ad26	57.8	29.6	10.4	2.3
Ad35	89.2	7.9	2.2	0.6
Ad36	48.9	41.4	8.1	1.7
Ad48	84.3	13.4	1.9	0.4
Ad49	82.8	15.8	1.4	0.0
Ad50	89.7	8.4	1.4	0.5

seroprevalence of Ad26 was 44.0% (IQR 18.0–65.4%), whereas the median seroprevalence of Ad35 was only 8.4% (IQR 3.3–17.1%) (Figure 1A, Table 1), which was significantly lower than that of Ad5. In published research reports, the seroprevalence of Ad35 is mostly below 20%, while Ad26 spans a wide range from 10% to 70%. There are two main factors contributing to this situation. The first is the regional difference. The antibody levels in sub-Saharan African countries are significantly higher than those in Europe and the United States [34,40,41]. Second, the age distribution of the tested population varied, and the seroprevalence of young children was significantly lower than that of adults [40]. The seroprevalence of Ad26 varies greatly between developed and developing countries, while the seroprevalence of Ad35 is relatively low globally. The Ad26 seroprevalence in the United States and Europe is low, at 13.35% (IQR 9.7–22.8%) and 4.9% (IQR 3.9–6.0%), respectively. The Ad26 seroprevalence is high in Asia and Africa, at 50.8% (IQR 44.1–

56.3%) and 64.6% (IQR 34.6–71.0%), respectively (Figure 1(B), Table 2). For Ad35, the seroprevalence is low, less than 15% globally (supplementary Table 1). Ad35 has not yet established broad herd immunity and has the potential to become a widely used adenoviral vector.

We further analysed serum NATs of Ad26 and Ad35 in China. We found that Ad26 NAT is concentrated in the low titres of 18–200, accounting for 29.6% (IQR 13.1–44.9%) (Table 3), while Ad26 NAT in high titres (>1000) was also only 2.3%. Ad35 NAT in high (>1000) and medium (200–1000) titres were only 0.6% and 2.2%, and in the low titres (18–200) was only 7.9% (Figure 2(A,B), Table 3). This result suggests that Ad35 may be a more suitable candidate vector than Ad26. Compared with Ad5 and Ad6, Ad35 and Ad26 have a lower proportion of high-titre neutralizing antibodies (Figure 2(A,B)), suggesting Ad35 and Ad26 may be more useful as vectors.

Several other rare serotype adenoviruses have also been attempted as vectors, and the seroprevalence has been studied [43,44]. The median seroprevalence was 10.0% (IQR 10.0–10.0%) for Ad24, 17.0% (IQR 6.0–58.0%) for Ad28, 10.8% (IQR 6.3–16.4%) for Ad48, 9.0% (IQR 7.5–21.2%) for Ad49, and 10.8% (IQR 7.4–14.9%) for Ad50 (Figure 1, Table 1). There are almost no high NATs (>1000) and only about 10% of the low NATs (18–200) of Ad48, Ad49, and Ad50 (Figure 2(A,B), Table 3). These findings suggested that lower herd immunity of these adenoviruses may offer good potential for vector development.

Interestingly, there is a correlation between Ad36 seroprevalence and obesity [24,45]. Statistical analysis showed that the median seroprevalence of Ad36 was 34.7% (IQR 24.7–63.0%). The Ad36 NAT was concentrated in the low titres of 18–200, accounting for 41.4% (IQR 24.5–55.6%) (Figure 2(A,B), Table 3). The seroprevalence of Ad36 is significantly higher in obese individuals [46,47]. The underlying mechanism should be investigated before Ad36 can be considered for development as a vector. For example, the E4 orf-1 gene should be deleted since it regulates the adipogenic cascade and induces fat production [48,49].

The seroprevalence of highly pathogenic adenoviruses

Species B and E adenovirus often cause respiratory infections, severe pneumonia, and even death. The main pathogenic serotypes are Ad3, Ad4, Ad7, Ad11, Ad14 and Ad55. Ad3 and Ad7 are widespread in children, causing acute respiratory infection and even death [50,51], while Ad55 often occurs in adults and leads to severe pneumonia [52]. There were serious outbreaks of Ad4 and Ad7 in the U.S. military after discontinuing the bivalent Ad4 and Ad7 vaccines, leading to the resume of this orally administered vaccine based on replication-competent wild-type viruses [53]. There is an unmet medical need to develop preventive and therapeutic measures for these highly pathogenic adenoviruses. Studies showed that the seroprevalence of Ad3 and Ad4 was higher than that of other adenoviruses, such as Ad7, Ad11, Ad14, and Ad55 (Figure 1(A), Table 1). Since 2000, Ad3 seroprevalence studies have included North American, European, and Asian populations (Supplementary Table 1), which showed that the median seroprevalence of Ad3 was 61.5% (IQR 39.1–79.0%). The median seroprevalence of Ad4 in North American and Asian adults was 50.2% (IQR 25.5–61.3%). The median seroprevalence of Ad7, Ad11, Ad14, and Ad55 was 26.0% (IQR 13.1–44.0%), 18.0% (IQR 6.3–26.0%), 24.8% (IQR 17.0–48.0%), and 19.8% (IQR: 13.2–28.2%) (Figure 1(A), Table 1), respectively. The median seroprevalence of Ad7, Ad11, Ad14, and Ad55 was at lower levels, suggesting that these adenoviruses could cause an epidemic. However, these reports only represented a designated region. The epidemiology of species B adenoviruses in other regions requires further investigation. Ad11 of species B adenovirus has also been explored as a vector. The distribution of serum NAT at low, medium, and high titres of Ad11 was relatively comparable and was below 30%. Seroprevalence of Ad11 was lower in European and American countries than in African countries [54].

Species F adenoviruses can typically cause gastrointestinal illnesses such as diarrhoea. However, serological studies of these adenoviruses are rare. Only a few papers have reported the seroprevalence of Ad41, with the median seroprevalence being as high as 94% (IQR 73.5–94.7%) in the Americas and Asia (Table 1, Supplementary Table 1). This may be because the samples were taken from immunocompromised individuals and may not reflect the actual situation in the population, which needs to be studied in healthy individuals.

The seroprevalence of non-human primate adenoviruses

In order to circumvent the preexisting immunity against common human adenoviruses for vector applications, a variety of non-human adenoviral vectors have been developed, such as bovine adenoviruses [55], canine adenoviruses [56] and chimpanzee adenoviruses [57]. Chimpanzee adenoviruses exhibit a high similarity to human adenoviruses, which has facilitated the more extensive development and utilization of chimpanzee adenoviral vectors, such as ChAd6, ChAd7, ChAd24, ChAd63, ChAd68 and ChAdY25. Since 2000, several population-based serological surveys for chimpanzee adenoviruses have been

conducted, with the results indicating the presence of neutralizing antibodies against these adenoviruses in the sera of a subset of the population. For example, antibody-positive sera for ChAd6, ChAd7, ChAd24, ChAd63, ChAd68, and ChAdY25 (ChAdOx1) were detected in the population, albeit at low levels, with a seroprevalence below 30% (Figure 1(A), table 1).

The seroprevalence of chimpanzee adenoviruses exhibited notable differences. The median seroprevalence of ChAd63 was 22.1% (IQR: 20.0–24.3%) in Kenyan healthy children, which was higher than that of ChAd6, ChAd7, ChAd68 and ChAdOx1 (Figure 1(A), Table 1). The median seroprevalence of ChAd1 was 4.0% (IQR 2.5–7.4%), which was significantly lower than that of ChAd6 (11.8%, IQR: 8.1–20.4), ChAd7 (13.1%, IQR: 12.9–17.2%) and ChAd68 (10.2%, IQR: 5.2–22.7%) (Figure 1(A), Table 1).

Further serological studies on chimpanzee adenoviruses revealed significant differences from the human Ad5 vector. For example, the seroprevalence of ChAd63 was only 4% among malaria patients, whereas the prevalence of Ad5 neutralizing antibodies in the same population was 23% [58]. The serum antibody titre to ChAd63 was found to be 1:139 in adults and 1:35 in children [59]. Additionally, some studies have examined the discrepancy between Ad5 and ChAd68 seroprevalence in healthy individuals and tumour patients. The findings indicate that Ad5 (71.57 vs 67.05%) is significantly higher than ChAd68 (23.53 vs 43.64%) [22]. The seroprevalence of ChAd68 in tumour patients was 43.64%, considerably higher than that in healthy people (23.53%) [22]. The adenovirus-vectored vaccine developed by AstraZeneca for treating SARS-CoV-2 infection uses the ChAdOx1 vector. The seroprevalence is 0% in the United Kingdom and 9% in The Gambia [60]. With the widespread use of vaccines, the seroprevalence of ChAdOx1 will increase.

The preclinical evaluation of adenoviral vectored vaccines employs rodents and non-human primates as animal models. However, neutralizing antibodies against adenoviruses in animals may impact the efficacy of adenoviral vectors. For instance, the seroprevalence of human Ad5 in marmosets was 28.6% [61]. Consequently, assessing the neutralizing antibodies in animal models corresponding to the adenovirus is important before initiating preclinical studies.

Factors influencing the seroprevalence of adenoviruses

Geographic region, age, and living environment

The prevalence of adenovirus antibodies is primarily influenced by three key factors: geographic region, age, and living environment. A given region's sanitary conditions and climate may vary considerably from one area to another. Some of the developing countries in Africa are characterized by having a warm and humid climate and poor hygienic conditions. Consequently, those at risk of infection are more likely to become infected with adenovirus, resulting in a higher level of herd immunity than in developed countries in Europe and the United States [24,38,41]. A study was conducted on adenovirus antibodies in children residing in urban and rural areas within the same region. The study demonstrated that the seroprevalence of urban children was 8-15%, whereas the seroprevalence of rural children during the same period was 62%. A further study demonstrated a similar pattern in Ad41 seroprevalence. The seroprevalence of children from urban, suburban, and rural areas was 22%, 47%, and 88%, respectively [20]. It has been demonstrated that an improvement in sanitary conditions is associated with a reduction in the prevalence of Ad5 in children. Furthermore, some studies have indicated that the seroprevalence of adenovirus exhibits seasonal variation in different geographical regions, with higher prevalence observed in the northern hemisphere during the winter months compared to the summer months in the southern hemisphere. The age of the subject has a more pronounced effect on adenovirus seroprevalence. As age increases, the probability of exposure to pathogens rises, accompanied by a notable increase in antibody positivity rates [62,63]. Several studies have demonstrated a positive correlation between the seroprevalence of different adenoviruses and age.

The randomness of sample sources

The randomness and representativeness of sample sources and the occupation may result in discrepancies in adenovirus seroprevalence testing. Most studies have demonstrated that gender, race, blood type, and health status do not influence the seroprevalence of adenovirus. For example, multiple studies have confirmed that in patients with HIV and chronic hepatitis, the seroprevalence of Ad5 is similar to that of healthy individuals [36,37]. Nevertheless, some studies have indicated that the seroprevalence of AdC68 was markedly elevated in certain tumour patients compared to that observed in healthy individuals [22]. Furthermore, studies have suggested that the seroprevalence of AdC63 in children is notably low, at only 4%. As a comparison, the seroprevalence of Ad5 in the same population is 23% [58,59], and the neutralizing antibody (NAb) titres of AdC63 in children are significantly lower than those in adults. Furthermore, as new adenovirus genotypes are isolated and identified, research on the seroprevalence of these new adenoviruses should be continued.

Detection methods

Another factor contributing to discrepancies in the study of adenovirus seroprevalence is the methodology employed for the measurement of antibodies. Since the twenty-first century, micro-neutralization (MN) assay (A highly sensitive and specific test for detecting virus-specific neutralizing antibodies) has become the predominant method for detecting adenovirus antibodies. However, different detection methods employ distinct protocols and standards for IC50 or IC90 (the concentration of drug required for 50% or 90% inhibition). The sensitivity of the various detection methods differs. Earlier studies mainly used cytopathic effect (CPE) or CPE combined with enzyme-linked immunosorbent assay (ELISA) to determine IC50 or IC90. Recent studies have used recombinant adenovirus carrying green fluorescent protein (GFP), secretory alkaline phosphatase (SEAP), or luciferase reporter genes to detect and calculate IC50 or IC90 by inhibiting the expression of the reporter gene [64–66]. Furthermore, different laboratories utilize disparate cells for testing, resulting in inconsistent judgment criteria. MN assays based on SEAP or luciferase-expressing adenoviral vectors have been reported to be more sensitive and objective than previously used CPE-based methods.

Strategies to address adenovirus seroprevalence

Development of alternative serotype or epitope chimeric adenoviral vectors

Seroprevalence surveys detect serum neutralizing antibodies against adenovirus in the population, which are also preexisting antibodies. The presence of neutralizing antibodies against Ad5 and other commonly used adenoviral vectors, either preexisting due to natural infection or following a single administration of vectored vaccines or gene therapy, is inevitable. This may be an important factor limiting the effectiveness of adenoviral vector applications. Therefore, how can the influence of pre-existing neutralizing antibodies against adenoviral vectors be circumvented? A common approach is to develop alternative rare serotype adenoviral vectors [38,41,67,68]. For example, to circumvent the high levels of Ad5-neutralizing antibodies in the population, Ad26 and Ad35 have been developed as vectors and used in humans [69,70]. As neutralizing antibodies against these adenoviruses increase after their application, the development of more new adenoviral vectors can be considered.

The adenovirus capsid protein hexon's hypervariable region (HVR) is the primary epitope for neutralizing antibodies [71–73]. Studies have also pointed out differences in recognizing epitopes by antibodies induced by natural infection and vaccine immunization. In natural infection, it is easier to induce antibodies against fibre, whereas vaccine immunization mainly induces neutralizing antibodies against hexon [74,75]. Therefore, another strategy to circumvent preexisting antibodies is to replace the Hexon HVR or Fiber knobs of rare serotypes and construct chimeric adenovirus vectors with the replacement of neutralizing epitopes [76,77]. For example, a chimeric rAd5 vector, in which the seven short hypervariable regions (HVRs) on the surface of the Ad5 hexon protein were replaced by the corresponding HVRs from the rare adenovirus serotype Ad48 [77]. In the presence of high levels of preexisting anti-Ad5 immunity, the immunogenicity of the HVR chimeric rAd5 vector was not detected to be suppressed, while the immunogenicity of the parental Ad5 vector was abolished. Ad5F35, which is a fibre that transforms the commonly used Ad5 vector into Ad35 fiber, which can avoid the influence of preexisting antibodies against Ad5 fibre [78]. But this approach can also quickly induce herd immunity against rare serotypes.

Immunization strategies

Other strategies for circumventing the preexisting antibodies include altering the immunization route or increasing the immunization dose. These strategies aim to overpower the local presence of neutralizing antibodies. For example, local administration of high-dose adenovirus may achieve breakthrough infection. In recent years, researchers have also tried to coat the adenoviral vector particles with materials for in vivo delivery to circumvent the impact of preexisting antibodies [79,80]. More effective methods to breakthrough the effect of neutralizing antibodies against adenovirus need to be further developed.

Since the outbreak of COVID-19, adenoviral vectored vaccines have become a key strategy in preventing the pandemic. Clinical studies using human Ad5, Ad26, and ChAdOx1 (ChAdY25) were conducted. Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare adverse reaction to adenovirus vectored vaccines [81], which was found in vaccinees injected with Ad26.COV2.S [82] or ChAdOx1 nCov-19 [83], but not Ad5 vectored vaccines. This may be related to the higher seroprevalence of Ad5 neutralizing antibodies, which neutralize Ad5 vaccines that leak into the bloodstream, thus preventing VITT. Therefore, neutralizing antibodies against an adenovirus may provide some safety assurance to adenovirus-based applications.

Conclusions

Since the discovery of adenovirus in 1953, extensive research has been conducted on the biological properties of adenovirus and the development of adenovirus-

based applications. Current research on adenovirus seroprevalence included commonly used serotypes such as Ad2 and Ad5, rare serotypes such as Ad26, Ad35, and Ad48, pathogenic adenoviruses such as Ad3, Ad7, Ad11, and Ad55, and chimpanzee adenoviruses such as ChAd6 and ChAd68 et al. Ad5 showed the highest seroprevalence, which may be related to the high infection rate of Ad5. With the use of adenovirus vectored vaccines, the level of herd immunity for the corresponding adenovirus may increase. New vectors or methods need to be developed to circumvent neutralizing antibodies. New adenoviruses are constantly being isolated and identified, providing researchers with more vector options. The seroprevalence of newly discovered adenoviruses should also be investigated to avoid cross-neutralizing antibodies influence of adenoviruses due to recombination.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Natural Science Foundation of China [grant number 32200759], the Guangdong Science and Technology Department [grant number 2022A1515012002, 2021A1515110549], the Open Fund from the State Key Laboratory of Respiratory Disease [grant number SKLRD-Z-202109], and the China Postdoctoral Science Foundation [grant number 2020M682942], Guangzhou Health Science and Technology Project [grant number 20231A011117], and the Construction of Major Subject of Huadu District People's Hospital of Guangzhou [grant number YNZDXK202202, 2022-2025].

Author contributions

Conceptualization (L.C. and Y.F.), writing and editing (Y.F., L.C., J.L, H.L, and W.Z), and funding acquisition (Y.F., H.L). Others (S.Z and Y.L). All authors have read and agreed to the published version of the manuscript.

References

[1] Fattouh R, Stapleton PJ, Eshaghi A, et al. A prolonged outbreak of human adenovirus A31 (HAdV-A31) infection on a pediatric hematopoietic stem cell transplantation ward with whole genome sequencing evidence of international linkages. J Clin Microbiol. 2022;60(11):e0066522, doi:10.1128/jcm.00665-22

[2] Cao B, Huang GH, Pu ZH, et al. Emergence of community-acquired adenovirus type 55 as a cause of community-onset pneumonia. Chest. 2014;145(1):79–86. doi:10.1378/chest.13-1186

[3] Bhatti Z, Dhamoon A. Fatal adenovirus infection in an immunocompetent host. Am J Emerg Med. 2017;35(7):1034.e1–1034.e2. doi:10.1016/j.ajem.2017.02.008

[4] Van Gelder RN, Akileswaran L, Nakamichi K, et al. Molecular and clinical characterization of human adenovirus E4-associated conjunctivitis. Am J Ophthalmol. 2022;233:227–242. doi:10.1016/j.ajo.2021.10.028

[5] Miro E, Del Cuerpo M, Rubio M, et al. Whole-genome analysis to describe a human adenovirus D8 conjunctivitis outbreak in a tertiary hospital. J Med Virol. 2021;93(8):4840–4845. doi:10.1002/jmv.26850

[6] Lee J, Bilonick RA, Romanowski EG, et al. Seasonal variation in human adenovirus conjunctivitis: A 30-year observational study. Ophthalmic Epidemiol. 2018;25(5–6):451–456. doi:10.1080/09286586.2018.1509096

[7] Doerfler W. Epigenetic mechanisms in human adenovirus type 12 oncogenesis. Semin Cancer Biol. 2009;19(3):136–143. doi:10.1016/j.semcancer.2009.02.009

[8] Graham FL. Adenoviruses as expression vectors and recombinant vaccines. Trends Biotechnol. 1990;8(4):85–87. doi:10.1016/0167-7799(90)90144-m

[9] Ono R, Nishimae F, Wakida T, et al. Effects of preexisting anti-adenovirus antibodies on transgene expression levels and therapeutic efficacies of arming oncolytic adenovirus. Sci Rep. 2022;12(1):21560, doi:10.1038/s41598-022-26030-3

[10] Sumida SM, Truitt DM, Lemckert AA, et al. Neutralizing antibodies to adenovirus serotype 5 vaccine vectors are directed primarily against the adenovirus hexon protein. J Immunol. 2005;174(11):7179–7185. doi:10.4049/jimmunol.174.11.7179

[11] Feng Y, Sun X, Ye X, et al. Hexon and fiber of adenovirus type 14 and 55 are major targets of neutralizing antibody but only fiber-specific antibody contributes to cross-neutralizing activity. Virology. 2018;518:272–283. doi:10.1016/j.virol.2018.03.002

[12] Burckhardt CJ, Suomalainen M, Schoenenberger P, et al. Drifting motions of the adenovirus receptor CAR and immobile integrins initiate virus uncoating and membrane lytic protein exposure. Cell Host Microbe. 2011;10(2):105–117. doi:10.1016/j.chom.2011.07.006

[13] Liu X, Li Z, Li X, et al. Neutralizing monoclonal antibodies protect against human adenovirus type 55 infection in transgenic mice and tree shrews. Emerg Microbes Infect. 2024;13(1):2307513, doi:10.1080/22221751.2024.2307513

[14] Smith JG, Cassany A, Gerace L, et al. Neutralizing antibody blocks adenovirus infection by arresting microtubule-dependent cytoplasmic transport. J Virol. 2008;82(13):6492–6500. doi:10.1128/jvi.00557-08

[15] Brandt CD, Kim HW, Jeffries BC, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease. II. Variation in adenovirus infections by year and season. Am J Epidemiol. 1972;95(3):218–227. doi:10.1093/oxfordjournals.aje.a121389

[16] Schmitz H, Wigand R, Heinrich W. Worldwide epidemiology of human adenovirus infections. Am J Epidemiol. 1983;117(4):455–466. doi:10.1093/oxfordjournals.aje.a113563

[17] Mennechet FJD, Paris O, Ouoba AR, et al. A review of 65 years of human adenovirus seroprevalence. Expert Rev Vaccines. 2019;18(6):597–613. doi:10.1080/14760584.2019.1588113

[18] Aoki K, Sawada H. [Seroepidemiological study of conjunctivitis related adenoviruses]. Nippon Ganka Gakkai Zasshi. 1987;91(2):181–186.

[19] D'Ambrosio E, Del Grosso N, Chicca A, et al. Neutralizing antibodies against 33 human adenoviruses in normal children in Rome. J Hyg (Lond). 1982;89(1):155–161. doi:10.1017/s0022172400070650
[20] Yang WX, Zou XH, Jiang SY, et al., prevalence of serum neutralizing antibodies to adenovirus type 5 (Ad5) and 41 (Ad41) in children is associated with age and sanitary conditions. Vaccine. 2016;34(46):5579–5586. doi:10.1016/j.vaccine.2016.09.043
[21] Li Q, Liu Q, Huang W, et al. Neutralizing antibodies against adenovirus type 2 in normal and HIV-1-infected subjects: implications for use of Ad2 vectors in vaccines. Hum Vaccin Immunother. 2017;13(6):1–8. doi:10.1080/21645515.2017.1281487
[22] Zhao H, Xu C, Luo X, et al. Seroprevalence of neutralizing antibodies against human adenovirus type-5 and chimpanzee adenovirus type-68 in cancer patients. Front Immunol. 2018;9:335, doi:10.3389/fimmu.2018.00335
[23] Fausther-Bovendo H, Kobinger GP. Preexisting immunity against Ad vectors: humoral, cellular, and innate response, what's important? Hum Vaccin Immunother. 2014;10(10):2875–2884. doi:10.4161/hv.29594
[24] Mast TC, Kierstead L, Gupta SB, et al. International epidemiology of human preexisting adenovirus (Ad) type-5, type-6, type-26 and type-36 neutralizing antibodies: correlates of high Ad5 titers and implications for potential HIV vaccine trials. Vaccine. 2010;28(4):950–957. doi:10.1016/j.vaccine.2009.10.145
[25] Feng Y, Li C, Hu P, et al. An adenovirus serotype 2-vectored ebolavirus vaccine generates robust antibody and cell-mediated immune responses in mice and rhesus macaques. Emerg Microbes Infect. 2018;7(1):101, doi:10.1038/s41426-018-0102-5
[26] Bullard BL, Corder BN, Gorman MJ, et al. Efficacy of a T cell-biased adenovirus vector as a Zika virus vaccine. Sci Rep. 2018;8(1):18017, doi:10.1038/s41598-018-35755-z
[27] Ura T, Yoshida A, Xin KQ, et al. Designed recombinant adenovirus type 5 vector induced envelope-specific CD8(+) cytotoxic T lymphocytes and cross-reactive neutralizing antibodies against human immunodeficiency virus type 1. J Gene Med. 2009;11(2):139–149. doi:10.1002/jgm.1277
[28] Majhen D. Human adenovirus type 26 basic biology and its usage as vaccine vector. Rev Med Virol. 2022;32(6):e2338, doi:10.1002/rmv.2338
[29] Gao W, Robbins PD, Gambotto A. Human adenovirus type 35: nucleotide sequence and vector development. Gene Ther. 2003;10(23):1941–1949. doi:10.1038/sj.gt.3302097
[30] Xu K, An Y, Li Q, et al. Recombinant chimpanzee adenovirus AdC7 expressing dimeric tandem-repeat spike protein RBD protects mice against COVID-19. Emerg Microbes Infect. 2021;10(1):1574–1588. doi:10.1080/22221751.2021.1959270
[31] Li M, Guo J, Lu S, et al. Single-dose immunization with a chimpanzee adenovirus-based vaccine induces sustained and protective immunity against SARS-CoV-2 infection. Front Immunol. 2021;12:697074, doi:10.3389/fimmu.2021.697074
[32] Folegatti PM, Jenkin D, Morris S, et al. Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: standardized template with key considerations for a risk/benefit assessment. Vaccine. 2022;40(35):5248–5262. doi:10.1016/j.vaccine.2022.06.008
[33] Sadoff J, Gray G, Vandebosch A, et al. Final analysis of efficacy and safety of single-dose Ad26.CO(V2).S. N Engl J Med. 2022;386(9):847–860. doi:10.1056/NEJMoa2117608
[34] Nwanegbo E, Vardas E, Gao W, et al., prevalence of neutralizing antibodies to adenoviral serotypes 5 and 35 in the adult populations of The Gambia, South Africa, and the United States. Clin Diagn Lab Immunol. 2004;11(2):351–357. doi:10.1128/cdli.11.2.351-357.2004
[35] Francisco AG, Reyes JCB, Tabios IKB, et al. Seroprevalence of human adenovirus type 5 neutralizing antibodies in the Philippines. PLoS One. 2023;18(12):e0293046, doi:10.1371/journal.pone.0293046
[36] Sun C, Zhang Y, Feng L, et al. Epidemiology of adenovirus type 5 neutralizing antibodies in healthy people and AIDS patients in Guangzhou, southern China. Vaccine. 2011;29(22):3837–3841. doi:10.1016/j.vaccine.2011.03.042
[37] Huang D, Hennequi M, Elvachev A, et al. The seroprevalence of anti-adenovirus 5 neutralizing antibodies is independent of a chronic hepatitis B carrier state in China. Arch Virol. 2015;160(4):1125–1130. doi:10.1007/s00705-015-2333-2
[38] Barouch DH, Kik SV, Weverling GJ, et al. International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. Vaccine. 2011;29(32):5203–5209. doi:10.1016/j.vaccine.2011.05.025
[39] Kostense S, Koudstaal W, Sprangers M, et al. Adenovirus types 5 and 35 seroprevalence in AIDS risk groups supports type 35 as a vaccine vector. AIDS. 2004;18(8):1213–1216. doi:10.1097/00002030-200405210-00019
[40] Thorner AR, Vogels R, Kaspers J, et al. Age dependence of adenovirus-specific neutralizing antibody titers in individuals from sub-Saharan Africa. J Clin Microbiol. 2006;44(10):3781–3783. doi:10.1128/JCM.01249-06
[41] Abbink P, Lemckert AA, Ewald BA, et al. Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D. J Virol. 2007;81(9):4654–4663. doi:10.1128/JVI.02696-06
[42] Zhang S, Huang W, Zhou X, et al., seroprevalence of neutralizing antibodies to human adenoviruses type-5 and type-26 and chimpanzee adenovirus type-68 in healthy Chinese adults. J Med Virol. 2013;85(6):1077–1084. doi:10.1002/jmv.23546
[43] Emini Emilio A, Shiver John W, Bett Andrew J, et al. Adenovirus serotype 24 vectors, nucleic acids and virus produced thereby. 2003, EMINI EMILIO A.
[44] Farrow AL, Peng BJ, Gu L, et al. A novel vaccine approach for chagas disease using rare adenovirus serotype 48 vectors. Viruses. 2016;8(3):78, doi:10.3390/v8030078
[45] Atkinson RL. Prevalence of infection with adenovirus-36 in Belgium and holland and association with obesity. Obesity (Silver Spring). 2011;19(1):2; author reply 3, doi:10.1038/oby.2010.107
[46] Cancelier ACL, Rezin GT, Fernandes J, et al. Adenovirus-36 as one of the causes of obesity: the review of the pathophysiology. Nutr Res. 2021;86:60–67. doi:10.1016/j.nutres.2020.12.004

[47] Shang Q, Wang H, Song Y, et al. Serological data analyses show that adenovirus 36 infection is associated with obesity: a meta-analysis involving 5739 subjects. Obesity (Silver Spring). 2014;22(3):895–900. doi:10.1002/oby.20533
[48] da Silva Fernandes J, Schuelter-Trevisol F, Cancelier ACL, et al. Adenovirus 36 prevalence and association with human obesity: a systematic review. Int J Obes (Lond). 2021;45(6):1342–1356. doi:10.1038/s41366-021-00805-6
[49] Rogers PM, Fusinski KA, Rathod MA, et al. Human adenovirus Ad-36 induces adipogenesis via its E4 orf-1 gene. Int J Obes (Lond). 2008;32(3):397–406. doi:10.1038/sj.ijo.0803748
[50] Duan Y, Xu B, Li C, et al. Molecular characteristics of human adenovirus type 3 circulating in parts of China during 2014-2018. Front Microbiol. 2021;12:688661, doi:10.3389/fmicb.2021.688661
[51] Wei J, Zang N, Zhang J, et al. Genome and proteomic analysis of risk factors for fatal outcome in children with severe community-acquired pneumonia caused by human adenovirus 7. J Med Virol. 2023;95(11):e29182, doi:10.1002/jmv.29182
[52] Jing S, Zhang J, Cao M, et al. Household transmission of human adenovirus type 55 in case of fatal acute respiratory disease. Emerg Infect Dis. 2019;25(9):1756–1758. doi:10.3201/eid2509.181937
[53] Choudhry A, Mathena J, Albano JD, et al. Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits. Vaccine. 2016;34(38):4558–4564. doi:10.1016/j.vaccine.2016.07.033
[54] Holterman L, Vogels R, van der Vlugt R, et al. Novel replication-incompetent vector derived from adenovirus type 11 (Ad11) for vaccination and gene therapy: low seroprevalence and non-cross-reactivity with Ad5. J Virol. 2004;78(23):13207–13215. doi:10.1128/JVI.78.23.13207-13215.2004
[55] Sayedahmed EE, Hassan AO, Kumari R, et al. A bovine adenoviral vector-based H5N1 influenza -vaccine provides enhanced immunogenicity and protection at a significantly low dose. Mol Ther Methods Clin Dev. 2018;10:210–222. doi:10.1016/j.omtm.2018.07.007
[56] Keriel A, Rene C, Galer C, et al. Canine adenovirus vectors for lung-directed gene transfer: efficacy, immune response, and duration of transgene expression using helper-dependent vectors. J Virol. 2006;80(3):1487–1496. doi:10.1128/JVI.80.3.1487-1496.2006
[57] Ewer K, Rampling T, Venkatraman N, et al. A monovalent chimpanzee adenovirus ebola vaccine boosted with MVA. N Engl J Med. 2016;374(17):1635–1646. doi:10.1056/NEJMoa1411627
[58] Dudareva M, Andrews L, Gilbert SC, et al., Prevalence of serum neutralizing antibodies against chimpanzee adenovirus 63 and human adenovirus 5 in Kenyan children, in the context of vaccine vector efficacy. Vaccine. 2009;27(27):3501–3504. doi:10.1016/j.vaccine.2009.03.080
[59] Nebie I, Edwards NJ, Tiono AB, et al. Assessment of chimpanzee adenovirus serotype 63 neutralizing antibodies prior to evaluation of a candidate malaria vaccine regimen based on viral vectors. Clin Vaccine Immunol. 2014;21(6):901–903. doi:10.1128/CVI.00723-13
[60] Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One. 2012;7(7):e40385, doi:10.1371/journal.pone.0040385
[61] Sun YC, Li TT, Wang YL, et al. Detection of neutralizing antibody to human adenovirus type 5 in marmosets. Nan Fang Yi Ke Da Xue Xue Bao. 2016;36(4):582–587.
[62] Yi H, Wang Q, Deng J, et al. Seroprevalence of neutralizing antibodies against adenovirus type 26 and 35 in healthy populations from Guangdong and Shandong provinces, China. Virol Sin. 2022;37(5):716–723. doi:10.1016/j.virs.2022.06.006
[63] Zheng X, Rong X, Feng Y, et al., seroprevalence of neutralizing antibodies against adenovirus type 14 and 55 in healthy adults in southern China. Emerg Microbes Infect. 2017;6(6):e43, doi:10.1038/emi.2017.29
[64] Liu Q, Nie J, Huang W, et al. Comparison of two high-throughput assays for quantification of adenovirus type 5 neutralizing antibodies in a population of donors in China. PLoS One. 2012;7(5):e37532, doi:10.1371/journal.pone.0037532
[65] Liu Z, Tian X, Liu W, et al. A sensitive and high-throughput flow cytometry-based assay for measuring antibody neutralization of human adenovirus type 3. Virol Sin. 2021;36(3):537–544. doi:10.1007/s12250-020-00295-2
[66] Wang Q, Sun Y, Xu Y, et al. Seroprevalence of human adenovirus type 5 neutralizing antibody in common marmosets determined by a new set of two assays. Viral Immunol. 2019;32(8):348–354. doi:10.1089/vim.2019.0054
[67] Moffatt S, Hays J, HogenEsch H, et al. Circumvention of vector-specific neutralizing antibody response by alternating use of human and non-human adenoviruses: implications in gene therapy. Virology. 2000;272(1):159–167. doi:10.1006/viro.2000.0350
[68] Brouwer E, Havenga MJ, Ophorst O, et al. Human adenovirus type 35 vector for gene therapy of brain cancer: improved transduction and bypass of preexisting anti-vector immunity in cancer patients. Cancer Gene Ther. 2007;14(2):211–219. doi:10.1038/sj.cgt.7701010
[69] Geisbert TW, Bailey M, Hensley L, et al. Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect non-human primates against ebolavirus challenge. J Virol. 2011;85(9):4222–4233. doi:10.1128/jvi.02407-10
[70] Falsey AR, Hosman T, Bastian AR, et al. Long-term efficacy and immunogenicity of Ad26. RSV.preF-RSV preF protein vaccine (CYPRESS): a randomised, double-blind, placebo-controlled, phase (2b). study. Lancet Infect Dis. 2024;24(9):1015–1024. doi:10.1016/s1473-3099(24)00226-3
[71] Sumida SM, Truitt DM, Lemckert AAC, et al. Neutralizing antibodies to adenovirus serotype 5 vaccine vectors are directed primarily against the adenovirus hexon protein. The Journal of Immunology. 2005;174(11):7179–7185. doi:10.4049/jimmunol.174.11.7179
[72] Pichla-Gollon SL, Drinker M, Zhou X, et al. Structure-based identification of a major neutralizing site in an adenovirus hexon. J Virol. 2007;81(4):1680–1689. doi:10.1128/JVI.02023-06
[73] Bradley RR, Maxfield LF, Lynch DM, et al. Adenovirus serotype 5-specific neutralizing antibodies target multiple hexon hypervariable regions. J Virol. 2012;86(2):1267–1272. doi:10.1128/JVI.06165-11

[74] Cheng C, Gall JG, Nason M, et al. Differential specificity and immunogenicity of adenovirus type 5 neutralizing antibodies elicited by natural infection or immunization. J Virol. 2010;84(1):630–638. doi:10.1128/JVI.00866-09

[75] Yu B, Dong J, Wang C, et al. Characteristics of neutralizing antibodies to adenovirus capsid proteins in human and animal sera. Virology. 2013;437(2):118–123. doi:10.1016/j.virol.2012.12.014

[76] Bruder JT, Semenova E, Chen P, et al. Modification of Ad5 hexon hypervariable regions circumvents preexisting Ad5 neutralizing antibodies and induces protective immune responses. PLoS One. 2012;7(4):e33920, doi:10.1371/journal.pone.0033920

[77] Roberts DM, Nanda A, Havenga MJ, et al. Hexon-chimaeric adenovirus serotype 5 vectors circumvent preexisting anti-vector immunity. Nature. 2006;441(7090):239–243. doi:10.1038/nature04721

[78] Flickinger JC Jr., Singh J, Carlson R, et al. Chimeric Ad5.F35 vector evades anti-adenovirus serotype 5 neutralization opposing GUCY2C-targeted antitumor immunity. J Immunother Cancer. 2020;8(2):e001046. doi:10.1136/jitc-2020-001046

[79] Wang G, Cao RY, Chen R, et al. Rational design of thermostable vaccines by engineered peptide-induced virus self-biomineralization under physiological conditions. Proc Natl Acad Sci U S A. 2013;110(19):7619–7624. doi:10.1073/pnas.1300233110

[80] Wang X, Sun C, Li P, et al. Vaccine engineering with dual-functional mineral shell: a promising strategy to overcome preexisting immunity. Adv Mater. 2016;28(4):694–700. doi:10.1002/adma.201503740

[81] Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC subcommittee on platelet immunology. J Thromb Haemost. 2021;19(6):1585–1588. doi:10.1111/jth.15341

[82] Muir KL, Kallam A, Koepsell SA, et al. Thrombotic thrombocytopenia after Ad26. CO(V2). S Vaccination. N Engl J Med. 2021;384(20):1964–1965. doi:10.1056/NEJMc2105869

[83] Schultz NH, Sorvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384(22):2124–2130. doi:10.1056/NEJMoa2104882