

CONTINUING MEDICAL EDUCATION

Vaccination Recommendations for Germany

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SUMMARY

Background: Vaccination is an effective means of preventing infectious diseases. In Germany, the Standing Vaccination Committee at the Robert Koch Institute (*Ständige Impfkommission*, STIKO) issues recommendations on vaccination to prevent the occurrence and spread of infectious diseases in the nation's population.

Methods: Selective literature review, including consideration of the current STIKO recommendations.

Results: The annually updated vaccination calendar currently includes recommendations for vaccination against diphtheria, tetanus, pertussis, type b *Haemophilus influenzae*, hepatitis B, poliomyelitis, and pneumococci, beginning at the age of eight weeks. From the age of twelve months onward, children should be vaccinated against measles, mumps, rubella, varicella, and serogroup C meningococci. In later childhood and adolescence, booster vaccinations are recommended, in addition to the provision of any vaccinations that may have been missed. Girls aged 12 to 17 years should be vaccinated against human papilloma virus. Adults should have their tetanus and diphtheria vaccinations refreshed regularly, and their pertussis vaccination refreshed once; from age 60 onward, they should be vaccinated against pneumococci and influenza.

Conclusions: The vaccinations recommended by the STIKO are available to all German citizens free of charge and provide effective protection against infectious disease.

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Vaccination is an effective means of preventing infectious diseases (e1). The primary goal of vaccination is to protect the vaccinated person against the disease in question (individual immunity). If a large enough percentage of the population is vaccinated, then the spread of the pathogenic organism will be reduced to such an extent that non-vaccinated persons are protected as well (herd immunity) (e2). Sustained vaccination of a high percentage of the population against a pathogen for which man is the only reservoir can result in its regional or even, in the ideal case, global elimination (1). The total elimination of smallpox and the marked reduction of the incidence of poliomyelitis worldwide are impressive examples of the benefits of immunization (*Figure 1*) (e3).

Methods

In Germany, the Standing Vaccination Committee (*Ständige Impfkommission*, STIKO) at the Robert Koch Institute (RKI, the German equivalent of the Centers for Disease Control in the United States) issues recommendations on vaccination after systematic review of all available scientific data on the vaccines in question. The RKI also takes its own surveillance data and the findings of vaccine approval studies into account, as well as issues of practical implementation, public acceptability, and evaluation of the vaccination program once it is in progress. All of the data that have been considered in the deliberative process before the issuance of a recommendation are summarized on the RKI website, in which the STIKO explains the scientific basis for each decision taken (see www.rki.de > English > Prevention of infection > Vaccination). This article is based on the STIKO's explanations of its decisions and on a selective review of the pertinent literature.

Learning objectives

The learning objectives for readers of this article are:

- to gain knowledge of the rationale for, and practical implementation of, the STIKO's current recommendations

The goals of vaccination

- Protecting the vaccinated person from the disease in question (individual immunity)
- Protecting unvaccinated persons as well, if the vaccination rate is high (herd immunity)

for vaccination of persons in all age groups against various diseases (as of July 2011);

- to understand how the protection that vaccines afford children, adolescents, and adults against infectious disease is established and consolidated.

The current STIKO recommendations on vaccination (as of July 2011)

The STIKO's updated recommendations are published at least once a year (in the 30th calendar week of each year) in the *Epidemiologisches Bulletin* (2), and the scientific basis of these recommendations is explained in subsequent *Bulletin* issues. When events warrant, e.g., in epidemic or pandemic outbreaks of disease, timely recommendations are issued in addition to this annual update (e4, e5).

The central element of the STIKO recommendations is the vaccination calendar, in which the recommended optimal times for standard vaccinations in infants, children, adolescents, adults, and senior citizens are listed (*Tables 1 and 2*). Missed vaccinations are to be made up as soon as possible; the underlying principle is that every previously administered vaccination contributes to the achievement of a state of full immunity.

Vaccination recommendations up to the age of 11 months

In an infant's first year, vaccinations are provided against:

- diphtheria (D),
- tetanus (T),
- pertussis (aP),
- *Haemophilus influenzae* type b (Hib),
- poliomyelitis (IPV),
- hepatitis B (HB), and
- pneumococci (Pnk; 10- or 13-valent conjugate vaccine).

These vaccines are administered thrice at 4-week intervals from the age of 8 weeks onward.

Fortunately, these infectious diseases are now under effective control in childhood and adolescence, as a consequence of the population-wide vaccination of infants and children. None of them, however, has yet been totally eliminated (3).

Even though diphtheria and tetanus are now very rare in Germany, the prevalence of either or both of these diseases could rise again if the vaccination rate

fell, or if general hygienic conditions became worse. In 1990–1997, as a result of the collapse of the Soviet Union and the ensuing destabilization of the Russian medical system, there were more than 115 000 cases of diphtheria in the Russian Federation, which led to at least 3000 deaths (e6). In Germany, the RKI is notified of 0 to 4 cases of diphtheria per year, all of which are acquired outside the country and then imported across its borders (e7). The situation regarding tetanus is comparable: at least 15 persons develop tetanus in Germany each year, mostly elderly persons without adequate immunization (e8). In countries with a low hygienic standard, tetanus tends to arise in neonates, who lack immunity because their inadequately immunized mothers do not produce protective antibodies. The World Health Organization (WHO) reports that 59 000 neonates died of tetanus around the world in 2008 (e9).

Vaccination against pertussis, type b *Haemophilus influenzae*, and pneumococci protects infants and children, in particular, against severe invasive infections. The acellular pertussis vaccine was introduced in 1995; more than 85% of children under 6 years of age are now vaccinated against pertussis. The incidence of pertussis in this age group has dropped as a result, from 4000–6000 per 100 000 children per year (an estimate for the Lower Rhine region for the period 1987–1990) to 40–90 per 100 000 children per year (surveillance figures from the federal states in the former East Germany) (4). Currently, pertussis among neonates and as yet unvaccinated infants remains a critical concern. These often life-threatening infections are usually acquired from adults with undiagnosed pertussis.

Life-threatening infections caused by invasive type b *Haemophilus influenzae*, such as epiglottitis, pneumonia, and meningitis, have only been diagnosed in rare, sporadic cases since vaccination began (e10). Likewise, vaccination against pneumococci has lowered the incidence of invasive pneumococcal infection among children under 2 years of age from 16.7 to 7.4 per 100 000 per year (5). The incidence of pneumococcal infection has dropped not only in children, but also in persons over age 65 (e11). This reflects the reduced transmission of pneumococci from children to adults and is thus a manifestation of herd immunity.

The comprehensive vaccination of infants worldwide against poliomyelitis is the cornerstone of the effort to eliminate this disease, which is currently among the leading objectives of global health policy.

The vaccination calendar

The central element of the STIKO recommendations is the vaccination calendar, in which the recommended optimal times for standard vaccinations in infants, children, adolescents, adults, and senior citizens are listed.

The standard vaccinations

Diphtheria (D), tetanus (T), pertussis (aP), *Haemophilus influenzae* type b (Hib), poliomyelitis (IPV), hepatitis B (HB), pneumococci (Pnk)

The vaccination of infants against hepatitis B is intended to prevent hepatitis B infection and the associated chronic disease state, which, in turn, promotes the development of hepatocellular carcinoma. If an infant becomes infected with hepatitis B, the risk of a chronic, persistent course is nearly 90% (e12). With the modern, multivalent combined vaccines (TDaP-Hib-HB-IPV) that are now available, children can be vaccinated easily and with minimal discomfort, as scheduled in the vaccination calendar. Children born prematurely are vaccinated according to their chronological age. Children born in the 28th gestational week or earlier should be given their first (combined) vaccine under observation in the hospital, so that vaccination reactions such as bradycardia or apnea can be promptly recognized and treated (e13). Likewise, children who have unexpected reactions after their first vaccination should receive all further vaccinations up to the age of six months under observation in the hospital; subsequent vaccinations can be given on an outpatient basis (6).

Vaccination recommendations for infants aged 12 to 23 months

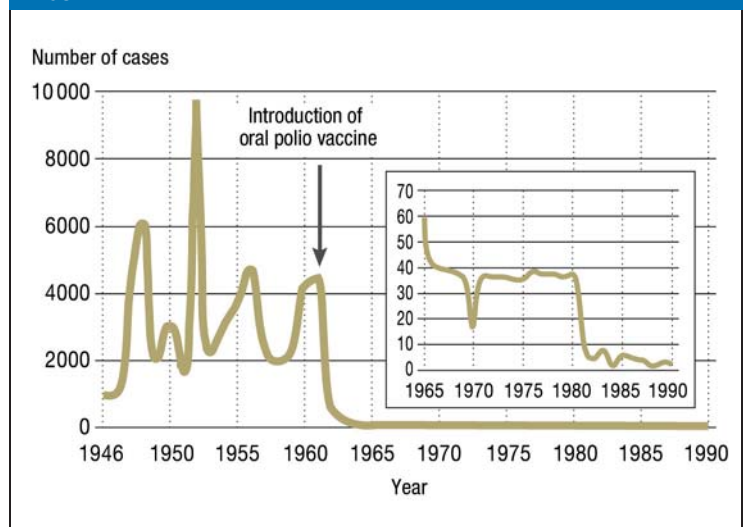
A boost of baseline immunization (TDaP-Hib-HB-IPV and Pnk) is recommended for all children after they have reached the age of 11 months. This fourth vaccination completes the child's baseline immunization. Many studies have also documented the importance of a further boost in the second year of life. In Great Britain, for example, there was a resurgence of type b *Haemophilus influenzae* infection because of declining immunity during the second year of life; the problem was solved by the introduction of the Hib booster in the second year (e14).

The following vaccinations should also be given during the child's second year:

- Vaccination against serogroup C meningococci (MenC) to prevent invasive infection and meningitis caused by MenC (single vaccination with conjugate vaccine);
- two vaccinations with live vaccine against measles, mumps, and rubella (MMR, as a combined vaccine) and against varicella-zoster virus (VZV, either as a single vaccine or as a combined MMR-VZV vaccine [MMRV]) (Table 1).

The second vaccination against MMR and VZV should be given no earlier than at the age of 15 months, and the two MMR or MMR-VZV vaccinations should be given at

FIGURE 1



Reported cases of poliomyelitis in Germany, 1946–1990; the smaller chart concerns the few cases reported since 1965.

TABLE 1

Vaccination calendar (for standard vaccinations) of the Standing Vaccination Committee (STIKO) for infants and children aged 0-23 months¹ (2)

Vaccination	Age (months)				
	2	3	4	11–14	15–23
Tetanus (T)	G1	G2	G3	G4	
Diphtheria (D)	G1	G2	G3	G4	
Pertussis (aP)	G1	G2	G3	G4	
<i>Haemophilus influenzae</i> type b (Hib)	G1	G2 ²	G3	G4	
Poliomyelitis (IPV)	G1	G2 ²	G3	G4	
Hepatitis B (HB)	G1	G2 ²	G3	G4	
Pneumococci (Pnk)	G1	G2 ²	G3	G4	
Meningococci (MenC)					G1 (≥ 12 months)
Measles, mumps, rubella (MMR)					G1 G2
Varicella-zoster virus (VZV)					G1 G2

G, baseline immunization (in up to 4 vaccinations, designated G1–G4);
¹ RKI: Recommendations of the Robert Koch Institute's Standing Vaccination Committee (STIKO) as of July 2011; Epid. Bull. 30/2011.

² This dose can be omitted if a monovalent vaccine is used.

Vaccination recommendations for the 2nd year

All children should receive a boost of their baseline immunizations after reaching the age of 11 months. During the second year, they should be vaccinated against measles, mumps, rubella, varicella, and meningococci.

Recommendations for children and adolescents

- Further booster vaccinations against tetanus, diphtheria, and pertussis at age 5–6 years
- Against tetanus, diphtheria, pertussis, and poliomyelitis at age 9–17 years
- Girls should be vaccinated against HPV.

TABLE 2

Vaccination calendar (for standard vaccinations) of the German Standing Vaccination Committee (STIKO) for children from age 5 onward, adolescents, and adults (2)¹

Vaccination	a Age (years)				
	5–6	9–11	12–17	18–59	60 and onward
Tetanus (T)	A1		A2	A (N, if indicated) Boosters at 10-year intervals. The next due Td vaccination is given once as Tdap, or, if indicated, as a combined Tdap-IPV combined vaccination.	
Diphtheria (d)	A1		A2		
Pertussis (ap)	A1		A2		
Poliomyelitis (IPV)			A1	N, if indicated	
Hepatitis B (HB)	N				
Pneumococci (Pnk)					S ²
Meningococci (MenC)	N				
Measles (M)					S ³
Mumps, rubella (MR)	N				
Varicella-zoster virus (VZV)	N				
Influenza					S annual vaccination
Human papilloma virus (HPV)	G1–G3 standard vaccination for girls and young women				

A, booster; S, standard vaccination; N, vaccination making up for a missed one (baseline immunization of all as yet unvaccinated persons and completion of incomplete vaccination series); G, baseline immunization.

¹RKI, recommendations of the Robert Koch Institute's Standing Vaccination Committee (STIKO) as of July 2011; *Epid. Bull.* 30/2011.

²Single vaccination with polysaccharide vaccine, booster recommended only for special indications.

³Single vaccination (preferably with MMR vaccine) for those born after 1970 age 18 or older who were vaccinated no more than once as children or with unknown vaccination status.

least four weeks apart. Double vaccination against MMR is necessary for the maintenance of lifelong immunity against measles, which not only protects immunized individuals but is also an important step in the eradication of the disease.

Vaccination recommendations for children and adolescents

For lasting immune protection, further booster vaccinations against tetanus, diphtheria, and pertussis are recommended at the age of 5 to 6 years, and against these three diseases and poliomyelitis at age 9 to 17 years. Because the tetanus, diphtheria, and pertussis vaccines are more likely to provoke a local reaction in older children, vaccines with lower antigen content

(Tdap[-IPV]) are recommended from age 5 onward. In the German-speaking countries, the tetanus component is designated “T,” independently of its antigen content.

Reinforcement of immunity against pertussis with a booster vaccination is especially important, because protection against pertussis lasts only four to seven years, on average, after vaccination or after a “wild” pertussis infection (e15). Reinforcement of immunity against poliomyelitis should not be missed, either; this is delivered in the last recommended repetition of IPV vaccination. Vaccination against human papilloma virus (HPV) in three doses has been recommended since 2007 for all girls aged 12 to 17 (ideally, before the first sexual intercourse). The available vaccines reliably confer immunity to two HPV strains (HPV 16

Poliomyelitis vaccination

The IPV booster at age 9-17 is the last required booster of poliomyelitis vaccination.

Pertussis

Because immunity to pertussis is lost four to seven years after infection or vaccination, adults who do not receive a booster vaccination can develop a pertussis infection despite having been vaccinated (or infected) in childhood.

and 18) that together account for about 70% of all cases of HPV-associated cervical cancer (e16). The concept of HPV vaccination is based on the well-established relationship between persistent HPV infection and the later development of cervical cancer, as will be discussed below in greater detail.

In general, the age window from 9 to 17 years should be used to close vaccination gaps and to make up for any standard vaccinations for infancy, childhood, and adolescence that may have been missed. There are two exceptions to this rule: missed anti-pneumococcal vaccinations must be made up for by the child's second birthday, and missed Hib vaccinations by the age of 5 years (Table 2).

Vaccination recommendations for adults

Booster vaccinations against tetanus and diphtheria are recommended at ten-year intervals, so that the immunity acquired through vaccination in childhood and adolescence can be maintained in adulthood.

It has been recommended since 2009 that adults who were last vaccinated against pertussis more than 10 years ago should receive a single booster vaccination against tetanus, diphtheria, and pertussis (e17). Because immunity to pertussis is lost four to seven years after infection or vaccination (as already mentioned above), pertussis infection might otherwise recur in adulthood. Studies have shown that 17% to 30% of adults who suffer from cough for more than three weeks are, in fact, infected with *Bordetella pertussis*. Pertussis in adults takes an atypical course and often goes unrecognized; if it then spreads to young infants who have not yet been vaccinated, life-threatening infection can result (e18). At present, 60% of all patients hospitalized for complicated pertussis infections are either infants in the first year of life or elderly adults (4). Pertussis vaccination in adulthood is recommended not just to protect the adults themselves, but also to protect the as yet unvaccinated neonates and young infants to whom the infection might spread (7).

Clinical studies have shown that adolescents and adults with unknown vaccination status or unknown immune status can be reliably protected against pertussis with a single vaccination (8). Pertussis vaccine is currently available only in combination with d and T vaccines. There is, however, no basis to the oft-expressed concern that adverse effects might arise more frequently if booster vaccinations are given too early, e.g., if the Tdap vaccine is given within 5 years of the

TABLE 3

Measles incidence in Germany, overall and in infants less than 1 year old, based on cases reported to the Robert Koch Institute as required by law, 2001-2009 (e21)

Year	Overall cases per 100 000	Cases in infants under 1 year old, per 100 000
2001	7.3	15.7
2002	5.7	22.8
2003	0.9	5.7
2004	0.1	2.1
2005	1.0	5.6
2006	2.8	22.8
2007	0.7	3.5
2008	1.1	4.1
2009	0.7	7.3

last Td vaccination. In one study, Canadian adolescents who received a Tdap booster vaccination 18 to 30 months after their last Td vaccination did not have more adverse effects than those who received it at intervals longer than 9.5 years (e19). Adults who received a Td vaccination and then a Tdap-IPV vaccination four weeks later did not have more adverse effects than those who received a placebo (9).

Persons whose vaccination status is unknown (e.g., because of missing documentation) or who did not receive their baseline vaccinations against tetanus, diphtheria, pertussis, and/or poliomyelitis should unquestionably make up for their missed vaccinations in adulthood. The available combination vaccines with lower antigen content have been approved only for use as boosters; therefore, baseline vaccination in adulthood must be provided with single tetanus, diphtheria, and IPV vaccines, or with a tetanus-diphtheria combined vaccine. In such cases, baseline vaccination with a Tdap-IPV combination vaccine suffices to confer immunity against pertussis.

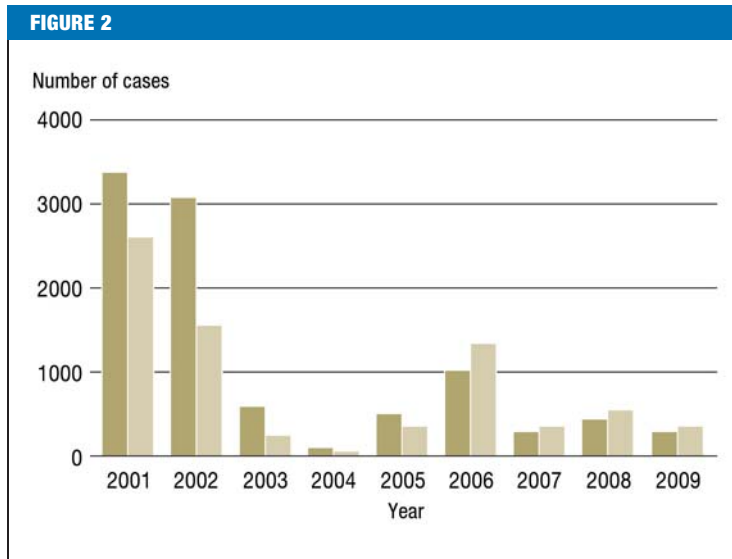
Adults are often naturally immune to varicella and, if they were born before 1970 (i.e., before population-wide MMR vaccination), to measles, mumps, and rubella as well. The elimination of measles and rubella in Europe by the year 2015 has been set as an objective by

Natural immunity

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Vaccination recommendations for persons over age 60

From age 60 onward, annual vaccination against (seasonal) influenza is recommended, as is a single vaccination against pneumococci with a multivalent polysaccharide vaccine.



The incidence of measles in Germany by age, 2001–2009, calculated from the numbers of cases reported to the Robert Koch Institute as required by law (e21). Dark bars, children under age 10; light bars, children age 10 or older and adults.

both the World Health Organization and the German government (10, e20). Surveillance data of the Robert Koch Institute, however, reveal that the rates of measles infections among adults aged 20 to 39 and among infants have actually increased (Table 3, Figure 2) (e21). The rising incidence among not-yet-vaccinated infants is attributable to a lower rate of immunity conferred during gestation via maternal antibodies from immune mothers (e22, e23). On the other hand, the rising incidence of measles among 20-to-39-year-olds reflects a gap in immunity, which has two causes: first, the failure to obtain primary and/or booster vaccination, and, second, a lower rate of natural immunity due to prior measles infection. In 2005, a seroprevalence study among first-year medical students at the University of Frankfurt am Main (aged 20 to 45 years) revealed adequate immunity to measles in only 84% (11). To stem the continuing endemic spread of measles in Germany, it has been recommended since July 2010 that all persons born after 1970 who were vaccinated against measles only once in childhood, or not at all, should now be given MMR vaccine (e21). The STIKO does not recommend measles vaccination for unvaccinated

persons born before 1970. Nonetheless, if such a person is reliably known never to have had measles, then vaccination should certainly be considered.

As the human immune system functions less well with advancing age, the elderly are at greater risk of severe, invasive infection. For this reason, persons aged 60 and above should receive annual vaccinations against (seasonal) influenza (e24) and a single anti-pneumococcal vaccination with a multivalent polysaccharide vaccine. Repeated vaccination with the non-conjugated anti-pneumococcal vaccine is not recommended, not only because of the increased risk of adverse reactions with repeated vaccination, but also because immunity may continue to decline despite the booster (underresponsiveness) (e25, e26). Only persons at high risk of pneumococcal infection, e.g., because of chronic heart or lung disease, should have a second anti-pneumococcal vaccination five years after their initial one (as stated in the product information for physicians) (12).

Controversies about vaccination

Human papilloma virus (HPV)

The available scientific evidence implies that persistent infection with at least one of the 15 so-called high-risk types of HPV is a prerequisite for the development of cancer of the uterine cervix (13, 14). 70% of all cases of solid, invasive cervical tumors are associated with just two of these high-risk types, namely, types 16 and 18 (e27). Each year in Germany, 13 of every 100 000 women newly develop cervical cancer (e28). The Federal Statistical Office reports that 1566 women died of this disease in Germany in 2007. There has not been any systematic assessment to date in Germany of the disease burden of preliminary stages of uterine cancer, known as cervical intraepithelial neoplasia (CIN), or of the burden of persistent HPV infection. It has, however, been estimated from insurance claims data that 140 000 cervical operations (conizations) and 2200 hysterectomies are performed in Germany each year for the diagnostic assessment and/or treatment of suspected cervical cancer (e29, e30).

A vaccine against HPV types 6, 11, 16, and 18 has been available since 2006, and a further vaccine against types 16 and 18 has been available since 2007. Types 6 and 11, though not among the high-risk types for cancer, are responsible for the formation of condylomata acuminata. With the goal of lowering the incidence of cervical cancer, vaccination against HPV (types 16

Human papilloma virus

With the goal of lowering the incidence of cervical cancer, vaccination against HPV (types 16 and 18) has been officially recommended in Germany since March 2007 for all girls aged 12 to 17.

The timing of HPV vaccination

The series of three doses of the vaccine should be given between age 12 and age 17 and completed before the first sexual intercourse, if possible.

and 18) has been officially recommended in Germany since March 2007 for all girls aged 12 to 17 (e16). The series of three doses of the vaccine should be completed before the first sexual intercourse, if possible.

The years 2008 and 2009 witnessed a public controversy in Germany about the efficacy and possible harm of HPV vaccination. The issues raised for critical discussion included for the following:

- The STIKO recommended vaccination before the results of important studies of the efficacy of the vaccine were published (15).
- The drug approval authorities accepted the use of preliminary stages of cancer (CIN 2 and 3, and carcinoma in situ) as endpoints for clinical studies of efficacy, even though these conditions are only surrogate markers for the disease to be prevented, i.e., cervical cancer. Thus, in the strictest scientific sense, vaccination has only been shown to prevent precancerous conditions, rather than cancer itself.

Persistent infection with high-risk types of HPV is an indispensable prerequisite for the development of cervical cancer. It is, therefore, biologically plausible to suppose that the prevention of HPV infection by vaccination can also prevent the subsequent development of cancer. Decades generally elapse from the onset of chronic, persistent HPV infection to the appearance of cervical cancer. It would be ethically unacceptable for a treatment known to prevent precancerous conditions (CIN 2+) to be withheld from the patients participating in the trial, merely to await the formal demonstration 10 to 20 years later that it can also prevent the definitive endpoint, i.e., the development of cancer itself.

No serious adverse effects of HPV vaccination have yet been observed, either in the course of the approval studies or afterward, when the vaccine was given to millions of women. In 2007, two young women died—one in Germany, one in Austria—shortly after being vaccinated against HPV. The Paul Ehrlich Institute investigated both deaths in its ongoing pharmacovigilance program, and then released its final assessment (e31): no causal relationship between HPV vaccination and death was established in either case, and the temporal nearness of vaccination and death in both of these tragic cases is presumed to have been no more than a coincidence. Nonetheless, reports of these two deaths in the popular press markedly lessened public confidence in the safety of the HPV vaccine. The vaccination rate among 12- and 13-year-old girls, at one time 40%, has now dropped to about 10% (e32).

In August 2009, the STIKO published an evidence-based reassessment of HPV vaccination that took account of all available studies on the safety and efficacy of HPV vaccines (e30). Both of the approved vaccines were found to be more than 90% effective for the prevention of HPV 16- or 18-associated CIN 2+ in women who were seronegative for HPV 16 and/or 18 before vaccination and who received all three doses of the vaccine (e30). In the approval studies for the quadrivalent HPV vaccine, HPV 16-associated CIN 1+ lesions were seen after 42 months of observation in 6 of 6648 vaccinated women, compared with 97 of 6257 who had received a placebo instead of the vaccine; HPV 18-associated CIN 1+ lesions were seen in 1 of 7158 vaccinated women, compared with 47 of 7092 who had received placebo (16). These figures correspond to 94.0% efficacy for HPV 16 and 97.9% efficacy for HPV 18. In the approval study for the bivalent vaccine, HPV 16/18-associated CIN 2+ lesions were seen in 4 of 7344 vaccinated women and 56 of 7312 who had received placebo during an observation period of 34.9 months, corresponding to 92.9% efficacy for the prevention of CIN 2+ lesions (17). The available data also document cross-protection by this vaccine against further oncogenic types of HPV (types 31, 33, and 45) (18). Either HPV vaccine confers a lesser benefit if HPV infection is already present at the time of vaccination (e33). After its reevaluation, the STIKO still recommends that all girls aged 12 to 17 should be vaccinated against HPV. The currently available data do not answer the question whether booster vaccination is needed.

Rotavirus (RV)

Rotavirus infection is the most common cause of acute gastroenteritis in infants and small children around the world. Each year, some 440 000 infants and small children die of rotavirus infection, mainly in the so-called developing countries (34). The surveillance data of the Robert Koch Institute reveal that, in Germany, rotavirus infection causes many hospitalizations of children below the age of five years (19). From 2001 to 2008, an annual average of 39 609 rotavirus infections was reported to the RKI (range, 28,134 to 47,619); out of this number, 17 636 infections per year (44%; range, 12 383 to 23 263) were in hospitalized children. Nonetheless, long-term damage to health, or death, due to rotavirus infection is extremely rare in Germany. From 2004 to 2008, a total of 8 deaths due to rotavirus

The efficacy of HPV vaccination

The two approved HPV vaccines are more than 90% effective for the prevention of HPV 16- or 18-associated CIN 2+ in women who were seronegative for HPV 16 and/or 18 before vaccination.

Rotavirus infection

Each year, some 440 000 infants and small children die of rotavirus infection, mainly in the so-called developing countries.

infection in children under 5 years of age were reported to the RKI. This corresponds to a lethality of less than 0.001% (19). Thus, any recommendations regarding possible vaccination against rotaviruses must proceed from a very different factual base in Germany than in developing countries where rotavirus causes a heavy burden of disease and death.

Two vaccines against rotavirus have been approved in Germany since 2006, one for infants aged 6 to 24 weeks and the other for infants aged 6 to 26 weeks. The clinical approval studies found both vaccines highly effective for the prevention of rotavirus-mediated diseases of all levels of severity, as well as for the prevention of severe cases in particular (74% effectiveness [95% CI, 67–80%] and 85% effectiveness [95%CI, 72–92%], respectively) (20, 21). For one subgroup in the approval study for one of these two rotavirus vaccines, the efficacy of the vaccine was tested in a population in Finland and the USA (20). 83 of 2384 vaccinated children and 318 of 2839 children who had received placebo developed an RV infection. These figures correspond to an absolute risk reduction (ARR) of 8.3% and to a number needed to vaccinate (NNV) of 12 in relation to the population studied. The follow-up after vaccination was for at least one infection season. The effectiveness of the two rotavirus vaccines is revealed mainly by the figures relating to rotavirus-related hospitalization and treatment in emergency rooms (ERs); in the approval studies, the vaccines prevented these events with 85–100% effectiveness (20, 21). Only 20 of 34 035 vaccinated children were hospitalized or treated in an ER because of rotavirus infection, compared to 383 of 34 003 children who had received placebo (20). This corresponds to an ARR of 1.1% and an NNV of 91 in relation to the study population. In countries where RV vaccination has been carried out on a large scale, including the USA, Mexico, and Austria, a marked reduction of the disease burden has been reported (22, e35–e37). Moreover, since the introduction of population-wide vaccination in these countries, the infection rates among older, unvaccinated children have declined, indicating that herd immunity has developed as well.

With respect to the safety of RV vaccines, no higher risk for any type of severe complication was found in the approval studies, which involved more than 70 000 infants; in particular, there was no higher risk of intussusception (20, 21). On the other hand, data on vaccination side effects that were spontaneously collected after the introduction of RV vaccination in Mexico, Brazil, and Australia were reported in the summer of 2010 to provide

initial evidence of a mildly elevated incidence of intussusception after vaccination, in comparison with a historically determined background incidence (23). In Australia, the relative risk of intussusception was found to be elevated 1 to 21 days after administration of the initial dose of RV vaccine (e38). A recent study from Mexico and Brazil likewise indicates that intussusception is more common after RV vaccination (e39). The American authorities, having weighed this small risk against the known benefit of vaccination, have not yet considered changing their recommendations, but prior intussusception is now listed as a contraindication for rotavirus vaccination in the information for physicians that is provided with each of the two vaccines (24).

In early 2007, the STIKO took a generally positive view of RV vaccination but did not recommend it for population-wide use (e40). As RV-associated disease in Germany tends to be an acute and transient event, with only very rare cases of severe or lethal infection, any RV vaccine must be shown to be highly safe and well tolerated before a general recommendation can be given to vaccinate. Initial studies that have already been performed, and further ones that are underway, regarding the association between RV vaccination and intussusception are expected to shed more light on the subject. As the RV vaccines are also very expensive, a health-economic analysis would also be advisable (such analyses have already been performed in other European countries) (25, e41). RV vaccination is now paid for by many statutory health insurance carriers and can, of course, be reimbursably administered in the manner for which it was approved (e42, e43). The STIKO is now carrying out a new epidemiologic risk-benefit analysis of population-wide RV vaccination.

Conflict of interest statement

The Center for Child and Adolescent Medicine at the University of Mainz has received honoraria for Prof. Zepp's advisory and teaching activities on behalf of GSK, SPMSD, Chiron, Novartis, and Sanofi Pasteur, as well as reimbursement of expenses for clinical trials from GSK and Medimmune. Prof. Zepp has received an expert consulting fee from Chiron Novartis, as well as reimbursement of participation fees for conferences organized by GSK, Sanofi, Novartis, InfectoPharm, and EudiPharm in which he has delivered lectures. He is the director of, and thus carries primary responsibility for, the reference laboratory for cellular immunity of the University of Mainz Faculty of Medicine (a cooperative basic science project of the University of Mainz and GSK).

Dr. Tertilt and Dr. Wiese-Posselt state that no conflict of interest exists.

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

At what interval after their last pertussis vaccination should adults be given a booster vaccination?

- a) 5 years
- b) 10 years
- c) 15 years
- d) 20 years
- e) 25 years

Question 2

When and how should vaccinations against measles, mumps, and rubella be given?

- a) As the measles vaccine is a live vaccine, the first vaccination should be given no earlier than the second birthday, and the second at some time before age 5.
- b) These three vaccinations should be given individually between the ages of 11 and 14 months.
- c) A single MMR vaccination is given in the child's third year and does not need to be repeated.
- d) The first MMR vaccination is given between 11 and 14 months and the second one before the end of the second year.
- e) The MMR vaccine is reserved for high-risk patients, regardless of age.

Question 3

What atypical manifestations are seen in adult pertussis infection?

- a) Staccato cough on standing up or after exercise
- b) Persistent cough for more than 3 weeks
- c) Voluminous expectoration for months at a time
- d) Impaired respiratory performance on sustained exercise
- e) Orthopnea and acute dyspnea when lying down and during sleep

Question 4

Which of the following is an important fact about vaccination in premature neonates (i.e., those born before the 28th gestational week)?

- a) They should receive their vaccinations intravenously through a central venous catheter 48 hours after birth to minimized the risk of infection.
- b) They should be vaccinated according to the STIKO vaccination calendar, but at a delay corresponding to their gestational (not chronological) age.
- c) They should be fed exclusively on mother's milk so that they will have adequate baseline immunity during the entire first year of life.
- d) They should be vaccinated against rotavirus and hepatitis A and B right after birth, because they will be spending a long time in the hospital.
- e) They should be vaccinated according to the STIKO calendar at the same times as full-term babies, by their chronological (not gestational) age.

Question 5

To what value has the incidence of invasive pneumococcal infection in children under 2 been reduced by anti-pneumococcal vaccination?

- a) 3.4/100 000
- b) 4.4/100 000
- c) 5.4/100 000
- d) 6.4/100 000
- e) 7.4/100 000

Question 6

According to the STIKO recommendations, who should be vaccinated against human papilloma virus, when, and how?

- a) Boys and girls aged 12-15, before the first sexual intercourse if possible
- b) Girls aged 12-17, before the first sexual intercourse if possible
- c) Boys aged 15-18, after the first sexual intercourse if possible

- d) Boys aged 12-15, before the first sexual intercourse if possible
- e) Girls aged 15-18, after the first sexual intercourse if possible

Question 7

What should persons over age 60 be vaccinated against?

- a) Influenza (annually) and pneumococci (once)
- b) Meningococci and *Haemophilus influenzae* type b
- c) Pneumococci (once) and varicella-zoster virus
- d) Diphtheria and tetanus (both annually)
- e) Influenza and pneumococci (both annually)

Question 8

A 27-year-old student who grew up in Germany comes to the emergency room after a fall from his bicycle in which he sustained cutaneous scrapes and bruises. He tells you, apparently reliably, that he received all the usual vaccinations as a child, but none since then. What do you advise?

- a) No vaccination
- b) Tetanus booster vaccination
- c) TD booster vaccination
- d) Td booster vaccination (with reduced antigen content)
- e) Tdap booster vaccination

Question 9

A 12-year-old girl who has never been vaccinated comes to your office. She has learned in school that there is a vaccine against sexually transmitted diseases. Her parents want to know what vaccinations should now be given. She has never had chickenpox, nor has she had measles, mumps, or rubella, as far as she or her parents know. What vaccinations should she receive for baseline immunization, according to the STIKO recommendations?

- a) 2 × T, d (or Td), IPV, third vaccination with Tdap-IPV, 3 × HB, 3 × HPV, 2 × MMR-VZV, 1 × MenC
- b) 3 × sixfold vaccine Tdap-IPV-Hib-HB, 2 × MMR-VZV, 3 × HPV, 1 × MenC
- c) 2 × T, d (or Td), IPV, third vaccination with Tdap-IPV, 3 × HB, 1 × MMR-VZV, 1 × MenC, 1 × HPV
- d) 3 × Tdap-IPV, 3 × HB, 2 × MMR-VZV, 1 × MenC, 3 × HPV
- e) 3 × T, d, IPV, 3 × HB, 2 × MMR, 1 × MenC, 3 × HPV

Question 10

The parents of a 20-month-old girl show you her vaccination certificate, which documents her having received the sixfold Tdap-Hib-HB-IPV vaccine four times and a conjugate Pnk vaccine four times. Having moved to a new city and changed pediatricians, the parents admit they are no longer sure what vaccinations the child has received. They ask you whether everything is up to date. What is your assessment?

- a) All vaccinations have been given according to the STIKO recommendations, and no further ones are needed for the moment.
- b) All vaccinations have been given according to the STIKO recommendations until now, and it is time for the first MMR vaccination.
- c) According to the STIKO recommendations, the next scheduled vaccination is the one against human papilloma virus.
- d) Among the standard vaccinations recommended by the STIKO, the HB vaccination and the first MMR vaccination have been missed. These should be made up for as soon as possible.
- e) Among the standard vaccinations recommended by the STIKO, the first MMR-VZV vaccination has been missed. It should be made up for as soon as possible. The vaccination against type C meningococcus that is recommended during the child's second year should also be given.

CONTINUING MEDICAL EDUCATION

Vaccination Recommendations for Germany

by Miriam Wiese-Posselt, Christine Tertilt, and Fred Zepp

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