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# Molecular Epidemiology of Adenoviruses: Global Distribution of Adenovirus 7 Genome Types

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**Adenovirus 7 (Ad7) is the adenovirus species that most frequently has been associated with severe illness. Seven distinct genome types of adenovirus 7, Ad7p, Ad7a, Ad7b, Ad7c, Ad7d, Ad7e, and Ad7f, can be identified by using restriction endonucleases *Bam*HI and *Sma*I. We analyzed the distribution of the different Ad7 genome types among 314 isolates from patients and healthy shedders. The Ad7b and Ad7c genome types accounted for 90% of the isolates from patients and appeared to be mutually exclusive. A shift from Ad7c to Ad7b genome types occurred in 1969 in Europe and in 1975 in Australia. During the last decade, Ad7b genome types predominated in Australia, Europe, and North America. Ad7c was detected in South Africa, Ad7d was detected in China, Ad7e was detected in Brazil, and Ad7f was detected in Australia. The Ad7p and Ad7a genome types dominated among isolates obtained from healthy shedders and appeared scattered through the years and the geographical areas. The prevalence of Ad7 infections is high in Japan as judged by the herd immunity. However, the low percentage (2%) of Ad7 isolates among all adenovirus isolates chiefly from patients, coupled with 30 to 50% antibody prevalence, argues for a high proportion of inapparent infections and, hence, Ad7 strain(s) of low pathogenicity.**

Up to now, 41 human adenovirus serotypes have been recognized (4). They have been divided into six subgenera (17, 20). Among these, members of subgenus B and, in particular, adenovirus 7 (Ad7) have been frequently associated with epidemic outbreaks of systemic infections with high fever, pneumonia, gastroenteritis, central nervous system symptomatology, or a combination of these. In infants these infections are particularly severe and may be fatal (1, 3, 7, 9, 13, 14, 16). In older children the disease may be severe, but the outcome is usually favorable (reviewed in reference 23). The highest prevalence of antibodies against Ad7 has been reported from Japan and Taiwan (15), whereas isolates from sick individuals are rare in these countries.

Berge et al. (2) isolated the prototype strain Gomen of Ad7 (Ad7p), whereas Rowe et al. (11) recognized a second subtype of Ad7, Ad7a (strain 1051). Four different genome types of Ad7 have previously been identified by using restriction endonucleases (20, 22). The distribution of the Ad7 genome types in Europe has been studied (20, 23). The Ad7p and the Ad7a genome types were rarely found, whereas the Ad7b and the Ad7c genome types were, by far, dominant among isolates from patients and showed a mutually exclusive appearance.

It is the purpose of this communication to report the detection of three new Ad7 genome types (Ad7d, Ad7e, and Ad7f) and to compare the distribution of the seven Ad7 genome types among strains isolated from patients in Africa, Asia, Australia, Europe, and North and Latin America with the distribution of Ad7 genome types among the Ad7 strains isolated during the Seattle Virus Watch (VW) program. This program was initiated on the basic assumption that, for any given virus, many if not most infections would be inapparent, and continuous virological surveillance of families with a newborn infant was used for up to 2 years or longer (6).

## MATERIALS AND METHODS

**Virus strains.** Virus isolates were recovered from nasopharyngeal swabs, sputum, lung aspirate, autopsy lung, or fecal specimens. All strains were propagated in A-549 cells, at the Department of Virology, University of Umeå, Sweden, and before 1981 at the Department of Virology, Karolinska Institutet. A-549 is a continuous oat cell carcinoma cell line (provided by W. A. Nelson Rees, Berkeley, Calif.). The viral DNA was analyzed after one or two passages in A-549 cells. All strains reacted as Ad7 in neutralization tests. Fecal specimens obtained during the Seattle VW program occasionally contained enteroviruses in addition to adenoviruses or even two adenoviruses. In these cases adenoviruses could only be isolated after typing the enteroviruses, followed by blocking with specific antisera. In four instances, the second virus (Ad2 in one instance and poliovirus in three instances) overgrew Ad7 in passage so that the Ad7 was not available for genome typing.

**Preparation of viral DNA.** Viral DNA was initially extracted from adenovirus particles purified by centrifugation on a discontinuous and subsequent continuous CsCl gradient

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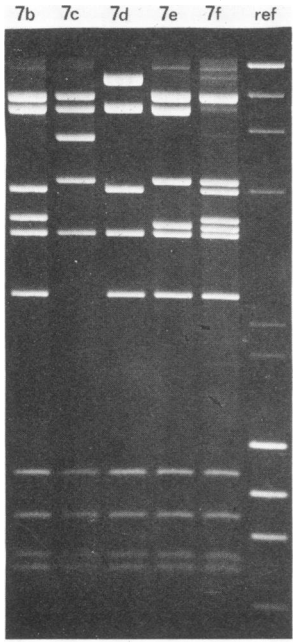


FIG. 1. DNA restriction patterns after digestion of DNA from the Ad7b, Ad7c, Ad7e, and Ad7f genome types with *Bam*HI. The DNA fragments were separated by electrophoresis in 1.2% agarose slab gels.

as previously described (25). A method for extraction of intracellular DNA by a modification of the Hirt procedure (18) was found to be most feasible for analysis of numerous wild-type isolates.

**DNA restriction.** The restriction endonucleases *Bam*HI and *Sma*I were purchased from New England Biolabs and Boehringer Mannheim Biochemicals. *Bam*HI was incubated in 100 mM NaCl–10 mM Tris-hydrochloride (pH 7.9)–10 mM $MgCl_2$–6 mM 2-mercaptoethanol, and *Sma*I was incubated in 20 mM KCl–10 mM Tris-hydrochloride (pH 9.2)–6 mM $MgCl_2$–6 mM 2-mercaptoethanol. All enzyme reactions were carried out for 2 h at 37°C with 1 μg of DNA. The reaction was terminated by the addition of 1/10 volume of 37% (wt/wt) Ficoll 400 (Pharmacia Fine Chemicals, Uppsala, Sweden)–50 mM EDTA–0.3% bromophenol blue (24).

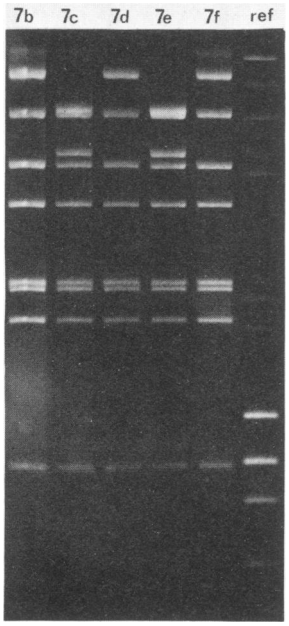


FIG. 2. DNA restriction patterns after digestion of DNA from the Ad7b, Ad7c, Ad7e, and Ad7f genome types with *Sma*I. Lambda DNA cleaved with *Hin*dIII and φx174 digested by *Hin*cII were included as molecular weight.

**Agarose electrophoresis of DNA.** The DNA fragments were separated by electrophoresis on 1.2% (wt/vol) vertical agarose slab gels (14 by 17 by 0.4 cm) at 2.5 V/cm at 4°C or in submerged horizontal slab gels at room temperature. The HGT SeaKem agarose was purchased from FMC Corp., Marine Colloids Div., Rockland, Maine. The agarose gels were prepared and run in 89 mM Tris–89 mM boric acid–2.5 mM EDTA (pH 8.3). After completion of the electrophoresis the gels were stained in the same buffer with 0.5 μg of ethidium bromide per ml and photographed with a mid-range 302 transilluminator (U.V.P. International Inc., San Gabriel, Calif.), Wratten no. 29 filter, and Plus X film (Eastman Kodak Co., Rochester, N.Y.).

## RESULTS

**Global distribution of Ad7 genome types.** DNA restriction with *Bam*HI and *Sma*I revealed seven Ad7 genome types among 314 isolates (Fig. 1 and 2 and Table 1). The different Ad7 genome types are presented in Fig. 3 and were distributed as detailed below.

(i) **Africa.** Twenty-two Ad7 strains isolated in Johannesburg during the period of 1967 and 1976 were analyzed. The first strain isolated in April 1967 was genome typed as Ad7b.

TABLE 1. Origin of the Ad7 strains

| Location | Period | No. | Source |
|---|---|---|---|
| Africa | | | |
| Johannesburg | 1967– | 22 | B. D. Schoub |
| Australia | | | |
| Victoria | 1968– | 7 | M. Kennett |
| New South Wales | 1973– | 47 | A. McKenzie |
| Camperdown | 1981– | 11 | L. M. De Silva |
| Brazil | | | |
| Belem | | 5 | A. da Costa Linhares |
| Rio de Janeiro | 1981 | 3 | J. Nascimento |
| China | | | |
| Peking | 1958–1959 | 6 | Ren Gui-fang |
| Europe | | | |
| The Netherlands | 1958– | 70 | J.C. deJong |
| Sweden | 1964– | 42 | S. Wolontis |
| United Kingdom | 1974– | 48 | R. N. P. Sutton, M. Pereira |
| Oslo | 1965–1967 | 5 | L. Flugsrud |
| Budapest | 1975–1978 | 4 | M. Toth |
| Hanover | 1979 | 5 | H. Willers |
| Brussells | 1980 | 2 | G. Zissis |
| Japan | | | |
| Mie and Saitama | 1969–1970 | 3 | R. Kono |
| United States | | | |
| Seattle | 1965–1969 | 12 | M. Cooney |
| San Francisco | 1962– | 11 | C. Smith |
| San Diego | 1980 | 11 | M. A. Thompson |

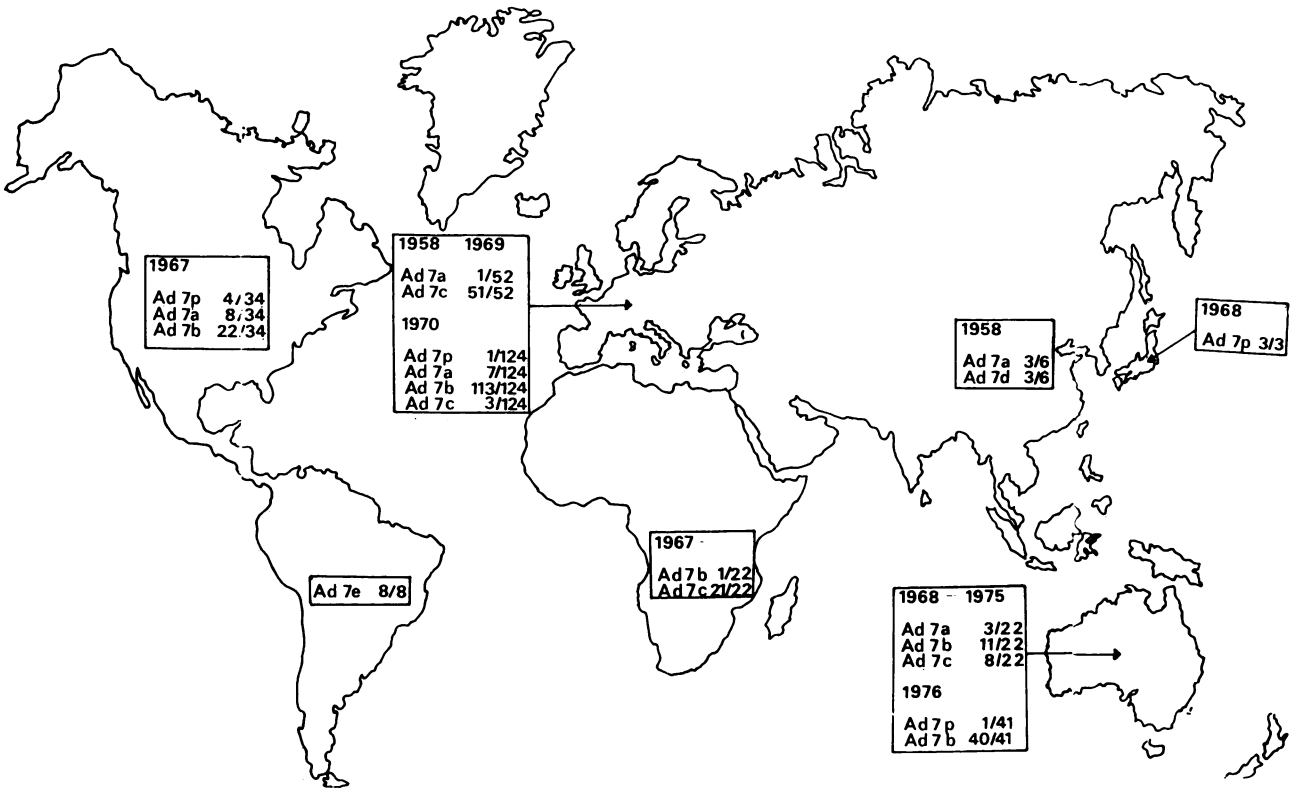


FIG. 3. Global distribution of the Ad7 genome types.

All of the remaining strains were identified as Ad7c. The Ad7 strain isolated from an autopsy case of a child dying from an adenovirus infection complicating measles, which was serologically typed as Ad7a (9), has been genome typed by us as Ad7c.

**(ii) Australia.** The five genome types Ad7p, Ad7a, Ad7b, Ad7c, and Ad7f were identified. This composition is similar to the distribution of Ad7 genome types in Europe, the differences being that Ad7c was isolated up until 1975 in Australia (Fig. 4) and that one isolate was genome typed as Ad7f (Fig. 1). Ad7a was preferentially isolated during the period of transition from genome type Ad7c to Ad7b in both Australia and Europe (20).

**(iii) Brazil.** Ad7e was only detected in Brazil and also was the only genome type detected among eight isolates from both Belem and Rio de Janeiro.

**(iv) China.** Severe outbreaks of Ad7-associated pneumonia with high mortality among infants occurred in 1958 (7, 16). Three strains recovered from autopsy cases in 1958 could be analyzed and were genome typed as Ad7a. In addition, three strains isolated in 1981 from pharyngeal swabs of children with pneumonia with a favorable outcome were genome typed as Ad7d, a newly identified genome type.

**(v) Europe.** Ad7 isolates sampled from adenovirus collections available since 1958 in the Netherlands, 1964 in Sweden, and 1974 in the United Kingdom and small clusters of strains from outbreaks in Norway, Hungary, Germany, and Belgium were genome typed. Two outbreaks of Ad7-associated disease in 1958 to 1959 and 1964 to 1965 were caused by the Ad7c genome type, whereas all investigated outbreaks of Ad7-associated respiratory disease since 1969 have been caused by Ad7b. A few scattered isolates were genome typed as Ad7p and Ad7a (20). The Ad7c genome type has not altogether vanished from Europe since three Ad7c strains have been isolated in Europe since 1970: in Budapest in 1975, from a Swedish tourist returning from a visit to Marbella, Spain, in 1978, and in London in 1980.

**(vi) Japan.** A high prevalence of Ad7-specific antibodies was noted in Japan. However, only 2% of isolated adenovirus strains were typed as Ad7 (Fig. 5). This is in striking contrast to Ad3 accounting for 52% of all typed adenoviruses during the period of 1966 to 1979 (Fig. 5). One Ad7 strain isolated in 1969 from a throat swab of a patient with pharyngo conjuctival fever and two Ad7 strains described as sporadic isolates recovered from eye swabs in 1971 and 1979 were genome typed as Ad7p.

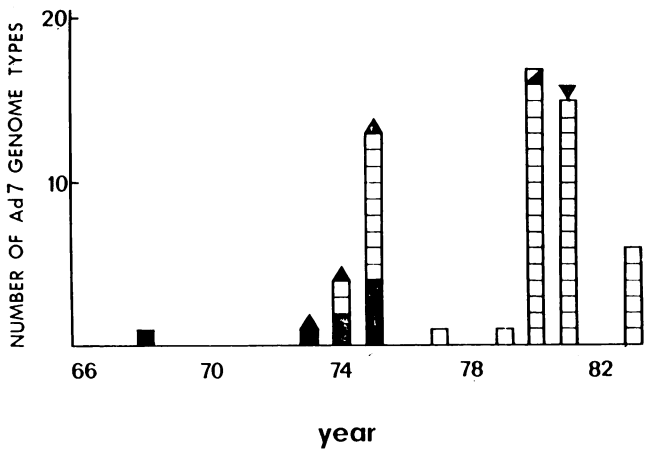


FIG. 4. Number of genome-typed Ad7 isolates recovered in Australia from 1968 to 1983. The Ad7p (▼), Ad7a (▲), and Ad7b (□), Ad7c (■), and Ad7f (◪) genome types are represented.

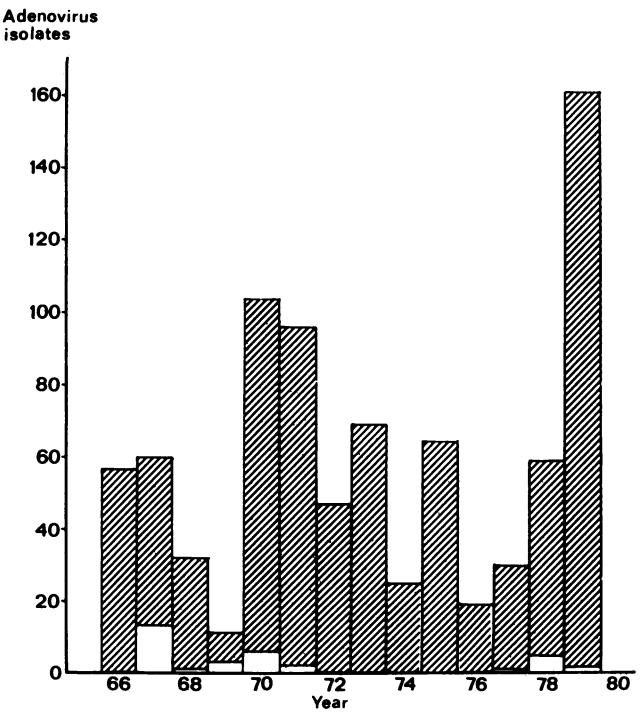


FIG. 5. Distribution of Ad3 (hatched columns) and Ad7 (open columns) in Japan from 1966 to 1979.

**(vii) United States.** Ad7b predominated among the 34 Ad7 isolates collected on the West Coast since 1962. The portion of Ad7p and Ad7a amounted to one-third of the Ad7 isolates. This relatively high share was due to the contribution of Ad7 isolates from the VW program in Seattle, Wash. (see below). The Ad7c, Ad7d, Ad7e, and Ad7f genome types were not found.

**Occurrence of different Ad7 genome types among the Ad7 strains recovered during the Seattle VW program.** During the Seattle VW program from 1965 to 1969, 520 total isolations, representing 258 adenovirus infections, were made. Of these, 15 infections were Ad7. All were new infections. It was possible to prepare adenovirus DNA from 12 isolates, whereas the remaining tissue culture fluids yielded only enteroviruses. The Ad7p, Ad7a, and Ad7b genome types were detected in the Seattle VW material. Of the Ad7 strains, 6 were recovered from a family with six members, four of whom had respiratory disease. These isolates were all of the Ad7b genome type, alone or in one fecal specimen, together with a Ad7a genome type (Table 2). The remaining Ad7 strains were isolated from healthy shedders. Four of these strains were genome typed as Ad7a, and only one was genome typed as the Ad7 prototype.

## DISCUSSION

Ad7 is the adenovirus serotype that has been most frequently associated with outbreaks of respiratory disease. Ad7 accounted for 19.7% of all adenovirus isolates that were typed and reported to the World Health Organization during the period of 1967 to 1976 (12).

DNA restriction endonucleases *Bam*HI and *Sma*I were used to analyze the Ad7 isolates since they can discriminate between all the established human adenovirus prototypes.

The identification of Ad7b, Ad7c, Ad7d, Ad7e, and Ad7f genome types in addition to the Ad7 prototype and Ad7a described by Berge et al. (2) and Rowe et al. (11) may suggest that some or all of these genome types are newly emerging viral entities. Ad7b was, however, identified as the cause of the severe Ad7 epidemic in Paris in 1956 (3, 23), and Ad7c was isolated in 1958 (20).

The analysis of the distribution of the Ad7 genome types among the different continents revealed a preponderance of Ad7c and Ad7b in both Europe and Australia. However, a shift from Ad7c to Ad7b was noted in 1969 in Europe (20) but was not detected until 1975 in Australia. The reason for the alternation from Ad7c to Ad7b as causative agents in Ad7 respiratory outbreaks is not known.

TABLE 2. Characteristics of 12 persons from whom Ad7 was isolated during the Seattle VW program

| Case | Person | Age | Symptoms | Specimen Type | Specimen no. | Date of specimen collection | Adenovirus genome type |
|---|---|---|---|---|---|---|---|
| 1 | 70-1 | 7 mo | Fever 39.4°C, eyes teary, nose stuffed and runny, ear infection, anorexia | TNS | 12495 | 8-14-1967 | Ad7b |
| 2 | 70-2 | 7 yr | Fever 40°C, eyes teary, nose stuffed and runny, anorexia | F | 12574 | 8-14-1967 | Ad7b and Ad7a |
| 3 | 70-10 | Mother | None | F | 12499 | 8-12-1967 | Ad7b[a] |
| 4 | 70-11 | Father | Nose stuffed and runny, sore throat | F | 12501 | 8-12-1967 | Ad7b |
| 5 | 70-20 | 9 yr | Fever 40°C, eyes teary, nose stuffed and runny, sore throat | F | 12503 | 8-13-1967 | Ad7b |
| 6 | 70-21 | 10 yr | None | TNS/F | 12504/12505 | 8-14-1967 | Ad7b/Ad7b[a] |
| 7 | 7-1 | 2 yr | None | F | 12822 | 8-23-1967 | Ad7a |
| 8 | 21-2 | 19 mo | None | F | 14901 | 10-17-1967 | Ad7p |
| 9 | 65-1 | 15 mo | Fever 37.8°C, nose stuffed and runny | F | 22913 | 5-28-1968 | Ad2 |
| 10 | 98-1 | 8 mo | None | F | 26677 | 10-17-1967 | Ad2 and Ad7a |
| 11 | 111-1 | 4 mo | None | F | 27437 | 11-19-1967 | Ad7a |
| 12 | 57-2 | 6 mo | None | F | 30784 | 4-15-1969 | Ad7a |

[a] Coxsackie B3 also was isolated.

Ad7c was never detected among isolates from North or Latin America. In Japan only Ad7p was found. Ad7d and Ad7e were only detected in China and Brazil, respectively. This means that Africa, Brazil, and Japan are the only regions where Ad7b has not been detected in recent years.

The prevalence of Ad7-specific neutralizing antibodies in Cleveland, Ohio, among children 5 years old and their mothers was 10 and 20%, respectively (8). In Japan and Taiwan, however, the prevalence of Ad7-specific antibodies was 30% among children and 50% among adults (15). The relatively low prevalence of type-specific Ad7 antibodies in Europe and North America is an indication of low herd immunity to Ad7, which is a prerequisite for the epidemic outbreaks that have been particularly frequent among military recruits (12).

The epidemic outbreaks of Ad7 can be widespread and have been reported to comprise several European countries (20). The VW program in Seattle, Wash., from October 1965 to September 1969 provided information on the prevalence of adenovirus types in this region. Only 19 of the 520 isolations (15 of 250 infections) were typed as Ad7 (6). Of Ad7 infections detected during the Seattle VW program, none could be demonstrated to be recrudescent (6). This means either that the VW study covered an interepidemic interval or that Ad7 is shed for shorter periods than the adenovirus types belonging to subgroup C. According to Fox et al. (5) "the proportions of infections which result in illness is a measure of pathogenicity." This proportion can be estimated by studies designed like the VW program in Seattle. It therefore is of interest that the Ad7 and Ad7a genome types represent the major portion of the Ad7 strains isolated from healthy carriers. The Ad7 prototype is infrequently isolated, possibly because this genome type is less virulent than the Ad7b and Ad7c genome types. The Ad7 infections in Japan resulted in a high prevalence of antibody, yet the Ad7 isolates represented only 2% of all adenovirus strains isolated in Japan (Fig. 5).

The available information on the virulence of the Ad7a genome type is contradictory. Ad7a is the most frequently isolated genome type from healthy shedders in the Seattle VW and also in Sweden (6, 22). Ad7a isolates have, however, been associated with disease (20), and three strains have now been identified from autopsies in Beijing. The Ad7 vaccine strain used in the United States is of the Ad7a genome type (22). A report on a fatal Ad7 pneumonia in a military recruit 15 days postadministration of a live Ad7 vaccine illustrates a need to genome type the Ad7 strains from the index case and from contemporary isolates obtained from the basic training center to evaluate the pathogenicity of the live Ad7 vaccine (10). This vaccine is administered via enteric-coated capsules and gives ample protection against respiratory illness (17). To our knowledge, no information on the virulence of the Ad7 vaccine strain after intranasal or other parenteral administration has been published.

An extended analysis of all available Ad7a strains should be performed to ascertain whether a genetic heterogeneity exists.

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