

# Vaccines to Children

## Protective Effect and Adverse Events

A Systematic Review

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*Summary and Conclusions of the SBU Report:*

# Vaccines to Children

## Protective Effect and Adverse Events

### A Systematic Review

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# SBU's Conclusions

Few medical interventions have had as great an impact on global health as immunisation of children. Extensive immunisation programmes have eradicated smallpox completely and eliminated polio in all but a handful of countries. Thus, the benefits of immunisation are indisputable. But it is important to critically examine an intervention that is recommended for all infants. Routine immunisation must provide reasonable protection against potentially serious diseases, while the risk of serious adverse events must be low. Experience shows that immunisation coverage tends to decline if there is widespread concern about adverse events. Therefore, a solid body of knowledge is needed. Thus, SBU has been requested to review the published scientific literature regarding some vaccines included in the immunisation programme for children in Sweden.

The present scientific review and the experience from many years of the routine immunisation programme have shown that:

- ❑ The benefits of immunisation far outweigh the risks of adverse events.
- ❑ Immunisation has virtually eliminated the morbidity and mortality of many diseases previously common among both children and adults.

## **Immunisation with *Haemophilus Influenzae* type b Vaccine**

- ❑ Immunisation with *Haemophilus influenzae* type b (Hib) vaccine effectively protects against Hib infections, which can be serious (Evidence Grade 1). The protective effect lasts at least three years. Immunisation against Hib reduces carriage of Hib in the pharynx of children (Evidence Grade 3). Routine

immunisation of infants also reduces the frequency of serious Hib infections in unvaccinated individuals, so called herd immunity (Evidence Grade 3). There is no data suggesting a causal relationship between Hib conjugate vaccines and serious adverse events such as death, sudden infant death syndrome, seizures, type 1 diabetes mellitus and Guillain-Barré syndrome, a neurological disease.

### **Immunisation with Pertussis Vaccine**

- ❑ Immunisation with pertussis vaccine protects children against pertussis (Evidence Grade 1). The protective effect lasts at least 5 years after three or four doses of acellular pertussis vaccine (Evidence Grade 3). Routine immunisation programmes that include acellular pertussis vaccine reduce the need of hospitalisation due to pertussis among vaccinated children younger than 2 years of age (Evidence Grade 3). There is no evidence of a higher frequency of or deaths from serious bacterial infections after immunisation with acellular pertussis vaccine (Evidence Grade 1). The scientific literature provides no substantial indication of a causal relationship between acellular pertussis vaccine and the few serious adverse events described in case reports or in national adverse event reports. Health economic models show that immunisation against pertussis is socioeconomically warranted. However, the cost-benefit ratio varies substantially according to assumptions on incidence of pertussis, vaccine efficacy and percentage of immunised children.

### **Immunisation with Measles-Mumps-Rubella Vaccine**

- ❑ Combination measles-mumps-rubella (MMR) vaccines currently in use provides protection against all three diseases and their complications (Evidence Grade 3).

- ❑ MMR vaccine increases the risk of febrile seizures during the first two weeks after immunisation, when fever commonly occurs, but does not increase the risk of later epilepsy (Evidence Grade 3). MMR vaccine does not cause type 1 diabetes or serious infections requiring hospitalisation (Evidence Grade 3). MMR vaccine does not cause autism or autism spectrum disorder (Evidence Grade 3).

### **Immunisation with Hepatitis B Vaccine**

- ❑ Immunisation with hepatitis B vaccine protects children against hepatitis B (Evidence Grade 1). More than 90% of immunised children develop protective antibody levels after the first dose (Evidence Grade 1). Serious hypersensitivity reactions have been reported following hepatitis B immunisation, but very rarely. There is insufficient scientific evidence to rule out or confirm an association between hepatitis B immunisation and multiple sclerosis (MS). Available data taken together suggest that there is no such correlation. The literature provides no substantial indication of a causal relationship between hepatitis B vaccine and other serious adverse events described in case reports: death, neurological disease other than MS, arthritis and chronic fatigue syndrome. Health economic models indicate hepatitis B vaccine to be cost-effective from a healthcare perspective.

### **Immunisation Against Tuberculosis**

- ❑ Bacille Calmette-Guérin (BCG) vaccine administered during the neonatal period or shortly thereafter protects children against tuberculosis at least until 5 years of age. Protection against all forms of tuberculosis is approximately 75% (Evidence Grade 2). Efficacy against disseminated (miliary) tuberculosis and tuberculous meningitis is higher around 75 to 85% (Evidence Grade 2). Fatal disseminated BCG infection occurs after BCG immunisation, but very rarely (Evidence Grade 1).

The risk is approximately 1 case per 100 000 immunised infants. The condition is mainly contracted by children with a rare genetic immunodeficiency disease that also increases the risk for other diseases. To further reduce the risk of this serious but rare adverse event, BCG immunisation in Sweden is deferred till 6 months of age, allowing time to identify infants with this rare immunodeficiency disease and exclude them from BCG immunisation.

### **Adverse Events Following Combination Vaccines**

- There is no indication of clinically significant differences in the frequency of redness, swelling or fever after administration of vaccines that contain different combinations of the following vaccines: diphtheria (D), tetanus (T), pertussis (Pa), polio (IPV), hepatitis B (HBV) and *Haemophilus influenzae* type b (Hib) (hexavalent vaccine; DTPa-IPV-HBV/Hib, pentavalent vaccine; DTPa-IPV/Hib, tetravalent vaccine; DTPa-IPV or trivalent vaccine; DTPa) (Evidence Grade 2).

No evidence is available suggesting a greater frequency of hypotonic hyporesponsive episode or persistent inconsolable crying after administration of combination hexavalent, pentavalent or tetravalent vaccine than trivalent vaccine (DTPa) (Evidence Grade 3). The overall literature provides no substantial indication of a causal relationship between immunisation and the very occasional serious adverse events, including death, described in case reports or national adverse event reports (insufficient scientific evidence).

## Fact Sheet 1 Study Quality and Relevance, Evidence Grade.

**Study quality and relevance** refers to the scientific quality of a particular study and its ability to reliably address a specific question.

**Evidence grade** refers to the total scientific evidence for conclusion.

### **Evidence Grade 1 – Strong Scientific Evidence**

A conclusion assigned Evidence Grade 1 is supported by at least two studies with high quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

### **Evidence Grade 2 – Moderately Strong Scientific Evidence**

A conclusion assigned Evidence Grade 2 is supported by at least one study with high quality and relevance, as well as two studies with medium study quality and relevance, among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

### **Evidence Grade 3 – Limited Scientific Evidence**

A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be insufficient or contradictory.

### **Insufficient Scientific Evidence**

If no studies meet the study quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

### **Contradictory Scientific Evidence**

If different studies are characterized by equal study quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions can be drawn.

# SBU's Summary

## Background and Purpose of the Project

The principle of immunising people in order to prevent infections has a long successful history. An individual is protected against the natural infection if all or part of a pathogen is introduced into her body in a controlled way. The immunisation activates specific antibodies and memory cells in the immune system. If the person is subsequently exposed to infection, the immunological defense is already prepared and no disease develops. Immunisation has induced immunity to the disease.

WHO regards global child immunisation programmes as highly successful in terms of controlling and even eradicating certain diseases. Both WHO and the World Bank rank immunisation among the most cost-effective health care measures available.

Sweden introduced immunisation against smallpox in the early 19th century. It became possible to immunise against tuberculosis in the 1920s but a routine child immunisation programme was not adopted until diphtheria and tetanus vaccines were added in the 1940s. Paediatric and school health services now offer children in Sweden immunisation against eight diseases: diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b infection, measles, mumps and rubella (as of 2009, Sweden has also adopted routine immunisation of pneumococcal conjugate vaccine against pneumococcal disease). Combination vaccines are generally administered against the first five diseases, while another combination vaccine

is used against measles, mumps and rubella (MMR). Certain children at risk are also immunised against tuberculosis and/or hepatitis B (a virus-associated type of jaundice).

As is the case of other preventive interventions, the benefit of immunisation should be weighed against potential harm. From the point of view of the individual, the ability of vaccine to protect against disease and the risk of adverse events are the two primary factors to consider. With regard to communicable diseases, routine immunisation also may have another important influence. The protective effect in the entire population reflect the percentage of the population who have been immunised. Once enough people are immune, “herd immunity” may follow. This means that unimmunised individuals also are indirectly protected when the infection no longer circulates in the community. Thus, the percentage of immunised in a population may have a major impact on the frequency of a disease. As a result, sufficient high participation in an immunisation programme also reduces the risk of disease among individuals with deficient immune system, ie due to congenital disease or immunosuppressive therapy, who cannot be immunised.

Assessment of the duration of the protective effect of a vaccine is complex for several reasons. Many vaccines for children have not been used long enough to permit such assessments. Due to herd immunity, a vaccine may provide enhanced protection once a routine programme has been introduced. But protection may also seem to decrease when most of the population has been immunised, and most remaining cases occur among the immunised. Furthermore, routine immunisation may change the pathogen’s properties over time rendering the vaccine less effective. Thus, it is difficult to draw any firm conclusions regarding the long-term protective effect of a vaccine until it has been used for many years.

Participation in the Swedish child immunisation programme is very high. That indicates widespread trust in the child and school health services. But it should not be taken for granted that almost every parent want her child to be immunised. In the late 1990s, a British researcher raised suspicions about a possible association between measles vaccine and development of autism. As a result of the concern and uncertainty that arose among parents, the percentage of young children who received MMR vaccine declined in Sweden and many other countries. Following a number of thorough studies, the theory that measles immunisation causes autism was discredited. The episode illustrates the importance of providing parents with complete and reliable information, permitting them to decide with confidence whether to immunise their child. Thus, a body of solid knowledge is needed regarding the protective effect and potential adverse events of vaccines included in the child immunisation programme in Sweden.

## **The Project Group's Assignment**

SBU tasked the project group to systematically review research on vaccines included in the child immunisation programme in Sweden. The primary objective was to examine the scientific evidence for the protective effect and of risks associated with a number of the vaccines. The goal was not to propose a new programme but rather to assess the individual vaccines.

## **Questions and Delimitations**

Previous SBU reports have mainly dealt with methods of preventing, diagnosing or treating specific diseases. This task was to assess the effect of a general principle of preventive medicine – the immunisation of children. The basic concept is to provide

protection against many different diseases by administration of a number of vaccines, each of which has a different mode of action and profile of adverse events.

Given the large amount of scientific publications on immunisation, the project group focused on a systematic review of the protective effect efficacy and of adverse events associated with the following vaccines and combination of vaccines:

- Vaccine against *Haemophilus influenzae* type b (Hib)
- Acellular vaccine against pertussis (Pa)
- Vaccine against measles-mumps-rubella (MMR)
- Vaccine against hepatitis B (HBV)
- Vaccine against tuberculosis (BCG)

For each vaccine, the project group addressed a number of specific questions with regard to protective effect and adverse events. The review of combination vaccines looked at adverse events only. The review of pertussis, Hib and hepatitis B vaccines also considered health economic studies.

Thus, the report did not involve a systematic review of the entire general immunisation programme for children in Sweden. Nor did the project assess new vaccines that may be incorporated into the programme. Focus was on vaccines that presently could be judged to pose any question regarding protective effect or adverse events. Diphtheria, tetanus and polio vaccines were part of the programme (in year 2008) but were not covered by the review. Additives in the various vaccines were not specifically examined.

Given the wide scope of the topic, the project group considered it appropriate to include a few general introductory chapters elucidating principles common to all vaccines. These brief outlines were not part of the systematic review of the literature. Rather,

the purpose was to provide a background for the assessment of the scientific literature on individual vaccines.

The general introductory chapters are as follows:

### **The immune defense and how immunisation may protect against disease**

The chapter describes the various pathogens, the immune system of child and what should be demanded of a vaccine.

### **General considerations about immunisation and vaccines**

The chapter examines the protective effect of vaccine (efficacy), how to measure protection levels in blood samples, various types of studies, adverse events, immunisation schedules and the current child immunisation programme in Sweden.

### **Ethical aspects of immunisation of children**

Prior to immunisation of a child questions are raised about benefits and risks, and the interest of the society versus the interest of the individual. These are difficult choices that ultimately open into what is best for the child.

### **Economic aspects of immunisation**

This chapter offers a brief overview of health economic analyses used to assess which vaccines are suitable for inclusion in a general immunisation programme.

## **Methodology for Systematic Review of the Literature**

For each vaccine, the project group first posed a number of specific questions in order to delimit the type of vaccine and the type of measure of protective effect that should be assessed. A systematic review of the literature was performed through search of databases

containing individual research studies, systematic reviews and meta-analyses (compilation of multiple studies). The review covered literature published until June 2006. Detailed descriptions of the databases, time periods, search terms and questions appear in the corresponding chapters. Two individuals examined independently the articles identified by the search. To ensure greatest possible objectivity, they used specific templates designed to assess the scientific quality of the articles. The templates were used to score various aspects of a study with respect to reliability and accuracy, leading to an overall assessment of its quality and relevance.

The evidence used in assessing the protective effect of a vaccine is subject to strict scientific criteria. The situation is often more difficult with regard to adverse event reports. Even in large, well-designed vaccine studies, establishing elevated risk for a highly uncommon adverse event may be difficult. Thus, customary criteria for scientific evidence cannot always be met. A suspected adverse event should serve as a warning signal even if it cannot be linked to a vaccine with statistical certainty. Hence, the project group reviewed studies, or reports of scattered cases, that associated adverse events with immunisation even though the publication could not be assigned formal quality and relevance.

The report also considers some health economic studies related to immunisation. All were model studies presenting theoretical estimates of the economic outcomes of various hypothetical immunisation programmes. Thus, these studies were not assigned any evidence grade.

## Results of the Systematic Review of the Literature

### Protective Effect of and Adverse Events Following *Haemophilus Influenzae* type b Conjugate Vaccine

*Haemophilus influenzae* (Hi) is a bacterium normally found in the respiratory tract of children. While a number of different types of *Haemophilus influenzae* are known, type b (Hib) is responsible for almost all severe Hi infections, including epiglottitis, meningitis and septicemia. Hib infections may occur at any age but are most common in children. Before immunisation was introduced in Sweden, approximately 150 children below 5 years of age annually developed meningitis caused by Hib and 5 to 10 children died of the infection. Approximately 20 developed a permanent neurological damage and an equal number developed impaired hearing.

Immunisation of infants against Hib infection only became feasible with the development of a conjugate vaccine, in which a protein is bound to substances in the bacterial capsule of Hib. Such a vaccine induces production of antibodies and memory cells even in the very young infants – who are most at risk of developing a serious infection. In 1992 Hib vaccine was included in the general child immunisation programme in Sweden.

Questions to be addressed by the systematic review of the literature:

- Does Hib conjugate vaccine protect children against severe Hib infections?
- How does immunisation affect the frequency of severe Hib infections?
- Does Hib conjugate vaccine affect the presence of Hib in the throat of a healthy child?

- Does Hib immunisation of infants also reduce the frequency of Hib infection among unimmunised children (herd immunity)?
- Is Hib vaccine followed by any serious adverse events?

### Conclusions

- ❑ Immunisation of Hib conjugate vaccine protects against severe Hib infections – such as epiglottitis, meningitis and septicemia – in which bacteria are present in the blood or cerebrospinal fluid (Evidence Grade 1). The protective effect lasts for at least three to five years. It is not known how much longer protection remains.
- ❑ General immunisation of Hib conjugate vaccines in infants is highly effective and reduces the frequency of severe Hib infections by 90% (Evidence Grade 3).
- ❑ Immunisation with Hib conjugate vaccine reduces carrier-ship of Hib in the throat of children (Evidence Grade 3). The degree of reduction, its relationship to the number of doses administered and the duration of protection have not been established.
- ❑ The fact that general immunisation with Hib conjugate vaccines in infants also reduces the frequency of serious Hib infections in unvaccinated people suggests decreased spread of the bacteria, herd immunity (Evidence Grade 3). The long-term impact of the conjugate vaccines on the spread of the bacteria and herd immunity has not yet been established.

## Serious Adverse Events

- Potential serious adverse events specifically examined are death including sudden infant death syndrome, seizures, type 1 diabetes mellitus and Guillain-Barré syndrome, a disease of the peripheral nervous system. There are no data suggesting an association of Hib conjugate vaccines and any of these conditions. Ideal prospective randomized studies of vaccines and such rare conditions cannot be conducted. Thus, observational studies must be relied upon despite their inherent weakness to beyond doubt confirm or rule out any associations.

## Protective Effect of and Adverse Events Following Acellular Pertussis Vaccine

Pertussis (whooping cough), a persistent respiratory infection with spasmodic coughing, is caused by the *Bordetella pertussis* bacterium. The bacterium uses a toxin to damage the fine cilia in the respiratory tract, producing thick viscous mucus that causes coughing. Vomiting may occur in connection with the coughing attacks, along with the characteristic whooping sound when inhaling. Pertussis is highly contagious. The symptoms can persist for several months. During the first few months of infancy the disease is serious and occasionally life-threatening. Because immunity wanes over the years following the disease, adults may also develop mild pertussis.

Sweden began immunisation against pertussis, along with diphtheria and tetanus – the diphtheria-tetanus-pertussis (DTP) vaccine – in the 1950s. The pertussis vaccine was a whole-cell vaccine, meaning that it contained killed whole pertussis bacteria. In 1996 acellular (containing only parts of the bacterium) pertussis vaccines were added to the general child immunisation programme in Sweden.

Questions to be addressed by the systematic review of the literature:

- Does immunisation with acellular pertussis vaccine protect children against typical pertussis?
- Does the protective effect of acellular vaccines depend on the number of pertussis components?
- Does immunisation with acellular pertussis vaccine provide protection for longer than three years?
- What is the protective effect of acellular vaccine in a population that has previously been unimmunised or given whole-cell vaccine. Is there any indication of herd immunity?

#### **Adverse Effects**

- Does the frequency of adverse events following immunisation differ between acellular and whole-cell pertussis vaccine, or between acellular and DT vaccine (or placebo)?
- Are there any differences depending on the number of pertussis components in the vaccine, the primary immunisation schedule, the number of doses administered or the age at immunisation?
- Do serious adverse events occur following immunisation with acellular pertussis vaccine in children?

#### **Conclusions**

- ❑ All studied acellular pertussis vaccines protect children against pertussis (Evidence Grade 1).
- ❑ Acellular vaccines provide better protection than most whole-cell vaccines (Evidence Grade 2). Some whole-cell vaccines provide better protection than certain acellular vaccines, particularly against mild pertussis (Evidence Grade 3).



- ❑ For both serious and mild pertussis, two studies found that acellular vaccines consisting of five components provide better protection than those consisting of two components (Evidence Grade 2). One study showed that a pertussis vaccine with three components had greater protective effect than one with two components. No important difference has been demonstrated between pertussis vaccines with three and five components (contradictory scientific evidence).

### **Long-term Protective Effect**

- There is evidence that the protective effect lasts for at least 5 years after three or four doses of acellular pertussis vaccine (Evidence Grade 3).
- General immunisation programmes that include acellular vaccine reduce hospitalisation for pertussis among immunised children below 2 years of age (Evidence Grade 3).
- One study of medium quality and relevance and two studies of low quality and internal validity found unchanged age-specific incidence of pertussis among unimmunised infants, suggesting insufficient herd immunity.

### **Adverse Effects**

- ❑ For primary immunisation with DTP vaccine, acellular pertussis vaccines cause fewer local reactions and less fever than whole-cell vaccines. No clinically important differences have been demonstrated among acellular pertussis vaccines with varying numbers of components (primary immunisation: Evidence Grade 1; booster doses: Evidence Grade 2).
- ❑ A booster dose of acellular pertussis vaccine in children who have previously received acellular vaccines causes a higher frequency of redness and swelling greater than 5 centimetres

than in children who have previously received whole-cell vaccines (Evidence Grade 2).

- ❑ A higher frequency of local reactions has been reported after a late booster dose of acellular pertussis vaccine at 5–6 years of age than before 3 years of age (Evidence Grade 2).
- ❑ An early booster dose of acellular pertussis vaccine causes a higher frequency of local reactions than primary immunisation during the first year of life (Evidence Grade 2).
- ❑ There is no evidence of a higher frequency of, or mortality from, invasive bacterial infections after administration of acellular vaccine (Evidence Grade 1).
- ❑ The overall literature provides no reliable basis for a causal relationship between immunisation against pertussis and the handful of other serious adverse events described in case reports or national reports of adverse events (insufficient scientific evidence).

### **Protective Effect of and Adverse Events Following Measles-Mumps-Rubella (MMR) Vaccine**

Measles is caused by a highly contagious virus. Thus, nearly all children in an unimmunised population are infected at one time or another. Measles is accompanied by high fever, conjunctivitis, coryza (runny nose) and cough. A irregular rash develops after a couple of days and spreads over most of the body. Measles often leads to complications, mainly inflammation of the middle ear, pneumonia and diarrhoea. Rarer complications are encephalitis (approximately 1 case per 1 000) and a fatal form called subacute sclerosing panencephalitis (SSPE), approximately 1 case per 100 000. World wide there are 1 to 3 deaths per 1 000 cases of measles.

Measles vaccine has been recommended in Sweden since 1971 and is since 1982 given in a combination with mumps and rubella vaccines (MMR).

Mumps is a viral disease that is contagious, though not to the same extent as measles. The symptoms may be diffuse, including fever, headache and discomfort. Characteristic of the disease is swelling of the salivary glands, causing the cheeks and jaw to have a rounder appearance. Although many cases are mild, complications may develop, such as pancreatitis, meningitis, impaired hearing and inflammation of the testicles. Death is very uncommon.

Rubella (German measles) is a contagious but usually mild viral disease. Sometimes the symptoms are barely noticeable. Malaise, moderate fever, a fine macular rash and enlarged nuchal lymph nodes are characteristic of the disease. The reason for immunisation is that rubella infection may cause serious complications during pregnancy. Severe foetal abnormalities – including heart anomalies, deafness, blindness, brain damage and foetal death – have been well documented. Routine immunisation of 12-year-old girls against rubella was introduced in Sweden in 1974. Despite high immunisation coverage, recurring outbreaks occurred because the disease continued to circulate in the general population. Spread of rubella was interrupted shortly after 1982 when the combination MMR vaccine was introduced at 18 months and 12 years of age to both girls and boys.

Questions to be addressed by the systematic review of the literature:

- Does the MMR combination vaccine protect children against developing measles, mumps, rubella and their complications, including foetal abnormalities from rubella?

- Does MMR immunisation provide lifetime protection against the diseases and their complications?
- Does MMR vaccine cause serious adverse events (ie those that involve a risk of permanent damage or death)?

### Conclusions

- ❑ Currently used MMR combination vaccine provides protection against measles, mumps and rubella (Evidence Grade 3).
- ❑ MMR vaccine offers protection for many years but there is insufficient scientific evidence to assess whether the protection is lifelong.
- ❑ For the vaccines when administered separately the following documentation is presented:
  - Separate measles vaccine (not available in Sweden) protects against measles and its complications (Evidence Grade 3).
  - Separate mumps vaccine (not available in Sweden) protects against mumps and its complications, but the quality and relevance of individual studies is limited (Evidence Grade 3).
  - No randomised controlled study has examined the protective effect of separate rubella vaccine (not available in Sweden). Following inclusion of MMR vaccine in the child immunisation programme in Sweden, the number of cases has declined sharply. Only occasional cases are reported each year, and no known foetal abnormality has been caused by the rubella virus since 1985. That illustrates that the absence of scientific evidence is not necessarily synonymous with lack of effect.

### Adverse Events

- ❑ MMR immunisation often causes fever and increases the risk of febrile seizures during the first two weeks after administration, but does not increase the risk of developing epilepsy later (Evidence Grade 3).
- ❑ MMR immunisation does not cause type 1 diabetes (Evidence Grade 3).
- ❑ MMR immunisation does not cause serious infections that require hospitalisation (Evidence Grade 3).
- ❑ MMR immunisation does not cause autism or autism spectrum disorder (Evidence Grade 3).

### Protective Effect of and Adverse Events Following Hepatitis B Vaccine

Hepatitis B is a type of jaundice. The disease is caused by a virus that may be transmitted by contact with blood and mucous membranes. Most infections in the West occur through intravenous drug use or sexual contacts. In other parts of the world, transmission is primarily from mother to child at birth, and from wounds and contact with mucous membranes during childhood. Symptoms do not appear until 2–6 months after the infection. Hepatitis B virus may cause an acute infection of the liver. The symptoms are nausea, fatigue and yellow skin and eyeballs, jaundice. Sometimes joint and muscular pain, and rash are noted. Most adults who develop hepatitis B are completely cured and no longer contagious. The younger the individual, the greater the risk of chronic disease. Newborns to whom the disease is transmitted at birth generally exhibit no symptoms, but approximately 90% develop long lasting infection and remain contagious carriers of the virus. Chronic infection also entails a risk of developing liver cirrhosis or liver cancer.

More than 350 million people worldwide, mostly in Asia, are estimated to have chronic hepatitis B.

The first vaccines against hepatitis B in the early 1980s were manufactured from the plasma of infected patients. Only vaccines prepared by a recombinant DNA technique are presently in use.

Questions to be addressed by the systematic review of the literature:

- Does hepatitis B immunisation protect against disease and against becoming a carrier?
- What percentage of children has protective antibody levels (anti-HBs >10 IU/L) in the blood after primary immunisation with hepatitis B vaccine?
- Do serious symptoms of disease occur more often in hepatitis B vaccine immunised than unimmunised individuals?

### Conclusions

- Immunisation with hepatitis B vaccine to children below 15 years of age provides good protection (Evidence Grade 1).
- More than 90% of immunised children have protective antibody levels after primary immunisation with hepatitis B vaccine (Evidence Grade 1).
- The duration of protection against hepatitis B infection is not fully known (insufficient scientific evidence).

### Serious Adverse Events

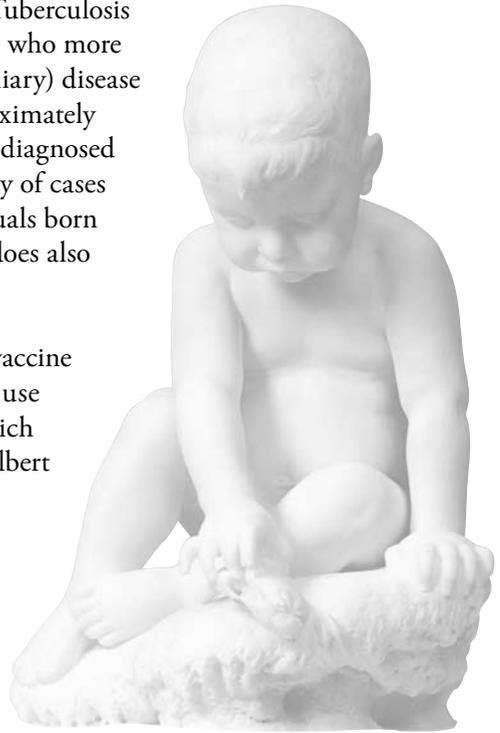
- Severe hypersensitivity reactions have been reported after hepatitis B immunisation, but very rarely (insufficient scientific evidence).

- ❑ There is insufficient scientific evidence to rule out or confirm a correlation between hepatitis B immunisation and multiple sclerosis (MS). The overall available data suggest that there is no such correlation.
- ❑ The overall literature provides no reliable basis for a causal relationship between immunisation against hepatitis B and other serious adverse events described in case reports: death, neurological disease other than MS, arthritis or chronic fatigue syndrome.

### **Protective Effect of and Adverse Events Following BCG Vaccine**

Tuberculosis is a serious disease caused by bacteria in the *Mycobacterium tuberculosis* complex. While many different organs may be affected, pulmonary tuberculosis is by far the most common and is the only form that entails a risk of transmission to others. The disease is present worldwide. An estimated one third of the world's population are carriers of the bacteria, but only a small percentage of people develop the disease and become contagious. Tuberculosis is particularly serious in children, who more readily develop disseminated (miliary) disease or tuberculous meningitis. Approximately 500 new cases of tuberculosis are diagnosed in Sweden each year. The majority of cases in recent years have been individuals born abroad but spread of the disease does also occur within Sweden.

Bacille Calmette-Guérin (BCG) vaccine against tuberculosis has been in use since the 1920s. The vaccine, which was developed by bacteriologist Albert



Calmette and veterinarian Camille Guérin, contains live attenuated bacteria that are closely related to tuberculosis bacteria. Sweden introduced the immunisation in 1928, as well as a general programme for newborns, schoolchildren and conscripts in the 1940s. Nowadays immunisation is recommended only for children with elevated risk, such as children living in close proximity to individuals with tuberculosis or children in regular contact with countries where the disease is common.

The protective effect of the vaccine is disputed and may vary with geographic, social and hygienic conditions. Overall protection in all age groups taken together varies from 0% (no demonstrable protection) to 80% in different studies.

The review of the literature was restricted to BCG vaccine administered before 1 year of age and the degree of protection against tuberculosis provided below 5 years of age. The reason for this limitation was the susceptibility of young children to severe tuberculosis. No such age limitations were imposed on the review of adverse events. In the first place, we wanted to avoid underestimating the rate of rare but serious adverse events. In the second place, adverse events following immunisation during the first year of life may show much later.

Questions to be addressed by the systematic review of the literature:

- Does BCG immunisation during the first year of life protect against severe tuberculosis below 5 years of age?
- Does immunisation with BCG vaccine during the first year of life cause serious adverse events (those that lead to death or permanent damage)?

## Conclusions

- BCG vaccine administered during the neonatal period or shortly thereafter protects children against tuberculosis through 5 years of age.
  - The protective effect against all types of tuberculosis is approximately 75% (Evidence Grade 2).
  - Protection against disseminated (miliary) tuberculosis and tuberculous meningitis is 75–85% (Evidence Grade 2).

## Serious Adverse Events

- A fatal disseminated BCG infection occurs after BCG vaccine, but very rarely (Evidence Grade 1). The risk is approximately 1 case per 100 000 immunised children but cannot be stated precisely. Disseminated BCG disease may develop in infants with a rare genetic immunodeficiency disease that also increases the risk for other severe diseases. To further reduce the risk of this serious but rare reaction, the current recommendation in Sweden states that BCG vaccine should be deferred until 6 months of age to permit identification of children with the immunodeficiency disease and exclude them from this immunisation.

## Adverse Events Following Combination Vaccines

Combination or polyvalent vaccines consist of antigens from several microorganisms and thereby permit immunisation against several diseases with the same injection. Sweden began using combination vaccines in the late 1940s when diphtheria-tetanus (DT) vaccine was introduced. The country added whole-cell pertussis vaccine (Pw) in the 1950s to form the trivalent DTPw vaccine. A number of countries, including France and the Netherlands, began combining DTPw with inactivated polio vaccine (IPV)

in the 1960s. The development in the 1990s of new vaccines against *Haemophilus influenzae* type b (Hib) and hepatitis B (HBV), as well as acellular pertussis vaccines (Pa), stimulated the development and introduction of combination vaccines based on DTPa. This section discusses those vaccines, with an emphasis on adverse events.

### **Vaccines Currently Used in Sweden**

Currently the child health services in general use a pentavalent vaccine against five diseases: diphtheria, tetanus, pertussis, polio and Hib (DTPa-IPV/Hib vaccine). Two such vaccines are available in Sweden. Pentavac<sup>®</sup>, manufactured by Sanofi Pasteur MSD, contains a two-component acellular pertussis vaccine (Pa2). Infanrix<sup>®</sup>- Polio+Hib, manufactured by GlaxoSmithKline, contains a three-component pertussis vaccine (Pa3). A hexavalent vaccine that also contains hepatitis B vaccine – DTPa-IPV-HBV/Hib (Infanrix<sup>®</sup>-Polio-Hepatitis B+Hib) – is also available. That vaccine is primarily used for children at increased risk of being infected with hepatitis B.

Questions to be addressed by the systematic review of the literature:

- Does the frequency of adverse events after immunisation with a tetravalent vaccine that contains inactivated polio vaccine (IPV), diphtheria vaccine (D), tetanus vaccine (T) and acellular pertussis vaccine (Pa) (DTPa) differ from the rate of adverse events after trivalent DTPa vaccine alone?
- Does the frequency of adverse events after immunisation with a pentavalent vaccine that contains Hib vaccine in addition to DTPa-IPV vaccine differ from the rate of adverse affects after DTPa or DTPa-IPV vaccine alone?

- Does the frequency of adverse events after immunisation with a hexavalent vaccine that contains hepatitis B vaccine (HBV) in addition to DTPa-IPV/Hib differ from the rate of adverse affects after DTPa, DTPa-IPV or DTPa-IPV/Hib alone?
  - For *non-serious adverse events*
- Do serious adverse events occur?
- Do previously unknown adverse events occur after administration of such vaccines children below 18 years of age?

### Conclusions

- No clinically significant differences have been found in the frequency of redness, swelling or fever after primary immunisation or booster doses of hexavalent DTPa-IPV-HBV/Hib, pentavalent DTPa-IPV/Hib or DTPa-HBV/Hib, tetravalent DTPa-IPV or trivalent DTPa vaccine (Evidence Grade 2).
- There is no indication of an increased frequency of hypotonic hyporesponsive episode (paleness, decreased responsiveness and decreased muscle tone) or persistent, inconsolable crying after immunisation with hexavalent, pentavalent or tetravalent vaccine than with trivalent DTPa vaccine (Evidence Grade 3).
- The overall literature provides no reliable basis for a causal relationship between combination vaccines and a few sporadic serious adverse events, including death, described in case reports or national adverse event reports (insufficient scientific evidence).

### Economic Aspects of Immunisation

Various types of health economic analyses are used to compare the benefits and costs of immunisation. The most common are

cost-benefit and cost-effectiveness analyses. The estimates are based on many different factors:

- how common the disease is
- risk of transmission
- percentage of immunised in the target group
- protective effect expressed as vaccine efficacy
- duration of protection
- cost of the vaccine and its administration
- direct healthcare costs for both immunised and unimmunised individuals
- production loss associated with the disease for immunised and unimmunised (parental absence from work, premature death)
- discount rate of interest.

An estimate is often specific to a particular country, rendering international comparisons difficult. Analyses of the economic consequences of immunisation programmes are generally based on monitoring immunised individuals over time. The dynamic impact of herd immunity may also be taken into account, ie indirect protection afforded unimmunised when a sufficient percentage of the population has been immunised. If participation in a immunisation programme is high enough, the infection can no longer spread and the disease disappears.

The systematic review of the literature concerning health economic research on vaccines against Hib, pertussis and hepatitis B found 36 model studies. Only two of them were based on epidemiology and healthcare costs in Sweden. Thus, considering that cost-effectiveness estimates are largely dependent on a country's particular conditions, regular evidence grading was not appropriate, and the results are only presented as general observations. The economic analyses used two perspectives. An healthcare perspective was limited to costs and revenues (reduced disease incidence)

within the health care system, whereas a societal perspective could also include costs for sickness leave and sometimes premature death.

### ***Haemophilus Influenzae* type b (Hib)**

Model studies indicate that the societal benefit of immunisation against Hib may be projected to exceed the cost of immunisation, dependant on what principle is used to estimate the value of a human life.

### **Pertussis**

Pertussis immunisation, examined in a number of model studies, has from a societal perspective been shown to be cost-effective. Model studies suggest that a booster dose can be administered at a reasonable cost per averted case of pertussis.

### **Hepatitis B**

Hepatitis B immunisation is insufficiently assessed in published model studies with a societal perspective. Model studies from a health care perspective suggest that combination vaccines against hepatitis B and Hib are most cost-effective when administered to infants in addition to risk groups. However, the cost per life-year saved is high.

## **Remaining Problems – Basis for Further Research**

The project group's objective was to review the efficacy of and adverse events following individual vaccines or combinations of vaccines used in the general immunisation programme. Thus, the review included both the results of clinical trials and follow-up of vaccines administered to children within a general programme. This dual perspective required different research strategies.

The protective effect or efficacy of individual vaccines can best be assessed by means of randomised controlled trials that compare immunised and unimmunised children. Such studies provide the opportunity to demonstrate efficacy and often to show potential adverse events.

However at the level of the population, the effect of a vaccine in general use cannot be determined by means of controlled experiments. Instead, such an effect, called effectiveness, is usually analysed by comparing the incidence of the disease before and after introduction of a new vaccine. Such studies are assigned lower quality and internal validity than randomized controlled studies and receive a lower evidence grade according to SBU's current grading of evidence. But experience from several countries persuasively demonstrates that immunisation has reduced or even eradicated disease.

Also the return of a disease after an immunisation programme has been terminated, as was the case with pertussis in Sweden, or coverage decreases as was the case with measles following an autism scare in the UK, can confirm the effectiveness of a vaccine, although high quality and relevance of the data could not be assigned in a strict scientific sense.

Assessment of adverse events, particularly rare and severe events, poses similar methodological difficulties:

- Controlled studies can never be designed large enough to rule out minute risks.
- Suspicion of an association between immunisation and autism could be refuted as a result of Danish studies using a national immunisation register and healthcare registers of diagnoses to compare autism among immunised and unimmunised children – a method that cannot be assigned the highest quality and relevance.

- Certain methods that use individuals as their own controls in time-series studies cannot be assigned high quality and relevance although they elegantly analyze the risk of a side reaction during the period that it may be expected to occur (such as fever and seizures within 48 hours after pertussis immunisation or encephalitis 7–14 days after measles immunisation).

A number of options are available to ensure more reliable data and higher quality regarding both the protective effect and adverse event reporting in the surveillance of immunisation programmes. Among desirable changes are the establishment of a Swedish immunisation register, enhanced reporting of vaccine preventable diseases and improved reporting of adverse event data that can be linked to the register.

Given that the duration of the protective effect is not known for most vaccines, recurrent seroepidemiological studies of the population are important. By measuring, in different age groups, the antibody levels of the pathogens targeted in the Swedish immunisation programme we may assess for each vaccine how much protection remains at different intervals after immunisation.

It is also important to follow the epidemiology of the microorganisms after introduction of general immunisation in order to determine at an early stage whether the composition of the vaccine requires modification. Pneumococcal vaccine added to the child immunisation programme on 1 January 2009 may serve as an example. The vaccine effectively protects young children against seven of the most common types of pneumococci, but there are more than 90 types of pneumococci. Several years after introduction of the vaccine in some populations, a few pneumococcal types not included in the vaccine increasingly have caused pneumococcal infection.

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# SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

## **Vaccines to Children – Protective Effect and Adverse Effects**

SBU's report on vaccines to children builds on a systematic, critical review of the scientific literature in the field.

The report is one in a series of reports published by SBU (Swedish Council on Technology Assessment in Health Care).

This document presents the summary and conclusions of the full report, which has been approved by SBU's Board of Directors and Scientific Advisory Council.