Pneumococcal Vaccination in Adults

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Current Infectious Disease Reports 2005, **7:**211–217
Current Science Inc. ISSN 1523-3847

Pneumococci remain the most common etiology of community-acquired pneumonia in adults, with significant attendant mortality in the elderly. With the recognition of increasing rates of drug-resistant *Streptococcus pneumoniae* in recent years, efforts to prevent disease through vaccination have gained greater impetus. The 23-valent pneumococcal vaccine is used widely in the United States and provides effective protection against bacteremic pneumococcal disease, particularly in the immunocompetent host. The 7-valent pneumococcal conjugate vaccine, licensed in the United States in 2000, has had a dramatic impact on pneumococcal disease in the pediatric population, and its use in children has had effects on incidence rates in nonimmunized adults as well. Future directions include efforts to improve vaccination coverage in targeted populations and the development of more immunogenic and efficacious vaccines for high-risk groups.

Introduction

Pneumococcal vaccine is the prototype of a capsular polysaccharide vaccine. In 1976, Austrian *et al.* [1] pioneered the production of the first 14-valent pneumococcal vaccine, which evolved into a 23-valent formulation in 1983. This vaccine consists of purified capsular polysaccharide antigen from 23 serotypes of pneumococci. These serotypes account for 88% of isolates from bacteremic cases, and antigen is cross-reactive with types causing an additional 8% of disease. Because the capsular polysaccharide is not immunogenic in children aged younger than 2 years, a protein conjugate 7-valent vaccine (Prevnar; Wyeth Pharmaceuticals, Madison, NJ) was developed and obtained licensure in the United States in 2000. As discussed later, this has been a major breakthrough in preventing invasive illness in children in this age group.

Polysaccharide Vaccine

More than 80 pneumococcal serotypes were described by 1940, and there are now more than 90 serotypes identified. Not all serotypes are implicated in causing invasive disease; the current polysaccharide vaccine was formulated representing a subgroup of highly prevalent serotypes. The vaccine (Pneumovax) is manufactured by Merck & Co. (Whitehouse Station, NJ); Wyeth Lederle ceased production and marketing of its licensed vaccine, Pnu-Imune, in 2002. The vaccine includes 25 μg of each of 23 purified capsular antigens, of serotypes 1, 2, 3, 4, 6, 6B, 7F, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19B, 20, 22F, 23F, and 33F.

Indications

In adults, the Advisory Committee on Immunization Practices (ACIP) currently recommends vaccination with polysaccharide vaccine for those aged older than 65 years, the immunocompromised (including those with HIV), and immunocompetent patients aged younger than 64 years with chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leaks, or asplenia (Table 1).

Cost analyses of the effect of extending the recommendation for vaccination of healthy adults to those aged 50 to 64 years suggest that a gain of a quality-adjusted year of life costs about $2500 for blacks and $8200 for nonblacks at low risk [2]. Extending pneumococcal vaccination to healthy adults aged 50 to 64 years would align this intervention at age 50 with screening to detect early disease, such as breast and colorectal cancer, and with the recommendation for yearly influenza immunizations. This approach is still under discussion.

Immunogenicity and duration of antibody level

Pneumococcal capsular polysaccharides stimulate production of type-specific antibodies and activation of complement that results in opsonization, phagocytosis, and destruction of invading pneumococci by polymorphonuclear leukocytes and other phagocytic cells. After immunization of healthy adults and the elderly, a twofold or greater antibody response develops within 2 to 3 weeks in more than 80% of recipients. In children aged younger than 2 years, antibody response to most capsular types is generally low. The antibody levels for most pneumococcal vaccine types remain elevated in healthy adults up to 5 years after immunization. Vaccination may provide protection for up to 9 years after receipt of the initial dose [3]. In immunocompromised patients, including those with leukemia, lymphoma, multiple myeloma, splenectomy, or AIDS, antibody responses to pneumococcal immunization are substantially diminished or absent.

Table 1. ACIP indications for pneumococcal polysaccharide vaccine

All adults aged 65 years or older
Medical indications
Chronic disorders of the pulmonary system (excluding asthma); cardiovascular diseases; diabetes mellitus; chronic liver diseases, including liver disease as a result of alcohol abuse (*eg*, cirrhosis); chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (*eg*, sickle cell disease or splenectomy); immunosuppressive conditions (*eg*, congenital immunodeficiency, HIV infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, generalized malignancy, or organ or bone marrow transplantation); chemotherapy with alkylating agents, antimetabolites, or long-term systemic corticosteroids; or cochlear implants
Geographic/ethnic indications
Alaska natives and certain Native American populations
Other indications
Residents of nursing homes and other long-term care facilities
Revaccination
One-time revaccination after 5 years for persons with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (*eg*, sickle cell disease or splenectomy); immunosuppressive conditions (*eg*, congenital immunodeficiency, HIV infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, generalized malignancy, or organ or bone marrow transplantation); or chemotherapy with alkylating agents, antimetabolites, or long-term systemic corticosteroids
For persons aged > 65 years, one-time revaccination if they were vaccinated > 5 years earlier and were aged < 65 years at the time of primary vaccination

ACIP—Advisory Committee on Immunization Practices.
(*Data from* US Centers for Disease Control and Prevention ACIP [27,60].)

Specificity of enzyme-linked immunosorbent assay (ELISA) of antipneumococcal polysaccharide antibody has recently been improved through adsorption of sera with serotype 22F polysaccharide, in addition to the use of common C-polysaccharide as an inhibitor. Serologic studies more than several years old should be viewed with this in mind because nonspecific antibodies, which are nonprotective, constitute a significant proportion of measured immunoglobulin G in the older ELISA [4].

Revaccination in selected high-risk populations has been examined and is recommended by the ACIP (Table 1). Revaccination in the elderly has been shown to be safe, and antibody titers increase significantly, although not to levels seen after primary vaccination [5].

Vaccine efficacy

The efficacy of polysaccharide vaccine in preventing invasive pneumococcal infection has been the subject of multiple trials, and efficacy in reducing nonbacteremic invasive disease remains an area of controversy in healthy adults aged older than 65 years and in immunocompromised subpopulations.

Early case-control and serotype prevalence studies reported vaccine effectiveness against invasive disease ranging from 56% to 81% [3,6–8]. Vaccine effectiveness (prevention of infection by pneumococcal serotypes included in the vaccine) of 65% to 84% was also demonstrated among patients with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia. Effectiveness in healthy persons aged 65 years and older in a US Centers for Disease Control and Prevention (CDC) serotype prevalence study was 75% [6].

More recent data have cast doubt on the vaccine's efficacy in preventing nonbacteremic disease. Although one retrospective study involving elderly patients with chronic pulmonary disease demonstrated a reduction in the risk of pneumonia-associated hospitalization [9], prospective trials have failed to confirm any such protective benefit [10–13]. Whereas vaccine efficacy in reducing pneumococcal bacteremia was found to be 44% in a retrospective cohort study of 47,365 elderly patients, vaccination did not alter the risk of pneumonia [14•]. Meta-analyses have similarly detected no reduction in risk of pneumonia through vaccination of the elderly [3,15,16].

Efficacy in at-risk immunocompromised groups, such as those with sickle cell disease, chronic renal failure, immunoglobulin deficiency, and hematologic malignancies, has not been confirmed. In HIV-infected patients who experience a 50- to 100-fold increased risk of invasive pneumococcal disease, vaccine efficacy may vary by degree of immunocompromise as reflected in CD4 count, and perhaps by ethnicity. In a randomized trial in 1392 HIV-infected adults in Uganda, a paradoxical increase in invasive pneumococcal disease caused by vaccine serotypes within 6 months of vaccination in the vaccinated cohort was observed, as was an increase in all-cause pneumonia [17]. Perhaps relevant to this result in sub-Saharan Africa, a case-control study of HIV-infected patients in San Francisco demonstrated a 76% reduction in invasive pneumococcal disease in whites, whereas there was merely a nonsignificant trend toward efficacy among blacks [18•].

The polysaccharide vaccine is not effective for the prevention of common upper respiratory tract disease, such as pneumococcal otitis media or sinusitis [19,20].

Adverse reactions

Pneumococcal polysaccharide vaccine has generally been considered safe. Approximately one third of vaccine recipients

show transient, mild, local adverse effects, such as pain at the injection site, erythema, and swelling usually persisting for less than 48 hours [16]. More significant systemic reactions, such as fever, myalgia, and severe local reactions, occur in fewer than 1% of recipients. Anaphylaxis is rare. No neurologic disorders such as Guillain-Barré syndrome have been associated with immunization with pneumococcal vaccine. Because the safety of polysaccharide antigens in pregnant women has not been intensively examined, women at increased risk should be immunized before becoming pregnant. Reports of adverse reactions should be forwarded to the Vaccine Adverse Event Reporting System (800-822-7967).

Limitations

Capsular polysaccharides are generally not immunogenic in children aged younger than 2 years. Furthermore, immunogenicity to some pediatric pneumococcal types, such as 6 and 14, is decreased in children aged younger than 5 years [21,22]. The efficacy in immunocompromised children and adults, such as patients with HIV infection or cancer, may be decreased further by impaired immune response. As experience with the 7-valent conjugate vaccine demonstrates, improved protection against pneumococcal infection can be achieved in children by the enhancement of immune response to capsular polysaccharide by the use of protein antigens that elicit a T-cell–dependent immune response (see following text).

Pneumococcal Conjugate Vaccine

In February 2000, the US Food and Drug Administration licensed the 7-valent pneumococcal conjugate vaccine for the prevention of invasive pneumococcal disease. Conjugation of bacterial capsular polysaccharides to carrier proteins had been shown to induce good humoral immune responses early in life [23–26]. The vaccine contains 2 μg each of six capsular polysaccharides (4, 9V, 14, 18C, 19F, 23F) and 4 μg of 6B, each conjugated to 20 μg of diphtheria CRM_{197} protein, a nontoxic variant of diphtheria toxin.

Indications

Universal immunization of infants, and selected immunization of children aged 2 to 5 years with certain features that place them at increased risk of pneumococcal infection, including children with cochlear implants [27], is recommended by the CDC.

Immunogenicity in prelicensure trials

Conjugation of polysaccharides to proteins changes the nature of the antipolysaccharide response from T-independent to T-dependent. This antigen complex stimulates a T-helper cell response, resulting a substantial primary response among infants and a strong booster response on re-exposure [28]. Success of *Haemophilus influenzae* serotype B (Hib) conjugate vaccine in reducing incidence of invasive Hib disease by 95% among young children after the vaccine's introduction for use among infants in 1990 is an earlier example of the potential efficacy of bacterial polysaccharide-protein conjugate vaccines. Immunogenicity has been shown to vary significantly among pneumococcal serotypes in terms of magnitude of antibody response. However, in children, all resulted in a significant increase in antibody to the serotypes contained in the vaccines. When 212 healthy infants were randomized to receive 7-valent conjugate vaccine or an investigational meningococcal conjugate vaccine at ages 2, 4, 6, and 12 to 15 months, vaccination with pneumococcal conjugate vaccine resulted in substantial increases in serum antibody concentrations to all seven serotypes, compared with baseline concentrations. After three doses of 7-valent conjugate vaccine, 92% (serotypes 6B and 23F) to 100% (serotype 4) of children had 0.15 μg/mL or more of type-specific antibody, and 51% (serotype 9V) to 90% (serotype 19F) achieved a level of 1 μg/mL or more against the vaccine serotypes. The fourth dose resulted in an anamnestic response to each of the seven serotypes [29].

Efficacy was consistently reported in prelicensure clinical trials of multivalent pneumococcal conjugate vaccines in children [28,30,31–39]. The conjugate vaccine was well tolerated, highly immunogenic, and provided immunologic memory.

Vaccine efficacy in postlicensure trials

In children, the efficacy of the pneumococcal conjugate vaccine has now been demonstrated in postapproval evaluations as well. A trial conducted in northern California showed that 7-valent conjugate vaccine was effective in preventing invasive pneumococcal infections caused by vaccine serotypes. It also resulted in a 9.3% reduction in frequent otitis media and a 20.1% reduction in the placement of ventilator tubes for otitis media [40]. In another study, the nasopharyngeal carriage rate was reported to decrease from approximately 25% to 9% and 7% after one and two doses of the vaccine, respectively [41].

There is now good evidence that the vaccine has had an impact on invasive pneumococcal disease in older children and adults as well [40]. The Northern California Kaiser Permanente study showed that there was a reduction in the rate of invasive pneumococcal disease after the use of pneumococcal conjugate vaccine in individuals aged 5 years or older, from an average of 11.37 cases per 100,000 person-years to 9.27 cases per 100,000 person-years (an 18% reduction). When stratified into age brackets of 5 to 19, 20 to 39, 40 to 59, and 60 years and older, the greatest impact was seen in the 20- to 39-year age group, with a 58% reduction, and the least reduction was seen in the 60-year or older age group, with a 14% reduction. These data indicate the possibility of decreased transmission of vaccine serotypes to adults.

Since licensing of the pneumococcal conjugate vaccine in the United States in February 2000, more than 70 million doses of the vaccine have been administered. The

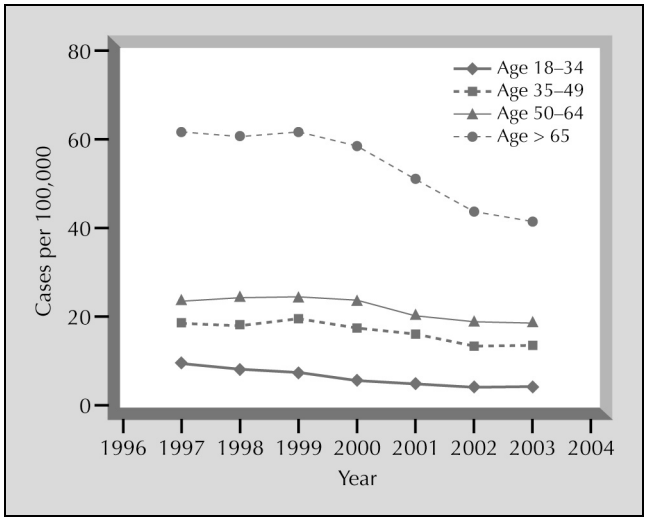

Figure 1. Rates of invasive pneumococcal disease among adults. (*Data from* the Active Bacterial Core Surveillance from 1997–2003 [preliminary]; Centers for Disease Control and Prevention, 1998–2004. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae*, 1997–2003.)

postlicensure evaluation conducted by the CDC (Active Bacterial Core Surveillance) documented a reduction in all invasive disease, from 24.3 cases per 100,000 during 1998 to 1999, to 17.3 cases per 100,000 in 2001. Moreover, rates of invasive disease decreased by 32% in adults aged 20 to 39 years and by 8% to 18% in older adults (Fig. 1) [42•].

In HIV-seropositive adults, similar benefits have been seen. Recent CDC population-based surveillance data show a decrease of 42% in invasive pneumococcal disease caused by 7-valent vaccine serotypes in HIV-positive patients, whereas nonvaccine serotype disease increased 56%, when comparing pre- and post-vaccine surveillance periods. An overall decrease of 12% in invasive pneumococcal disease was seen, although women and blacks showed no overall decrease in disease because of greater serotype replacement [43].

The basis for the reductions seen in invasive disease among adults after the introduction of infant vaccination with pneumococcal conjugate vaccine would appear to be a result of decreased nasopharyngeal carriage in vaccinated children, as noted earlier [41], with resultant decreased transmission to adult contacts. Molecular typing by pulsed-field gel electrophoresis of parent-child pairs of pneumococcal isolates in Japan has demonstrated high rates of transmission of penicillin-resistant *Streptococcus pneumoniae* [44]. However, intrafamilial transmission of *S. pneumoniae* could not be demonstrated in an Israeli study [45]. It is thought that changes in rates of adult disease are unlikely to be caused by the increased use of polysaccharide vaccine in the elderly, given the differential impact on serotypes included in the conjugate vaccine, and mathematical modeling of polysaccharide vaccine's effect on disease in the elderly [46].

Clinical trials have also examined whether conjugate vaccines administered to the elderly and in other high-risk groups will provide a more adequate and sustained immune response, compared with the polysaccharide vaccine, as summarized in a recent review [47]. Although immunogenicity of conjugate vaccines is seen, significantly improved titers are not, with little evidence of immunologic memory or priming. Possible explanations for this include low pre-existing titers of antibody to diphtheria toxoid, which served as the carrier protein in many of the candidate vaccines, in older adults. One trial demonstrated improved immunogenicity of the conjugate in patients with higher baseline titers against diphtheria protein [48]. Conjugate vaccine also contains lower amounts of antigen per serotype than does polysaccharide vaccine. Variable results may also relate to varying methodologies and different vaccines.

Serotype replacement

Because the protection offered by conjugate vaccine is specific to the capsular type(s) included in the vaccine, it has been suggested that reducing carriage of these vaccine types may leave open an ecologic niche that will be filled by serotypes not included in the vaccine [39]. Conjugate vaccine studies show considerable evidence of serotype replacement as measured by nasopharyngeal carriage of nonvaccine-type organisms. Increases in the carriage of nonvaccine serotypes have been shown in three trials. In Gambia, carriage of nonvaccine serotype was 79% in children receiving three doses of pneumococcal conjugate vaccine, compared with 42% in controls [39]. In another trial of a 9-valent vaccine in South Africa, carriage of nonvaccine serotypes increased from 21% in controls to 39% in vaccine recipients [49]. In a survey of invasive pneumococcal infections caused by vaccine-serogroup isolates in eight children's hospitals across the United States, rates decreased more than 75% among children aged 24 months or younger. In addition, penicillin resistance decreased in 2002, the last year for which data were reported. However, the percentage of all isolates of nonvaccine serotype increased from a prelicensure mean rate of 6% to 37.6% in 2002. The number of isolates in nonvaccine serogroups in these infants increased 28% in 2001 and 66% in 2002; this increase was particularly striking for serotypes 15 and 33 [50].

Effects on antimicrobial resistance

Widespread vaccination in children has resulted in dramatic decreases in the proportion of antibiotic nonsusceptible isolates, as shown in by recent data from Tennessee. Beginning in 2001 resistance rates decreased, and by 2002 marked reductions were noted; 26.4% of all isolates from normally sterile sites were penicillin nonsusceptible, 9.4% were cephalosporin nonsusceptible, and 18.1% were erythromycin nonsusceptible, compared with 40.8%, 34.9%, and 29.5%, respectively, in 2000 [51]. Similarly, the absolute number and prevalence of levofloxacin-resistant pneumococcal isolates increased until 2001 and appeared to decrease in 2002. The decrease may be related to the

introduction of pneumococcal conjugate vaccine; however, a different survey found a continuously increasing resistance rate reaching 1% in 2002 [52].

The CDC data also reveal decreasing rates of disease caused by penicillin-nonsusceptible isolates between 1999 and 2001 in those aged older than 65 years, from 16.7 to 12.6 (a 25% decrease). There was a 35% overall reduction in disease caused by penicillin-nonsusceptible pneumococci. Proportions of susceptible to nonsusceptible isolates did not change appreciably [42•]. Most nonsusceptible isolates are of 7-valent vaccine serotypes [53].

Vaccine Coverage

Pneumococcal vaccination coverage has improved dramatically within the past 15 years (Fig. 2). The Healthy People 2010 goals endorsed by the CDC call for vaccination rates of 90% for those aged 65 years or older and for institutionalized adults. Data from 2002 show that 56% of those aged older than 65 years had been vaccinated (CDC, National Center for Health Statistics, National Health Interview Survey). Improvements in coverage rates have been attributed to wider acceptance of preventive care by the public and expanded Medicare coverage of pneumococcal vaccination since 1993 [54].

A telephone survey by the CDC indicated an increase in pneumococcal vaccine coverage from 2002 to 2003 among adults aged older than 65 years; however, general coverage remains below the national health objectives for the year 2010 [55]. Median coverage level of vaccination among patients with diabetes was below the 2010 target of 60% for noninstitutionalized persons aged 18 to 64 years at high risk. Amongst the high-risk groups, those with diabetes and asthma in the age group of 18 to 49 years had substantially lower coverage. In the survey conducted in 2003, the state with the highest coverage rate among adults aged older than 65 years was Minnesota (73%), and the lowest rate was seen in Kentucky (59.6%), with a median coverage of 64.2%. Coverage among adults aged 18 to 49 years with diabetes was highest in Montana (58.2%) and lowest in Mississippi (22.6%), with a median of 37.1%. The huge variation in vaccination coverage observed in different states indicates that more effective interventions are needed to broaden coverage, especially among high-risk persons in the 18- to 49-year age group.

Barriers to achieving improved pneumococcal vaccination coverage have been recently reviewed [56]. Among physicians, an inability to determine a patient's pneumococcal vaccination status and uncertainty regarding vaccination decisions in such patients, as well as more general failure to offer vaccination, have been noted. Interventions such as the development of electronic medical records and nurses' screening of patients at visits have been found to be effective. Similarly, vaccinating emergency department and hospitalized patients before their discharge is seen as a useful tool.

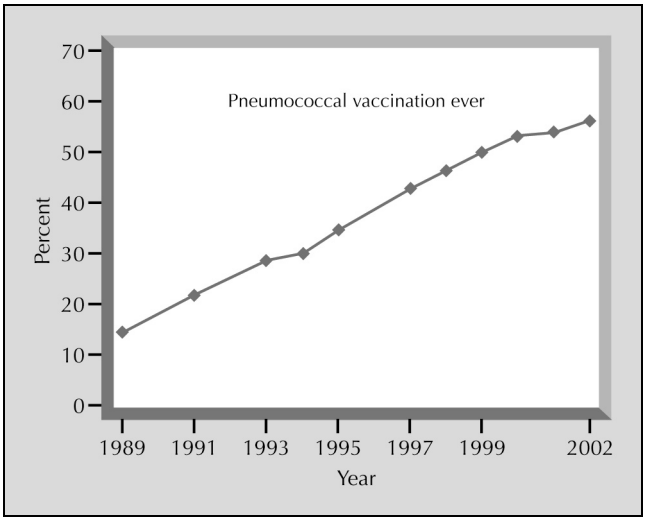

Figure 2. Pneumococcal vaccination rates for adults aged 65 years and older, 1989–2002, United States. (*Data from* US Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.)

Other Vaccines

Other candidate vaccine formulations in development are 9- and 11-valent polysaccharide vaccines conjugated to one or several carrier proteins [57•]. Moreover, efforts to develop vaccines against pneumococcal protein antigens are underway.

The pathogenicity of pneumococci is attributed to various virulence factors, which include capsular polysaccharide and protein antigens such as pneumolysin, autolysin, pneumococcal surface protein (Psp) A, pneumococcal surface adhesin, and hemin-binding protein. Some of these protein antigens can elicit protective immunity in mice and can be used as additional components when mixed with polysaccharide vaccine or as a carrier for conjugated polysaccharides. Mice have been protected from pneumonia after immunization with PspA and pneumolysin [58]. Through immunoscreening of *S. pneumoniae* genomic libraries, novel group-common, surface-exposed protective proteins have been identified, among them the family of pneumococcal histidine triad proteins (Pht family). Immunization of mice with one of these has elicited protective immunity against experimental sepsis and pneumonia [59].

Conclusions

Despite a lack of evidence that the 23-valent pneumococcal polysaccharide vaccine decreases the risk of nonbacteremic pneumococcal disease, bacteremic infections in susceptible adults have been reduced through application of the current recommendations for routine vaccination of those aged older than 65 years. Moreover, universal vaccination of infants and certain children aged 2 to 5 years has had an impact on adult disease, probably through decreased household transmission.

Serotype replacement has been demonstrated since the introduction of conjugate vaccine, although its effect on antimicrobial susceptibility will require continued monitoring.

Future developments are likely to include higher-valency conjugate vaccines, but the immunogenicity of conjugate vaccines and an effect on clinical endpoints in adults have not been shown consistently to be greater than that seen with the current polysaccharide vaccine. Improved coverage of high-risk adults through vaccination with polysaccharide vaccine and development of pneumococcal protein antigens as targets of immunization is an ongoing effort.

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