

SUMMARY OF THE VACCINATION GUIDELINE

The place of SYNFLORIX™ in the pneumococcal vaccination strategy in children under 5 years of age

February 2018

At the request of the Ministry of Solidarity and Health and as part of the market access procedure submitted by GlaxoSmithKline (GSK) for SYNFLORIX™ pneumococcal vaccine, the Haute Autorité de Santé (HAS) provides recommendations on the place of this vaccine in the current pneumococcal infection prevention strategy in children in France.

Following the assessment carried out, HAS recommends not including SYNFLORIX™ in the established vaccination strategy in the specific French context.

CURRENT PNEUMOCOCCAL INFECTION PREVENTION STRATEGY IN FRANCE IN CHILDREN

Pneumococcus

Pneumococcus (*Streptococcus pneumoniae*) is the cause of multiple diseases, including invasive infections (meningitis, septicaemia, pneumonia with bacteraemia) and non-invasive infections (community-acquired pneumonia without bacteraemia, acute otitis media and sinusitis). There are more than 95 different serotypes, some of which are responsible for invasive infections. Pneumococcus very frequently colonises the nasopharynx of children under 5 years of age and is transmitted by air. Children's throats are the main source of contamination of adults.

Pneumococcal infection prevention strategy in children

- The pneumococcal infection prevention strategy in children is currently based on vaccination by the 13-valent conjugate vaccine (PREVENAR 13®) in:
 - all children under 2 years of age, including premature babies and infants at increased risk¹ of pneumococcal infections;
 - children aged 2 years to under 5 years who are immunosuppressed or at increased risk¹ of pneumococcal infections.

Vaccination with PREVENAR 13® includes a first dose at age 2 months, followed by a second dose at 4 months and a booster dose at 11 months.

Vaccination regimens established based on age of vaccination are specified in the vaccination schedule and vaccination guidelines.

In addition, an enhanced vaccination regimen with 4 doses of PCV-13 (at 2, 3 and 4 months followed by a booster dose at 11 months of age) is recommended in premature babies and infants at increased risk of pneumococcal infection.

In children over 2 years of age who are immunosuppressed or at increased risk of pneumococcal infections due to an underlying disease, vaccination is also recommended, using a vaccination regimen that includes the 13-valent conjugate vaccine and the 23-valent polysaccharide vaccine (see vaccination schedule and vaccination guidelines).

1. Due to an underlying disease.

Pneumococcal conjugate vaccines

In France, the first pneumococcal conjugate vaccine containing 7 serotypes, PREVENAR® (PCV-7), was available starting in 2003 and was replaced in 2010 by the conjugate vaccine containing 13 serotypes, PREVENAR 13® (PCV-13).

To date, PREVENAR 13® is the only vaccine recommended in France for primary vaccination and booster against pneumococcal infections in newborns.

SYNFLORIX™ is a 10-valent pneumococcal conjugate vaccine (PCV-10) (containing serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) which has had Marketing Authorisation (MA) in Europe since 2009. Its current European MA is "active immunisation against invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* (Sp) in **infants and children aged 6 weeks to 5 years**".

Table 1. Composition of pneumococcal conjugate vaccines

Vaccines	Common serotypes	Additional serotypes		Carrier protein
PREVENAR®* (PCV-7)	4, 6B, 9V, 14, 18C, 19F, 23F			Modified diphtheria toxin CRM-197
SYNFLORIX™ (PCV-10)		1, 5, 7F		Protein D of nontypeable <i>H. influenzae</i> (except 18C, 19F) Tetanus toxoid (18C) Diphtheria toxoid (19F)
PREVENAR 13® (PCV-13)		1, 5, 7F	3, 6A, 19A	Modified diphtheria toxin CRM-197

*marketing stopped in 2010

- The vaccination regimen established by the MA of SYNFLORIX™ in **infants aged 6 weeks to 6 months** is based on:
 - a 3-dose primary vaccination regimen followed by a booster (3+1) with a first dose generally administered at age 2 months and an interval of at least one month between subsequent doses, then a booster dose preferably administered between 12 and 15 months of age (and at least 6 months after the last dose of the primary vaccination);
 - an alternative 2-dose primary vaccination regimen (2+1) as part of a widespread vaccination program in children, with a first dose that can be administered as early as 6 weeks, followed by a second dose administered 2 months later and then a booster dose preferably administered between 12 and 15 months of age (and at least 6 months after the last dose of the primary vaccination).

EPIDEMIOLOGY OF PNEUMOCOCCAL INFECTIONS

The introduction of widespread vaccination of children under 2 years of age in the vaccination schedule has considerably changed the epidemiology of invasive pneumococcal diseases (IPD).

While the introduction of PREVENAR® (7-valent) in 2003 allowed for a major reduction in the incidence of IPDs related to vaccine serotypes in children, this reduction was greatly overcome by a significant increase in the incidence of IPDs caused by non-vaccine serotypes, and especially serotypes 19A, 7F and, to a lesser extent, serotype 1.

The serotype replacement induced by vaccination, for which 19A was mainly responsible, led to a worldwide increase in IPDs between the pre-vaccination period of 2001-2002 and 2009. Only the change in the vaccination schedule in 2010, with the recommendation of vaccination by PREVENAR 13® (13-valent) – including the 3 serotypes most involved in the replacement phenomenon (19A, 1 and 7F) – instead of PREVENAR® (7-valent) helped to reverse the trend.

- Since the introduction of vaccination by PREVENAR 13® in infants, data up to late 2016 shows:
 - a **reduction in invasive diseases in all age groups**: in infants under 2 years of age (essentially direct effect), but also in age groups not targeted by the vaccination (indirect effect) and, in particular, in adults over 65 years of age, which highlights **the indirect and collective effect of vaccination through a significant reduction in nasopharyngeal carriage** of vaccine pneumococcal serotypes in vaccinated children and replacement with generally less pathogenic serotypes;

- a modification in the distribution of serotypes of invasive strains of Sp demonstrated by:
 - a significant reduction in vaccine serotypes and an increase in the proportion of numerous and diverse non-vaccine serotypes, but **without the emergence or prominence of one or more particular serotypes**,
 - a **decrease in the proportion of pneumococci with decreased sensitivity to beta-lactams** currently isolated;
- a change in age of onset of IPDs, which now affects individuals over 5 years of age in more than 90% of cases;
- in terms of public health, **the impact of the vaccination on the carriage of different serotypes has become the main issue concerning pneumococcus**.

DATA AVAILABLE WITH THE SYNFLORIX™ VACCINE

A significant clinical development and a significant experience in use

SYNFLORIX™ was the subject of a significant clinical development program and has been used since 2010 in many countries, including in Latin America, as part of widespread vaccination programs in infants. In Europe, some countries have made the choice to exclusively use PCV-13 or PCV-10 while others have recommendations for both vaccines.

SYNFLORIX™ – A demonstrated efficacy on IPDs

A demonstrated efficacy on vaccine serotypes

- SYNFLORIX™ induces an immune response above the threshold of protection on vaccine serotypes similar to those of other pneumococcal vaccines.
- However, the antibody titres obtained with SYNFLORIX™ are lower than those obtained with PREVENAR® for all vaccine serotypes except serotype 19F and lower than those obtained with PREVENAR 13® for most vaccine serotypes as well as for serotypes 19A and 6A (even if few studies conducted compared against PREVENAR 13®).
- It has demonstrated its clinical efficacy on IPDs and pneumonia caused by vaccine serotypes.

A more controversial cross-protection

- A certain degree of cross-protection (efficacy on non-vaccine serotypes) has been observed in immunogenicity studies and in observational studies (to varying degrees) conducted in children under 5 years of age. However, there is no proof of clinical efficacy on IPDs caused by serotype 19A in the clinical trials or cross-protection efficacy data on nasopharyngeal carriage.
- Epidemiological surveillance data in the countries that introduced PCV-10 confirm the efficacy of SYNFLORIX™ and a significant reduction of IPDs caused by vaccine serotypes in children under 5 years of age. However, these data are suggestive of a very limited impact of PCV-10 vaccination on the acquisition of serotype 19A nasopharyngeal carriage and the reduction of IPDs caused by serotype 19A in individuals over 65 years of age.

The safety profile of SYNFLORIX™ is comparable to that of other pneumococcal vaccines.

The WHO recognises the substantial effect of both conjugate vaccines on pneumonias, IPDs caused by vaccine strains and nasopharyngeal carriage. The WHO also emphasises the additional benefit of 13-valent conjugate vaccine in settings where diseases attributable to serotype 19A or serotype 6C is significant. This was the case in France before the introduction of PREVENAR 13®, as from 2007–2009, this serotype represented up to 26.5% of IPDs in children under 5 years of age and 14.9% of these infections in all ages combined.

ROLE OF SYNFLORIX™ IN THE CURRENT PNEUMOCOCCAL VACCINATION STRATEGY IN CHILDREN

Although there is interest in broadening the offering of paediatric pneumococcal vaccines from a pricing perspective and to avoid potential supply tensions, HAS believes that the French and international epidemiological data **do not currently support** the use of SYNFLORIX™ in the pneumococcal infection prevention strategy in the specific French context.

HAS does not recommend introducing SYNFLORIX™ to the French paediatric vaccination schedule

- The theoretical serotype coverage of SYNFLORIX™ in IPDs is similar to that of PREVENAR®, but over 10% lower than that of PREVENAR 13® in most age groups in 2016.
- Persistence in both carriage and in IPDs caused by serotype 19A, which demonstrates its antibiotic resistance and its main role in the serotype replacement observed in France after PREVENAR® vaccination, justifies particular attention to the potential impact of PCV-10 on this serotype and the risk of its possible re-emergence in France.
- SYNFLORIX™ has neither demonstrated clinical efficacy on IPDs caused by non-vaccine serotype 19A in clinical trials nor efficacy on nasopharyngeal carriage in terms of cross-protection.
- In countries that have introduced SYNFLORIX™, the data suggest a very limited impact of vaccination on both the acquisition of serotype 19A nasopharyngeal carriage and the reduction of IPDs caused by serotype 19A in individuals over 65 years of age, which now represent the populations most affected by pneumococcal diseases.

Therefore, HAS is not in favour of **adding vaccination with SYNFLORIX™ to the paediatric strategy for prevention of invasive pneumococcal diseases in the specific French context.**

However, this **position could be reassessed** in the context of a **temporary use, as an exception, especially in case of supply tensions** with PREVENAR 13®, which remains the only pneumococcal vaccine recommended in infants.



This document provides the main highlights from the vaccine guideline "Role of SYNFLORIX in the pneumococcal vaccination strategy in children under 5 years of age".

Date of validation by the Board: February 2018.

The full text of these guidelines and the scientific rationale can be consulted at www.has-sante.fr