

Pneumococcal Vaccination in High-Risk Individuals: Are We Doing It Right?

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Controversy exists regarding the optimal use of the 23-valent pneumococcal conjugate vaccine for the protection of high-risk individuals, such as children and adults with immunocompromising conditions and the elderly. The effectiveness and immunogenicity of 23-valent pneumococcal polysaccharide vaccine (PPV23) are limited in such high-risk populations compared to the healthy, with meta-analyses failing to provide robust evidence on vaccine efficacy against invasive pneumococcal disease (IPD) or pneumonia. Moreover, several studies have demonstrated a PPV23-induced state of immune tolerance or hyporesponsiveness to subsequent vaccination, where the response to revaccination does not reach the levels achieved with primary vaccination. The clinical significance of hyporesponsiveness is not yet clarified, but attenuated humoral and cellular response could lead to reduced levels of protection and increased susceptibility to pneumococcal disease. As disease epidemiology among high-risk groups shows that we are still in need of maximum serotype coverage, the optimal use of PPV23 in the context of combined conjugate/polysaccharide vaccine schedules is an important priority. In this minireview, we discuss PPV23-induced hyporesponsiveness and its implications in designing highly effective vaccination schedules for the optimal protection for high-risk individuals.

Streptococcus pneumoniae (the pneumococcus) is a major cause of life-threatening invasive infections accounting for considerable morbidity and mortality worldwide (1). Children and adults with certain medical conditions as well as the elderly are at increased risk for invasive pneumococcal disease (IPD) and pneumonia, with disease rates up to 20 times higher than those in the general population (2). High-risk groups consist of children and adults with chronic diseases and with primary and secondary immune deficiencies and of persons with functional or anatomical asplenia. Persons older than 65 years of age are also at increased risk for pneumococcal infection, due to attenuation of their immune response caused by advancing age, a phenomenon called immunosenescence (3). The number of patients in need for protection against IPD is continually increasing due to rising numbers of people with chronic disease or HIV infection and an aging population in many high-income countries.

Pneumococcal disease is usually more severe in such high-risk individuals than in immunocompetent subjects (4–6). While antibiotic resistance represents an additional hurdle for the successful treatment of pneumococcal infections (7, 8), optimal protection of such “high-risk” groups against *S. pneumoniae* infection through vaccination continues to be an important priority.

For more than 2 decades, a 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended for the protection of immunocompromised individuals and the elderly against invasive pneumococcal disease (IPD) and pneumonia (9).

The licensure of the pneumococcal polysaccharide vaccine (PPV) was based on trials of a 6-valent PPV and a 13-valent PPV among South African gold miners (10) and a 14-valent PPV trial in Papua New Guinean highlanders (11), which showed strong vaccine efficacy against bacteremic pneumonia. In 1983, a 23-valent formulation containing a reduced amount (25 µg) of each purified capsular polysaccharide replaced the earlier polysaccharide formulations without, however, additional prelicensure trials evaluating its efficacy against bacteremic pneumonia.

Today, two types of pneumococcal vaccines are available for

high-risk individuals, with different immunological characteristics and numbers of serotypes contained in each: the 23-valent pneumococcal polysaccharide vaccine, which induces a T-independent (TI) immune response with serotype-specific antibody formation but no immune memory, and a 10-valent pneumococcal conjugated vaccine (PCV10) and a 13-valent pneumococcal conjugated vaccine (PCV13), in which pneumococcal polysaccharides are coupled with a carrier protein and induce a T-dependent (TD) immune response (12). While PPV23 induces only serotype-specific antibodies, PCV13 generates the formation of both serotype-specific antibodies and B memory cells, which are associated with a longer duration of vaccine-induced immune responses.

PCV13 replaced a 7-valent formulation (PCV7) which was launched 15 years ago in the United States and was rapidly incorporated into the national immunization programs of many countries worldwide. PCV7 had to be replaced 10 years after its introduction by PCV13 due to the increased incidence of invasive pneumococcal disease (IPD) caused by non-PCV7 serotypes. PCV13 contains most emerging serotypes, e.g., serotype 19A, and is currently recommended for at-risk individuals of all ages (13–15).

In an effort to maximize protection against the pneumococcus for high-risk individuals, a combined schedule that includes PCV13 followed by PPV23 (13–15), with an additional PPV23 booster after 5 years, is recommended. PCV13/PPV23 immunization schedules have the theoretical benefit of combining establish-

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ment of immunological memory with maximum serotype coverage. However, controversy regarding PPV23 effectiveness among high-risk individuals (16), as well as evidence of PPV23-induced immunological hyporesponsiveness (17), causes skepticism about the optimal use of polysaccharide vaccines in the context of combined vaccination schedules.

In this article, we review the issue of PPV23-induced hyporesponsiveness and its implications in designing highly effective vaccination schedules for the optimal protection for immunocompromised individuals of all ages.

PNEUMOCOCCAL SEROTYPE EPIDEMIOLOGY IN HIGH-RISK INDIVIDUALS

Extended serotype coverage has long been the strongest argument in favor of PPV23 use in high-risk individuals, although the epidemiology of serotypes causing IPD in this population is not fully known.

There are over 90 different serotypes of *S. pneumoniae*; some are highly invasive, whereas others rarely cause disease. Among serotypes causing disease, there are significant differences in distribution between different age groups and geographical populations (18, 19).

The surveillance of pneumococcal disease after the introduction of PCV13 indicates that, similarly to what happened after the introduction of PCV7, the epidemiology is changing, with new emerging serotypes dominating carriage and disease, although it is predicted that serotype replacement following the introduction of PCV13 will not increase significantly the burden of IPD due to the low case-to-carrier ratios demonstrated for most of the replacement serotypes (20). The added value of continuing to include PPV23 in vaccination schedules for high-risk individuals in the years to come remains to be determined by monitoring whether the replacing serotypes causing IPD are covered by the 23-valent polysaccharide vaccine. Data reported from the United Kingdom since the introduction of PCV13 show that some of the emerging serotypes causing IPD in children over 5 years of age and in adults of all ages, such as serotypes 15A and 24F, are not included in PPV23 (21). Data from the United States, however, show that the proportion of IPD caused by serotypes unique to PPV23 in the elderly reached 38% in 2013 (15). Nevertheless, since the type and invasive potential of new serotypes are not easily predictable, careful monitoring of pneumococcal disease is necessary.

PPV23 EFFECTIVENESS IN HIGH-RISK INDIVIDUALS

PPV23 effectiveness against IPD and pneumonia in high-risk individuals and the elderly, the populations most in need for protection against pneumococcal disease, remains debatable despite its extensive use for over 25 years.

A number of randomized controlled trials and observational studies have been conducted among healthy adults with chronic diseases (22–25), adults with immunocompromising conditions (26–29), and the elderly (30–35), with inconclusive results regarding vaccine effectiveness against IPD and pneumonia. Differences were mainly due to study heterogeneity regarding study methodology, size, and design and population studied (16).

Moreover, such differences from individual original studies could not be resolved in several meta-analyses, which have also produced differing conclusions regarding levels of effectiveness against IPD and pneumonia in healthy and immunocompromised individuals (36–51).

The most recent Cochrane meta-analysis demonstrated effectiveness of PPV23 against IPD for healthy adults but no protection against pneumonia and all-cause mortality (52). Moreover, a subanalysis in high-risk populations of high-income countries showed no evidence of protective vaccination efficacy against IPD and pneumonia. However, the authors stressed that this could have been due to the lack of the statistical power necessary to demonstrate significant differences between the vaccinated group and the control groups (52).

The evaluation of PPV23 effectiveness with the use of immunological correlates of protection such as vaccine immunogenicity indicates that it induces antibodies in immunocompromised subjects but that antibody levels decrease substantially shortly after vaccination and that the duration of protection is relatively short-lived (53, 54). Moreover, advancing age and comorbidities have been associated with even lower antibody responses (55). Although it is not known what level of antibody should be considered protective for such high-risk individuals, it is expected that in older subjects, who are more susceptible to pneumococcal disease, PPV23 effectiveness might be diminished.

IMMUNOLOGICAL HYPORESPONSIVENESS

In an effort to protect individuals at risk, immunization with PPV23 used to be repeated every 5 years due to the exclusively humoral nature of the response induced by PPV23 and the waning of antibody levels shortly after vaccination (56).

However, the repeated use of PPV23 required for protection of high-risk individuals has been associated with hyporesponsiveness, a phenomenon where vaccine recipients are unable to mount an immune response to revaccination which represents a greater antibody response or at least a response of the same magnitude as the primary response.

Hyporesponsiveness was first described in the 1990s following vaccination with meningococcal polysaccharide vaccines and has been attributed to the immune tolerance induced by the vaccine polysaccharide antigens (57, 58). Since then, several studies demonstrated the same phenomenon following pneumococcal polysaccharide vaccination (59–68). These studies are summarized in Table 1.

The hyporesponsiveness effect of PPV23 in the establishment of PCV-induced immunological memory has been demonstrated in both pediatric and adult populations. In a study by Russell et al., infants who had received PPV23 12 months after PCV7 priming, after challenge with a small dose (20%) of PPV23 at 17 months, had antibody titers for all PCV7 serotypes that were significantly lower than the titers seen with those who had not received PPV23 (63). A similar study by Lazarus et al. performed in adults demonstrated immunologic hyporesponsiveness to PCV7 administered after PPV23, regardless of the different vaccination schedules used for PCV7 priming; such hyporesponsiveness was not restored by additional doses of PCV7 (61).

Interestingly, the magnitudes of hyporesponsiveness seem to differ among pneumococcal serotypes (PS), possibly due to the structural diversity of different pneumococcal antigens associated with different immunological properties, e.g., T-cell dependency and immunogenicity (65).

There is also evidence that hyporesponsiveness is not an exclusively vaccine-induced phenomenon; it has also been reported after IPD or nasopharyngeal carriage in pediatric populations. A study by Borrow et al. reported hyporesponsiveness in children

TABLE 1 Summary of trials demonstrating PPV23-related immune hyporesponsiveness

Study(ies)	Country	Vaccination schedule	Population	No. of patients	Summary of findings
Sigurdardottir et al. (2014) (59)	Iceland	PCV9/PCV9/PCV13	Children 7.5 yrs old	39	PPV23 vaccination of toddlers attenuated the subsequent response to PCV13
		PCV9/PPV23/PCV13		50	
Papadatou et al. (2014) (60)	Greece	PCV13 1–4 PPV23 doses given prior to the study	Asplenic adults with β -thalassemia	39	Prior history of PPV23 vaccination attenuated the response to PCV13 in a dose- and time-dependent manner
Clutterbuck et al. (2012) (62); Lazarus et al. (2011) (61)	United Kingdom	PPV23-PCV7-PCV7	Adults 50–70 yrs old	116	Prior vaccination with PPV23 attenuated the response to subsequent vaccination with PCV7
		PCV7-PPV23-PCV7		116	
		PCV7-PCV7-PPV23		116	
Russell et al. (2010) (63)	Fiji	1–3 PCV7 doses/mPPV23 ^a	Infants	276	The response to an mPPV23 challenge was lower in children who had received PPV23 at 12 mo of age
		1–3 PCV7 doses/PPV23/mPPV23		276	
Dransfield et al. (2009) (64)	United States	PCV7 PPV23	Adults with COPD	57	Prior vaccination with PPV23 reduced vaccine responsiveness to either PPV23 or PCV7
		1–4 PPV23 doses given prior to the study		63	
Orthopoulos et al. (2009) (65)	Greece	PCV7/PPV23/PPV23	Asplenic adults with β -thalassemia	17	Multiple PPV23 doses induced hyporesponsiveness for some serotypes
		PCV7/PCV7/PPV23 0–3 PPV23 doses given before the study		18	
Musher et al. (2008) (66)	United States	PCV7/PPV23	Adults who recovered from pneumococcal pneumonia	37	Prior recent (>1 yr) vaccination with PPV23 attenuated the response to PPV23 and PCV7; the PPV23/PCV7 schedule resulted in lower antibody responses than the PCV7/PPV23 schedule
		PPV23/PCV7 PPV23 doses given prior to the study		44	
de Roux et al. (2008) (67)	Germany	PCV7/PCV7	Adults >70 yrs old	43	PPV23 used as the primary dose induced hyporesponsiveness
		PCV7/PPV23		38	
		PPV23/PCV7		78	
Mufson et al. (1991) (68)	United States	PPV14/PPV23	Adults 56–79 yrs old	15	Antibody levels after revaccination were lower than after primary vaccination

^a mPPV23, small dose of PPV23.

with IPD who were subsequently vaccinated with PCV7 and failed to reach the protective threshold of antibodies against the pathogenic serotype (69). Furthermore, Dagan et al. demonstrated that pneumococcal nasopharyngeal carriage in early infancy shortly before vaccination with PCV7 can lead to serotype-specific hyporesponsiveness to subsequent vaccination for the carried PS, implying a mechanism of B-cell unresponsiveness following colonization (70).

Several mechanisms, acting separately or in combination, have been suggested to be responsible for this immunological phenomenon (61–63). Polysaccharide antigens induce a T-cell-indepen-

dent immune response, stimulating but not replenishing memory cells, thus resulting in overall depletion of the memory cell pool and attenuated responses on reexposure to the same PS. We have previously shown that, in contrast to vaccination with PCV13, which resulted in an increase of levels of antigen-specific memory B cells (MBCs), in splenectomized subjects with β -thalassemia, a history of previous vaccinations with PPV23 had an attenuating effect on antigen-specific MBC pool levels (60). Our findings are in accordance with recent data from studies in murine models as well as in human lymphocytes which have shown that, upon secondary challenge with a T-independent antigen, such as the anti-

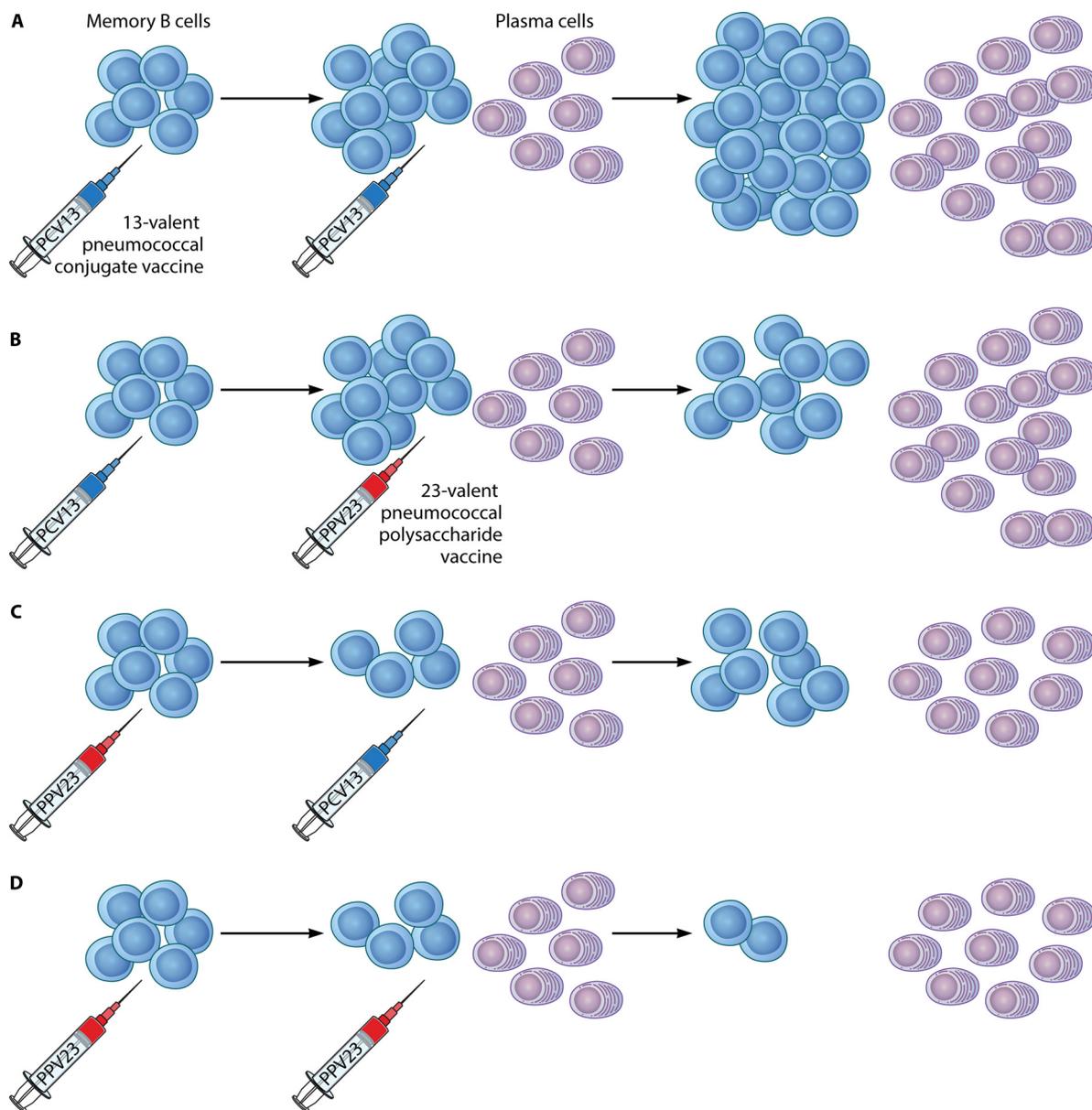


FIG 1 Priming and boosting with the 23-valent pneumococcal polysaccharide vaccine (PPV23) or the 13-valent pneumococcal conjugate vaccine (PCV13) and the effect on the pool of antigen-specific memory B cells (MBCs): a mechanism for immune hypo-responsiveness. (A) Priming and boosting with PCV13 result in incremental increases in the numbers of pooled MBCs. (B) Priming with PCV13 enriches the MBC pool, but a subsequent PPV23 booster depletes it. (C) Primary vaccination with PPV23 results in decreased numbers of antigen-specific MBCs. Subsequent vaccination with PCV13 enriches the depleted MBC pool. (D) Repeated immunizations with PPV23 lead to gradual depletion of the MBC pool.

gens contained in the PPV23 vaccine, IgM and IgG memory B cells differentiate terminally toward plasma cells. In contrast, rechallenge with a TD antigen, such as the PCV13 vaccine, leads IgM memory B cells to reenter germinal center (GC) reactions and promote the enrichment of antigen-specific immunological memory (71–73). The proposed mechanisms for the effect of PPV23 on the antigen-specific memory B-cell pool and in relation to previous or subsequent vaccination with a pneumococcal conjugate vaccine are illustrated in Fig. 1.

It is also been suggested that the response to secondary vaccination could be attenuated by large amounts of persisting circulating antigens, which can continuously bind to naive B cells and

neutralize polysaccharide-specific antibody, thus resulting in long-lasting hypo-responsiveness (74).

Finally, an immunosuppressive mechanism involving pneumococcal polysaccharide-induced interleukin-10 (IL-10) production by dendritic cells (DCs) *in vitro* has also been associated with downstream effects on regulatory T lymphocytes (Tregs) and antigen-specific antibody responses (75).

The magnitude of hypo-responsiveness seems to be related to the number of doses and the intervals between subsequent vaccinations. We have recently shown that multiple (>2) PPV23 doses and shorter intervals between vaccination associated with high levels of circulating antibodies have a greater impact

on hyporesponsiveness (60). The negative impact of high concentrations of circulating antibodies (76) and plasma cells (77) on GC reactions has also been demonstrated in animal studies.

Interestingly, there are findings implying not only attenuated protection but possibly an increased risk for IPD in individuals with severe immunodeficiency induced by the use of polysaccharide vaccines. Increased rates of all-cause pneumonia have been demonstrated among HIV-infected PPV23 recipients in Uganda compared to unvaccinated patients (78). Although the clinical significance of hyporesponsiveness in high-risk individuals is not yet clarified, taking such concerns into account, updated Paediatric European Network for Treatment of AIDS (PENTA) guidelines do not recommend PPV23 for use in HIV-infected children (79).

DO CURRENT GUIDELINES TAKE INTO ACCOUNT PPV23-INDUCED HYPORESPONSIVENESS?

In light of the evidence of the PPV23-related immune hyporesponsiveness, guidelines for the protection of those at risk have been updated and currently PCV13 is recommended for protection of high-risk individuals of all ages. PPV23 is still in use for broader serotype coverage, but, in contrast to previous practices, repeated doses have been abandoned, and administration of a maximum of two doses is now recommended for the majority of high-risk patients (13–15).

In the currently recommended PCV13/PPV23 combined schedule, administration of the conjugate vaccine precedes administration of the polysaccharide, in order for PCV13 to establish immunological memory for the 13 serotypes that it contains and for PPV23 to subsequently induce antibody responses to the 12 additional serotypes. However, there are accumulating data indicating that PPV23 could attenuate the immunological memory induced by conjugate vaccines even when it is given soon after PCV13. In a recent study by Bjarnarson et al., where neonatal mice were immunized with a pneumococcal conjugate vaccine followed shortly by a polysaccharide booster, the booster with plain pneumococcal polysaccharide caused abrogation of conjugate-induced reactions of germinal centers and depletion of antigen-specific antibody-secreting cells that had been created in response to the conjugate primary immunization (80). Similarly, in a study by Clutterbuck et al., a decrease in the number of memory B cells was recorded when PPV23 was administered after one or two doses of PCV7 (62).

Although these data suggest that PPV23 has a depleting effect on PCV13-induced immunological memory even when given after PCV13, there is evidence that the PPV23-inflicted attenuation of immune memory might be more significant when PPV23 is given before PCV13 (81).

It is thought that hyporesponsiveness induced by the PPV23/PCV13 schedule is caused by the combined effect of two different mechanisms, i.e., (i) the direct depletion of antigen-specific MBCs by the polysaccharide antigens and (ii) the large amounts of plasma cells and antibodies that are produced in response to PPV23, which could also block the stratification of naive B cells to germinal centers (GC) in response to subsequent PCV13 by a negative-feedback mechanism (76).

Unfortunately, current guidelines do not take into consideration that hyporesponsiveness is a time-dependent phenomenon and that conjugate vaccine-induced memory is affected more significantly when PCV13 is given shortly after PPV23. This is of high

importance to the majority of high-risk individuals today, as most would have already been vaccinated with at least one dose of PPV23 in the past, in accordance with previous recommendations. Short intervals between PPV23 vaccination and subsequent PCV13 vaccination for PPV23-experienced individuals are still allowed in the current guidelines; for children previously immunized with PPV23, it is recommended that a single PCV13 dose be given ≥ 8 weeks after the last PPV23 dose (14), whereas administration of a dose of PCV13 ≥ 1 year after the most recent PPV23 dose is recommended for immunocompromised adults and the elderly (81).

Such short intervals are expected to lead to suboptimal induction of immunity to vaccine antigens among the members of the populations most at risk, as the ability of PCV13 to induce a strong immunological memory is expected to be attenuated by the recent immunization with the polysaccharide vaccine. Evidence from studies performed with different intervals between PCV13 vaccination and subsequent PPV23 vaccination shows that the overall antibody response seen with a 3-to-4-year interval is superior to that seen with a 1-year interval (81). Such findings could be explained by the waning of circulating antibodies with time and the recharging of the B-cell pool by natural exposure to pneumococcal and cross-reacting antigens (60).

We have recently shown that PPV23 vaccination can affect immune responses to subsequent PCV13 vaccination in asplenic adults for as long as 6 years (82); we therefore propose that measurement of levels of anti-pneumococcus antibodies before vaccination could prove beneficial in optimizing intervals between vaccinations for such individuals. In the presence of high antibody levels, subsequent pneumococcal vaccination could be postponed, in order to maximize the potential of the immune response to future vaccination in terms of magnitude and longevity.

CONCLUSIONS

Significant progress has been achieved in recent years in incorporating accumulating research regarding PPV23-induced hyporesponsiveness and vaccine efficacy into clinical practice. The guidelines for the immunization of individuals at high risk of pneumococcus infection have significantly changed in the last 5 years, replacing the use of PPV23 alone with combined PCV13/PPV23 schedules for adults with immunocompromising conditions and introducing PCV13 into vaccination schedules of the elderly.

However, vaccination guidelines for high-risk individuals should be revised in order to maximize PCV13-induced immunological memory and long-term vaccine effectiveness. To that end, reassessment of pneumococcal vaccination policy with a special focus on the intervals between vaccinations in the context of combined conjugate/polysaccharide vaccine schedules is an important priority. Ongoing research on the mechanisms of establishment and maintenance of immunological memory is essential, and clinical trials on PPV23 effectiveness in high-risk populations are necessary in order to optimize vaccine protection against pneumococcal disease for individuals at risk.

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