



RAPID RISK ASSESSMENT

Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA

8 October 2015

Main conclusions and options for response

Early in 2015, a shortage of acellular pertussis-containing combination vaccines for use in EU/EEA immunisation programmes was brought to the attention of ECDC.

The shortage, currently affecting some of the EU/EEA Member States (Member States), already had direct consequences for the delivery of national vaccination programmes, with some countries having to revise their childhood vaccination policy.

Discontinuing or delaying primary vaccination schemes would have dramatic consequences, in particular for the prevention of pertussis and invasive disease due to *Haemophilus influenzae type b* in infants and young children.

As much as possible, the infant and young children immunisation schedule should be preserved in order to ensure the early and adequate protection of newborns. Preference should be given to the use of combined vaccines with the highest number of antigens.

In the childhood vaccination schedule, the following priorities should be considered to minimise the disease burden:

- Priority should be given to preserving the infant primary immunisation schedule (first year of life) over the first toddler booster dose (second year of life).
- If applicable, the first toddler booster dose should be prioritised over the school-entry booster dose.

Several options for the adaptation of the immunisation schedule due to vaccine shortage should be considered. These include:

- Possible adjustments to the primary immunisation series (0–2 years)
- Options for vaccine substitution in the immunisation schedule
- Building stockpiles to ensure immunisation programmes are maintained during future shortages.

An assessment of the temporary changes in vaccination schedules in the EU/EEA Member States is needed in order to better understand the epidemiological situation in the near future.

Errata: This risk assessment was amended on 14 October and 6 November 2015 to add information from the Czech Republic (Tables 2 and 3) and amend a statement on the priming schedules in Italy and Sweden. The amended sentence now reads: 'This priming schedule was introduced first in Italy in 1981 and in Sweden in 1986.'

Suggested citation: European Centre for Disease Prevention and Control. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA – 8 October 2015. Stockholm: ECDC; 2015.

Source and date of request

Directorate General for Health and Food Safety (DG SANTE), 25 September 2015

Public health issue

Early in 2015, a shortage of acellular pertussis-containing vaccines for use in the EU/EEA immunisation programmes was brought to the attention of ECDC. This shortage is believed to be the result of reduced production capacities of the acellular pertussis (aP) antigen used in the final vaccine formulation of numerous combination vaccines that are administered in EU/EEA Member States. Another reason for the shortage is an increased worldwide demand for combination vaccines.

This unexpected situation has forced some EU/EEA countries to adjust their vaccination programmes to address the vaccine shortage (see Table 2). ECDC has provided technical assistance pointing out possible solutions to EU/EEA Member States upon request.

The ongoing vaccine shortage – alongside a possible increased demand to vaccinate newly arrived irregular migrants and asylum seekers in the EU originating from areas where immunisation programmes have been disrupted due to conflict – prompted the European Commission to request a rapid risk assessment from ECDC.

The objectives of this rapid risk assessment are:

- to provide feedback on results of a brief consultation conducted on 25 September 2015 with EU/EEA Member States. The consultation was conducted with the aim of providing an update on the current situation with regard to the availability of vaccines for routine programmes and for the vaccination of migrants.
- to summarise changes to the regular vaccine schedules made by some EU/EEA Member States to overcome shortages; and
- to propose options to be considered by EU/EEA Member States in order to adjust their national vaccination schedules to overcome supply challenges and/or increased national demand. These principles are based on i) what is considered good practice and ii) on recent measures implemented by a number of Member States.

This rapid risk assessment focuses on childhood and maternal immunisation programmes, with an emphasis on acellular pertussis-containing combination vaccines as this vaccine appears to be the one primarily affected by current shortages (see Table 1).

This rapid risk assessment is not intended:

- to propose a universal EU vaccination schedule that can completely accommodate all national situations;
- to provide an extensive evidence-based review of options on how to modify vaccination schedules;
- to discuss specifics of the various combination vaccines available on the EU market, i.e. number and types of aP vaccine components, or the role of combined or concomitantly administered vaccines*;
- to address national vaccine procurement processes at the national level.

Consulted experts

ECDC experts: Tarik Derrough, Kari Johansen, Lucia Pastore-Celentano

External experts: Pierre Van Damme (University of Antwerp, Belgium), Daniel Levy-Bruhl (French Institute for Public Health Surveillance), Ingrid Uhnoo (Public Health Agency of Sweden)

Abbreviations

aP: acellular-pertussis (full-dose content)

ap: acellular pertussis (low-dose content)

wP: whole-cell pertussis

T: tetanus antigen

D: diphtheria antigen

d: diphtheria antigen (reduced dose)

DT: diphtheria and tetanus antigens combination vaccine

DTaP-IPV: combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose) and inactivated poliomyelitis antigens. Also referred to as 'tetraivalent' vaccine.

DTaP-IPV/Hib: combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose), inactivated poliomyelitis antigens and Hib antigen (to be reconstituted for some vaccine presentation). Also referred to as 'pentavalent' vaccine.

* It is understood that the use and type of vaccines should be in accordance with national vaccination policies and the summary of product characteristics of each vaccine.

DTaP-IPV-Hib-HepB: combination vaccines that contain diphtheria (full dose), tetanus, acellular pertussis (full dose) inactivated poliomyelitis antigens, Hib and Hepatitis B antigens. Also referred to as 'hexavalent' vaccine.

DTwP: combination vaccines that contain diphtheria (full dose), tetanus and whole-cell pertussis antigens.

Tdap: combination vaccines that contain tetanus, diphtheria (reduced dose content) and acellular pertussis (low antigen content).

Tdap-IPV: combination vaccines that contain tetanus, diphtheria (reduced dose content), acellular

pertussis (low antigen content) and inactivated poliomyelitis antigens.

Hib: *Haemophilus influenzae type b*

'2p+1' schedule: primary immunisation schedule corresponding to two doses of primary vaccination and a booster dose, usually all given within the first 12 months of life and starting as early as two months of life.

'3p+1' schedule: primary immunisation schedule corresponding to three doses, given in the first year of life, starting as early as two months of life, with a booster in the second year of life.

Background

Introduction

The quality of immunisation programme implementation and delivery in EU/EEA Member States is very high overall. Childhood and maternal immunisation programmes have shown a highly significant impact in all Member States by preventing most vaccine-preventable communicable diseases, or bringing them to a fairly good level of control. Despite their diversity, all childhood immunisation schedules in use in the EU have been shown to work well both in terms of safety and effectiveness.

Current vaccination schedules are the result of historical evolution, compliance with provision of health services, vaccine licensing mechanisms, resources, and competing priorities. They were designed on the basis of different needs related to how the healthcare system, but also the education system, are organised at national level. They are adapted to the local epidemiology of vaccine-preventable diseases, which varies between the EU/EEA Member States. It is important to note that vaccination programmes vary not only across countries, but also within countries at regional or subregional level. Finally, programmes recommend vaccination of different target populations; some vaccines are recommended to the entire population regardless of health status while others are only recommended for selected population groups (e.g. influenza vaccination for certain disease risk groups).

All EU/EEA Member States have introduced vaccination against diphtheria, tetanus, poliomyelitis, pertussis and *Haemophilus influenzae type b* (Hib) in their primary infant schedules, with the majority of countries also administering vaccines against invasive pneumococcal disease and hepatitis B [1]. In addition, all EU/EEA Member States recommend vaccines against measles, mumps and rubella. Vaccination against meningococcal C infection (MenC) is recommended in 18 EU/EEA Member States.

Tetanus, diphtheria and polio

In EU/EEA Member States, diphtheria and tetanus are no longer a risk for young vaccinated infants, thanks to high vaccination coverage rates. Poliomyelitis has been eliminated from the WHO European Region but vaccination remains in place as polio viruses still circulate in two countries [2].

Nevertheless, these diseases are severe, and any interruption in the vaccination programme could have dramatic consequences. The recent detection of paralytic cases of poliomyelitis linked to the circulation of vaccine-derived polioviruses strains (cVDPV) in Ukraine and the detection of a case of diphtheria in an unvaccinated child in Spain are reminders of these ongoing threats and the need to keep vaccination rates at a high level [3,4].

Pertussis and invasive bacterial disease caused by Hib

Pertussis vaccination has been used in Europe since the 1950s. There is a need for early protection of newborns and young infants against pertussis and infections due to *Haemophilus influenzae type b* (Hib). In 2013, pertussis still accounted for 63 000 deaths worldwide in children aged < 5 years [5]. Prior to the introduction of routine Hib vaccination, a study estimated that in Europe the combined overall incidence of meningitis and Hib disease in children between 0 and 4 years of age was 23 and 41 per 100 000, respectively, corresponding to 9 900 and 17 800 cases per year. Vaccination programmes in their current scheme prevent almost all Hib cases in cohorts that are age-eligible for vaccination [6]. Therefore, any shortage affecting combination vaccines that contain the pertussis and Hib antigens and are used as part of the primary immunisation schedule, is of great concern.

The objectives of pertussis vaccination programmes are not to eliminate the disease but to prevent severe disease and deaths among youngest infants (< 6 months):

- through direct protection by vaccinating infants soon after birth;
- through immunisation of those likely to infect young infants;
- through maternal immunisation (implemented in a few EU/EEA countries).

The basic assumption is the acceptance of six weeks of age as the minimum age to start DTwP/DTaP vaccination, with a primary immunisation schedule offering two to three doses in the first year of life [5]. Booster doses are usually offered from 11 months of age and throughout the second year of life, depending on schedules recommended by countries.

Pertussis vaccines do not exist as stand-alone vaccines. Difficulties in producing pertussis and Hib antigens affect a high number of combination vaccines that are used in infancy.

The current vaccination schedules applicable in EU/EEA Member States are available from the ECDC vaccine schedule platform and are summarised in Table 1 below [1].

Infant primary immunisation scheme

For practical reasons, only the pertussis vaccination policies are summarised in Table 1, with the understanding that Hib vaccination is provided as part of the primary immunisation scheme in all EU Member States. The only exceptions are the United Kingdom and Ireland that do not administer a pertussis booster dose in the second year of life (a combined Hib–MenC vaccine is given at 12–13 months).

The current schedules in EU/EEA Member States for vaccination below 24 months of age with acellular pertussis-containing vaccines can be divided into the following groups (Table 1):

- **A so-called '2p+1' schedule** corresponding to two doses of primary vaccination and a booster dose, with the vaccines given at three, five and 12 months (in AT, FI, IT, DK, SE, ICE, NO and SK) or at two, four and 11–12 months (in FR and RO).
- **A so-called '3p+1' schedule** corresponding to three doses given in the first year of life, starting as early as two months, with a booster in the second year of life (in BE, BG, HR, CY, CZ, EE, GE, GR, HU, IRE, LV, LI, LUX, MT, NL, PL, PT, SLO and ES).

The only exceptions to these schedules are the UK and Ireland that – after primary vaccination at two, three and four months of age – do not include a pertussis booster dose in the second year of life but rather between three and five years after primary immunisation.

All EU/EEA countries have shifted to acellular pertussis-containing vaccines except Poland that still uses whole-cell pertussis-containing combination vaccines for primary immunisation and the first booster dose.

A recent decision by WHO SAGE suggests that countries that have not shifted should remain using whole-cell pertussis containing vaccines due to the waning immunity observed following the use of acellular vaccines [5].

Table 1. Summary of vaccination schedules in the EU, adapted from the ECDC vaccine schedule platform

Schedule type	First year of life			Second year of life	Third year of life	Preschool booster	Adolescent booster	Country
'2p+1'	From 6 weeks to 6 months		Around first birthday					
	P1	P2	B1			B2	B3	F, IT, FI, NO, IS, SK SE*, DK, RO, AT
'3p+1'	P1	P2	P3	B1		B2	B3	BE, BG, CZ, EE, DE, GR, HU, LI, LU,
				B1		B2		HR, CY, LV, LI, MT, NL, PL, PT, SI, ES
					B1			UK
						B1	B2	IE
Vaccine combination generally used in EU/EEA	<ul style="list-style-type: none"> • DTaP-IPV-HepB/Hib ('hexavalent') • DTaP-IPV/Hib ('pentavalent') • DTaP-IPV ('tetravalent') • DTwP-IPV/Hib ('whole-cell pertussis combo') • Hep B (used in conjunction with pentavalent) 			<ul style="list-style-type: none"> • Hib-MenC combo 	<ul style="list-style-type: none"> • DTaP-IPV • Tdap • Tdap-IPV • Tdap 	<ul style="list-style-type: none"> • Td • Tdap • Tdap-IPV 		

P=primary dose; B=booster dose

* Starting with 2016, Sweden will include an adolescent booster dose in the national immunisation programme.

The various immunisation schedules in Europe for acellular-pertussis (full-dose content) contain vaccines that evolved from experiences gained from immunisation with whole-cell pertussis-containing vaccines (administered at two and three months and a third dose given at 4 or 6 months). The need for three doses was driven by the wP component while the D and T components – immunogenic and less reactogenic – could be given in two doses [7]. The two doses (with a three–five months schedule), on the other hand, was driven by the DT vaccines vaccination schedule. This priming schedule was introduced first in Italy in 1981 and in Sweden in 1986. This two-dose schedule was kept when acellular-pertussis antigen was added to DT. France moved in 2013 to the 2-dose schedule in the first year of life, offering the vaccine at two and four months of age [8].

Vaccination policies for older age groups

School-age children and adolescents

The objective of the pre-school and adolescent booster is i) to offer direct protection of those vaccinated by ensuring adequate circulating antibodies at protective levels in order to reduce the risk of infection due to waning immunity, and ii) to limit the risk of infections of younger unprotected siblings in a household.

School entry

To date, all countries except the UK offer a booster dose around the time of school entry (so-called 'pre-school booster'). This booster dose is to account for reduced vaccine effectiveness observed among pre-school and school-age children [7]. The mechanisms involved are not entirely clear but there is a body of evidence in the EU, particularly in Italy and Sweden [9,10]. In Sweden, a two-dose priming schedule at three and five months of age, with a booster dose at 12 months, was adopted for primary immunisation. Findings from the long-term enhanced pertussis surveillance scheme indicated that waning immunity in the first DTaP-vaccinated cohorts lead to pertussis among 7- to 8-year-olds and demonstrated waning of vaccine-induced protection from pertussis. These findings led to the addition of a pre-school booster dose of acellular pertussis vaccine starting in 2007 [9,11].

A large study in Italy of two aP-containing vaccines six years after completion of the primary immunisation series in children (with a 2-, 4-, 6-month schedule) showed protective efficacy of 76% and 85%, respectively, using two clinical definitions of pertussis [10,12].

During adolescence (11 to 18 years)

Seventeen EU/EEA Member State recommend booster doses during adolescence (11 to 18 years).

The objective of a dose given at this age is to extend protection until late adolescence and until childbearing age. There is little evidence of the impact on severe pertussis in infants but these strategies may have an impact on the targeted population. The indirect effect on infants is not well established [5].

Adults

Vaccination of adults can occur for different reasons:

- **As part of the regular booster policy:** Adults can be offered boosters of aP vaccine in combination with tetanus toxoid and reduced-dose diphtheria vaccine (Tdap) either once in their lifetime or every 10–20 years depending on the country (AT, BE, CZ, FR, DE, GR, IE, LI). Although these programmes (other than vaccination of pregnant women) have an impact on the directly targeted populations, there is as yet no substantial evidence that they have had a significant impact on severe pertussis in infants [5].
- **As part of the 'cocooning strategy':** Infants who are too young to be vaccinated are protected by vaccinating close contacts who could otherwise potentially become a source of infection. The cocooning strategy is recommended in some EU/EEA Member States (BE, FR, DE, LI). This strategy may have an impact on disease prevention in some settings if high vaccination coverage can be achieved in a timely manner. The overall impact and cost-effectiveness are likely to be substantially lower compare to maternal immunisation, which requires only one dose, whereas cocooning requires, as a minimum, multiple doses for parents and family members.
- **Maternal vaccination (during pregnancy):** A limited number of countries in the EU (BE, UK, IE and some regions in Spain) have introduced maternal Tdap vaccination during pregnancy to help prevent mortality due to severe pertussis infection in infants too young to be vaccinated. A Tdap vaccine is used for vaccination during pregnancy.

Recent evidence consistently indicates that maternal immunisation with aP-containing vaccine during the third trimester of pregnancy is safe and highly effective in protecting infants from pertussis and that it may have a high positive impact on morbidity and mortality in infants too young to have been vaccinated. Experience in the UK with the vaccination of pregnant women indicates high impact on infant pertussis-related mortality. This outcome is probably primarily due to the direct protection conferred by the transfer of maternal antibodies, with some contribution from reduced risk of transmission through reduced likelihood of peripartum pertussis in the mother.

The point estimate for the vaccine effectiveness of maternal vaccination > 7 days before birth was 91% (95% CI: 84%–95%) using the screening method, with adjusted vaccine effectiveness estimated at 93% (95% CI: 81%–97%) in an associated case-control study [13-15]. However, a recent study in the UK showed that maternal immunisation can blunt the subsequent responses to some vaccines in the infant immunisation schedule. This phenomenon needs to be further monitored and could be prevented by giving a booster dose of DTaP, Hib, MCC, and PCV-13 in the second year of life [16,17].

Event background

Since early 2015, a limited supply of combined vaccines for primary immunisation and booster series (as part of childhood and maternal immunisation programmes in the EU) was brought to the attention of the ECDC. Since March 2015, several EU/EEA Member State have been requesting technical assistance from ECDC, which lead to an information exchange between ECDC and EU/EEA Member States through the epidemic intelligence information services platform for vaccine-preventable diseases (EPIS-VPD) as well as during a Health Security Committee (HSC) teleconference in April 2015. In this communication, it became clear that some countries had a stockpile of vaccines for use in their routine programmes while others did not.

Vaccine shortage is believed to be due to reduced volume production capacities of the acellular pertussis antigen that enters the final vaccine formulation of numerous combination vaccines and increased global demand of combination vaccines that are used throughout the EU/EEA Member States and the world.

In September 2015, the ongoing supply issues – alongside possible increased demand to vaccinate newly arrived migrants in the EU – were further discussed during a HSC teleconference on 23 September 2015.

This unexpected situation has forced some EU/EEA countries to adjust their vaccination policies to overcome the shortage (see Table 2).

In order to collect information on vaccine availability and measures taken to vaccinate migrants and asylum seekers in the EU/EEA Member States, the Vaccine-preventable Diseases (VPD) Programme at ECDC conducted a survey on 25 September 2015 asking its National Focal Points for VPDs the following questions:

1. Do you currently experience a shortage of one or several vaccines, or do you anticipate having a shortage of vaccines within the next 12 months? If YES, please provide information on which vaccines.
2. Have you in the last 12 months considered changing your country's vaccination schedule in order to mitigate the risk of shortage of vaccine? If YES, please provide information on which vaccines.
3. Have you in the last 12 months tendered for vaccines without receiving bids/offers from the suppliers? If YES, please specify which vaccines.
4. Does your government/national vaccination programme currently offer vaccinations for irregular migrants and asylum seekers? If YES, please specify which vaccines and estimate the volume of vaccine given during 2015.
5. Has the provision of vaccinations to irregular migrants and asylum seekers exacerbated the shortage of vaccines in your country?
6. Do you expect that the provision of vaccinations to irregular migrants and asylum seekers will exacerbate the shortage of vaccines in the coming 12 months?

Table 2 summarises current and foreseeable shortage situations according to the information received from 17 of the 31 EU/EEA Member States contacted.

The table also provides details of forced changes or adaptation of the national immunisation policies that EU/EEA Member States had to introduce because of the shortages. The outcome of the survey confirms that shortages affect in particular acellular pertussis combination vaccines, i.e. those vaccines used as part of the primary immunisation schedule or as booster doses. This confirms information which has already been available since early 2015 from various EU/EEA Member States.

The shortage of acellular pertussis-containing combination vaccines has prompted some countries to adjust their immunisation policy in different aspects:

- temporary suspension of the primary immunisation scheme (e.g. Bulgaria)
- changes to the primary immunisation schedule age of dose administration (e.g. Romania, Hungary)
- modification of the vaccine formulation used as pre-school booster (e.g. Belgium, France)
- delayed introduction of a new antigen in the primary immunisation scheme (e.g. Norway)
- prioritisation of vaccine formulation for the primary immunisation scheme (e.g. Spain, Sweden)

The EU/EEA Member States were also asked about the current national vaccination policy for irregular migrants and asylum seekers currently entering the EU and residing in their countries. This is summarised in Table 3.

Some countries also report difficulties with the supply of BCG (Bacille Calmette-Guérin) vaccines against TB, and there is an ongoing discussion at the EU level about this issue as no manufacturer is currently able to ensure a continuous supply of BCG vaccines.

ECDC threat assessment for the EU

The shortage of combination vaccines in the EU that started in 2015, in particular the lower supply of acellular-pertussis combination vaccines, represents a public health threat to the EU. To date, there is no indication on how long this shortage will last. Therefore options for minimising its impact are suggested in this document.

Table 2. Overview of current shortage in EU/EEA Member States and impact on vaccination policy

Country	Date	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation	
				Primary immunisation	Booster doses
Belgium	25 Sep 2015	Communication to ECDC; official statement*	<ul style="list-style-type: none"> Current: aP combination vaccines – DTaP-IPV and hexavalent vaccines Monovalent IPV 	Limited: hexavalent vaccine substitution (in Wallonia) with the same vaccine but initially attributed to another country	High: pre-school booster affected. DTaP-IPV and temporary replacement by Tdap-IPV (same manufacturer but lower dose of diphtheria/tetanus/pertussis antigens)
Bulgaria	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: aP combination vaccines shortage: hexa-, penta- and tetravalent No applicants to tender in March 2015 for vaccines used as part of the primary immunisation schedule, second year of life booster dose and pre-school booster 	Very high: in 2014, temporary substitution of the hexavalent vaccine with a pentavalent vaccine and then with tetravalent. In 2015, donation of pentavalent vaccine from Turkey. Booster in second month of life discontinued	Very high: in 2014, temporary interruption of the pre-school booster with tetravalent vaccine as used for primary immunisation. In 2015, ongoing interruption due to lack of tetravalent vaccine.
Croatia	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: Td vaccine used for adult booster Expected: aP combination vaccine (hexavalent, DTaP, Tdap) 	Limited: introduction of hexavalent vaccination connected to, but not dictated by, shortage in pentavalent vaccine	None
Czech Republic	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> DTaP (used as a booster dose at 5–6 years) 	None	None
Estonia	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: aP combination vaccines – DTaP-IPV 	None	None
France	25 Feb 2015	Official statement†	<ul style="list-style-type: none"> Shortage of combination vaccine with lower pertussis antigen content (ap-combo family). Impact on pre-school booster. Decision to introduce Tdap-IPV at 6 years of age instead of DTaP-IPV combination vaccine 	None	High: pre-school booster affected. DTaP-IPV temporary replaced by Tdap-IPV and DTaP-IPV recommended for the booster for 11–13-year-olds of the cohort currently affected.
Finland	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> No shortage but limited stocks for BCG and DTaP 	None	None
Germany	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: aP combination vaccines – DTaP-IPV/Hib, Tdap-IPV, Tdap 	None	None
Hungary	25 Sep 2015	Communication to ECDC; official statement‡	<ul style="list-style-type: none"> Temporary changes to the primary immunisation schedule due to pentavalent vaccine shortage. Shortage/difficult supply in BCG 	Limited: switch from a 2, 4, 6 to a 2, 3, 4 months schedule	None
Iceland	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> None 	None	none
Ireland	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> BCG 	None	None
Latvia	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> BCG 	None	None
Lithuania	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: aP combination vaccines – DTaP-IPV/Hib, Tdap-IPV BCG 	None	None
Malta	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> No 	None	None
Norway	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Delayed delivery/reduced volume delivered for all aP-containing combination vaccines. 	Limited: inability to introduce HepB routine vaccine due to insufficient response to tender for hexavalent vaccine	None
Portugal	12 Mar 15	Technical advice request to ECDC	<ul style="list-style-type: none"> Shortage of combination vaccine with lower pertussis antigen content (aP-combo family). Impact on pre-school booster. ECDC provided technical advice to Portugal upon their request. 	-	-

* http://www.provac.org/pdf/TETRAVAC_Repevax-FAQ_Provac_sept2015.pdf

† <http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=480>

‡ <http://www.hgye.hu/hirek/atmeneti-valtozas-az-oltasi-rendben/>

Country	Date	Source	Current or anticipated shortages	Impact on vaccination policy and mitigation	
				Primary immunisation	Booster doses
Romania	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> Current: shortage of pentavalent, hexavalent, tetravalent and dT/dTap vaccines 	Limited: moving from pentavalent to hexavalent vaccine (moving to a '2+1' schedule) only due to lack of pentavalent vaccine	High: shortages of vaccines used as pre-school (tetravalent vaccine) and school (dT/dTap vaccine) boosters
Slovenia	25 Sep 2015	Communication to ECDC	<ul style="list-style-type: none"> BCG 	None	None
Spain	25 Sep 2015	Technical advice request to ECDC; communication to ECDC	<ul style="list-style-type: none"> Current: shortage of pentavalent and dTap vaccines 	Limited: prioritisation of hexavalent for primary immunisation. Pentavalent to be prioritised for the second-year-of-life booster dose.	High: booster at 6 years is delayed in a high proportion of children and immunisation for specific groups interrupted. Reinforcement of vaccination during pregnancy for concerned regions.
Sweden	29 Sept 15	Technical advice request to ECDC; official statement*	<ul style="list-style-type: none"> Shortages in DTaP-IPV (Tetravac) The Swedish authorities asked for pentavalent vaccines to be prioritised for the primary immunisation scheme (2+1 doses) of children. 	None	High: shortages of vaccine used as pre-school booster

Table 3. Provision of vaccinations to irregular migrants and asylum seekers

Country	Vaccinations offered to irregular migrants/asylum seekers?			Exacerbated shortage due to provision of vaccinations to irregular migrants/asylum seekers?	
	Children	Adults	Volume	Present	Future
Belgium	For all <18 years: according to the national vaccination programme	For asylum seekers: <ul style="list-style-type: none"> from Afghanistan, Pakistan, Somalia and Nigeria: IPV born after 1970: MMR Tdap booster 	Around 6 850 (January–August 2015)	Yes, for IPV	Yes, for IPV
Bulgaria	For asylum seekers <15 years: DTPa-IPV-Hib (pentavalent), MMR shortly after entry; then the schedule continues according to the national immunisation programme		Around 2 000, since November 2013	No	Yes, for DTPa-IPV-Hib (Pentavalent)
Croatia	For registered asylum seekers: According to the national vaccination program	For registered asylum seekers: Td, IPV, MMR	A few dozen	No	Maybe, depends on number of asylum seekers
Czech Republic	For those < 15 years: measles and polio			N/A	N/A
Estonia	No		N/A	No	No
Finland	For asylum seekers <18 years, according to the national vaccination program	For asylum seekers: <ul style="list-style-type: none"> IPV for those coming from polio-risk countries or those who share accommodations with them. MMR, Td 	No data	No	Maybe, depends on number of asylum seekers
Germany	According to official recommendations†		No data	Unknown	Yes
Hungary	For registered individuals, age-appropriate vaccinations to be offered, specifically MMR and IPV		No data	No	Maybe
Iceland	Yes, according to national vaccination programme		No data	No	No
Ireland‡	As per recommended guideline: <ul style="list-style-type: none"> DTaP/IPV/Hib/HepB (for children 2 months–10 years) Tdap/IPV (for children 10–18 years) MMR, PCV, Men C 	As per recommended guideline: Tdap/IPV and Td/IPV, MMR, MenC	Small amounts	No	No
Latvia	No, but the issue is under discussion		N/A	N/A	Maybe, depends on number of irregular migrants and asylum seekers
Lithuania	For registered individuals, age-appropriate vaccinations to be offered, specifically BCG, DTaP/IPV/Hib, MMR, PCV, HepB		Small number	No	No, unless the number of irregular migrants and asylum seekers would sharply increase.
Malta	Yes, diphtheria, tetanus, polio, MMR			No	Maybe, if the number of irregular migrants and asylum seekers would sharply increase.

* <http://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2015/september/atgarder-for-vaccintillgangen/>

† http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2015/Ausgaben/41_15.pdf

‡ <http://www.hpsc.ie/A-Z/SpecificPopulations/Migrants/File,14742,en.pdf>

Country	Vaccinations offered to irregular migrants/asylum seekers?			Exacerbated shortage due to provision of vaccinations to irregular migrants/asylum seekers?	
	Children	Adults	Volume	Present	Future
Norway	There is no special vaccination scheme for migrants/asylum seekers, but it is recommended that vaccination status is evaluated and completed. Focus mainly on polio, measles and tuberculosis			No	Limited impact
Romania	Yes, a legislative framework exists		nil	No	Maybe, depends on the number of irregular migrants and asylum seekers and their status (migrants or asylum seekers).
Spain	Undocumented migrants < 18years: assessment and vaccination according to immunisation programme. Adults: not provided at this moment. Registered asylum seekers, children and adults: assessment and vaccination according to immunisation programme.			No	Depends on the number of persons arriving and the migration dynamics
Slovenia	No (not yet) – under assessment		N/A	No	Yes, if the number of irregular migrants and asylum seekers increases.
Sweden	For children < 18 years: vaccination according to the national vaccination programme	Adults (not decided yet but an internal guidance report is under assessment)		No	Possible

Source: EU/EEA Member States survey, 25 September 2015

Options for response

In the current situation, the general principle should be to secure protection to all infants against the recommended vaccine-preventable diseases, including pertussis and Hib, with minimum disruption of ongoing vaccination practices. Therefore, primary immunisation programmes should be preserved as much as possible, as should be the maternal immunisation programmes in the concerned countries.

The following options may be considered should shortages at the national level exceed vaccine demand, with the understanding that the final options for response lie with the EU/EEA Member States.

Options for possible adjustments to the primary immunisation series (0–2 years)

The priority is to preserve the primary immunisation series with a minimum of three doses.

In case of severe shortages, the following options are suggested (in order of priority):

- If an alternative commercial vaccine or other vaccine presentations are available (see section on *Options for vaccine substitution in the immunisation schedule* below), prioritise their use rather than modifying the schedule (e.g. rather than switching from a '3p+1' to a '2p+1' schedule with the same product); ensure appropriate monitoring of safety and effectiveness.
- In countries with a '3p+1' schedule, one of the primary doses in the first year of life could be temporarily suspended, and the primary booster dose would then be offered at around the time of the first birthday. Some European countries have adopted a '2p+1' regimen (see above), and evidence suggests the high effectiveness of this vaccination scheme.
Infants should receive the third and last dose of the primary series at around the time of their first birthday [7]. This would correspond to the first booster dose of a '2p+1' schedule, with a two-month interval between doses. Supplementary school-entry booster vaccinations should be considered for these cohorts of children, in accordance with national vaccination policies.
- Combination vaccines that contain a low-dose pertussis antigen are not licensed for use in primary immunisation schedules and have not undergone clinical trials in the age groups targeted in the primary series. They are usually offered starting at three years of age. If it is absolutely necessary to use them at an earlier age, their use should be carefully monitored in terms of safety and effectiveness.

Options for vaccine substitution in the immunisation schedule

- Consider substituting the missing doses with a possible alternative combination/formulation (see below).
- Consider delaying adolescent/adult booster while preserving doses that have demonstrated benefit towards infants (e.g. primary and maternal immunisation)
- If a hexavalent vaccine (DTaP-IPV-HepB-Hib) is not available for any dose of the infant/toddler series, – a pentavalent vaccine (DTaP-IPV/Hib), co-administered with a HepB standalone vaccine, could be used.

- Alternatively, a tetravalent vaccine (DTaP-IPV), co-administered with a Hib standalone vaccine and a HepB standalone vaccine, could be used.
- Another alternative solution could be a trivalent vaccine (DTaP), co-administered with the recommended standalone vaccines.
- If a pentavalent vaccine (DTaP-IPV/Hib) is not available for any dose of the infant/toddler series,
 - a hexavalent vaccine could be used according to indication (even if there is no recommendation to routinely vaccinate against HepB) as the priority remains the protection against Hib and pertussis in infants, or
 - a tetravalent vaccine (DTaP-IPV), co-administered with a Hib standalone vaccine, could be an alternative solution, or
 - a trivalent vaccine (DTaP), co-administered with the recommended standalone vaccines, could be an alternative solution
- For the school-entry booster, if a tetravalent vaccine (DTaP-IPV) product is not available,
 - Tdap-IPV vaccine (or Tdap and IPV vaccines co-administered) can be an alternative [18,19].
 - In countries where this option is not possible (lack of available Tdap-IPV or Tdap vaccines), another alternative could be the administration of a Td-IPV vaccine or the co-administration of Td and IPV vaccines. In this case, however, no vaccination against pertussis would be offered.
 - For programmatic issues, delaying the administration of the booster dose until stock of pertussis-containing vaccine combination is brought back to normal levels should be considered as alternative option.
- In countries where vaccination during pregnancy is recommended, and if a Tdap vaccine is in short supply, it is suggested that doses for maternal immunisation should be preserved over adolescent or pre-school booster doses, as maternal immunisation directly benefit newborns. Similarly, pre-school and adolescent booster doses should be prioritised over adult booster doses.
This can be schematically summarised as follows in terms of the order of preference, should severe shortage occur at country level and prioritisation may be needed. The symbol '>' suggests that a preceding population group is a preferred target and vaccination policy, whenever applicable:
Maternal > Pre-school booster > Adolescent booster > Adult booster
- In countries where **vaccination in pregnancy is not recommended**, and with the aim of sparing doses of vaccines used for adolescent or adult boosters, vaccination during pregnancy could be considered as an alternative to adolescent or adult vaccination [15].

Potential impact of shortages on national immunisation policies

Shortages in acellular pertussis-containing combination vaccines require careful consideration if changes are to be made to national immunisation policies, as this will have both an operational and a technical impact:

Operational impact

- Need to communicate in a proper manner with public and healthcare professionals with regard to vaccine shortage and adaptation of vaccination schedules as well as to organise dedicated training for vaccine providers.
- Need to improve the documentation of individual vaccinations in order to later provide supplementary immunisation to those children inadequately vaccinated once stock is brought back to normal levels.

Technical impact

- Enhance or implement disease surveillance for selected vaccine-preventable diseases.
- Consider implementing sentinel hospital surveillance of severe pertussis in young children and improve diagnostic capacities.
- Periodically assess the level of protection through regular serosurveys in cohorts of children vaccinated with modified schedules/products.
- Enhance vaccine coverage monitoring of the cohorts vaccinated with a modified schedule.
- Periodically assess the safety profile of the used vaccine products.
- An assessment of the temporary changes in EU/EEA Member States is needed in order to better understand the epidemiological situation in the near future.

Building stockpiles to ensure immunisation programmes are maintained during future shortages

Shortages of vaccines occur worldwide and should be prepared for. The shortages currently seen in the EU/EEA seem more significant than in the past. It is therefore advisable for countries to plan for a stockpile in support of routine programmes to avoid disruptions of ongoing immunisation programmes in case of future shortages.

Obtaining vaccines from non-EU countries

In the current shortage situation, EU/EEA countries have been, to a limited extent, supporting each other by sharing available vaccine doses. This may not be sufficient in the long-term and other possibilities to acquire vaccine doses to secure ongoing immunisation programmes must be sought. Acquiring vaccines from non-EU countries could be considered under an appropriate regulatory scheme.

Conclusions

The vaccine shortage currently affecting some EU/EEA Member States already had direct consequences for the delivery of national vaccination programmes.

The following options may be considered should shortages at national level exceed the vaccine demand, with the understanding that the final options for response lie with the EU/EEA Member States.

As much as possible, the primary immunisation schedule should be preserved in order to ensure the early and adequate protection of newborns. If an alternative commercial vaccine or other vaccine presentations are available, it is suggested that their use should be prioritised, with appropriate monitoring of safety and effectiveness, rather than modifying the vaccination schedule. Preference should also be given to the use of combination vaccines with the highest number of antigens.

Priority should be given in the following order:

- to the infant primary immunisation series (first year of life)
- over the first toddler booster (second year of life) dose
- and, when applicable, to the first toddler booster dose over the school-entry booster.

In countries where vaccination during pregnancy is recommended, and if Tdap vaccine is in short supply, it is suggested that doses should be preserved for maternal immunisation over adolescent or pre-school booster doses, as maternal immunisation directly benefits newborns.

More evidence is needed in the following areas:

- Use of a low-antigen-content pertussis vaccine as pre-school booster instead of a regular-dose vaccine, and vaccination of these cohorts at a later age.
- Benefit and risk of using a penta- or hexavalent vaccine as pre-school booster.
- Maternal immunisation blunting the subsequent responses to some vaccines in the infant immunisation schedule.

References

1. European Centre for Disease Prevention and Control. Vaccine Scheduler [internet]. 2015 [cited 2015 Oct 07]. Available from: <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>.
2. Global Polio Eradication Initiative. Data and monitoring [internet]. 2015 [cited 2015 Oct. 07]. Available from: <http://www.polioeradication.org/Dataandmonitoring.aspx>.
3. European Centre for Disease Prevention and Control. Outbreak of vaccine-derived poliovirus type 1 (cVDPV1) in Ukraine, August 2015 [internet]. 2015 [cited 2015 Oct. 5]. Available from: <http://ecdc.europa.eu/en/publications/Publications/Poliomyelitis-Ukraine-rapid-risk-assessment-September-2015.pdf>.
4. European Centre for Disease Prevention and Control. A case of diphtheria in Spain, 15 June 2015 [internet]. 2015 [cited 2015 Oct. 5]. Available from: <http://ecdc.europa.eu/en/publications/Publications/diphtheria-spain-rapid-risk-assessment-june-2015.pdf>.
5. World Health Organisation. Pertussis vaccines: WHO position paper – September 2015. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2015 Aug 28;90(35):433-58.
6. Peltola H. *Haemophilus influenzae* type b disease and vaccination in Europe: lessons learned. The Pediatric infectious disease journal. 1998 Sep;17(9 Suppl):S126-32.
7. European Centre for Disease Prevention and Control. Scientific panel on childhood immunisation schedule: Diphtheria-tetanus-pertussis (DTP) vaccination [internet]. 2009 [cited 2015 oct. 5]. Available from: http://ecdc.europa.eu/en/publications/Publications/0911_GUI_Scientific_Panel_on_Childhood_Immunisation_DTP.pdf.
8. Haut Conseil de la Sante Publique France. Simplification du calendrier vaccinal [internet]. 2012 [cited 2015 Oct. 06]. Available from: <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=321>.
9. Carlsson RM, von Segebaden K, Bergstrom J, Kling AM, Nilsson L. Surveillance of infant pertussis in Sweden 1998-2012; severity of disease in relation to the national vaccination programme. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2015;20(6).
10. Gonfiantini MV, Carloni E, Gesualdo F, Pandolfi E, Agricola E, Rizzuto E, et al. Epidemiology of pertussis in Italy: disease trends over the last century. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2014;19(40):20921.
11. Gustafsson L, Hessel L, Storsaeter J, Olin P. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. Pediatrics. 2006 Sep;118(3):978-84.
12. Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi degli Atti ML, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. Pediatrics. 2001 Nov;108(5):E81.
13. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014 Oct 25;384(9953):1521-8.
14. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. Bmj. 2014;349:g4219.
15. Forsyth K, Plotkin S, Tan T, Wirsing von Konig CH. Strategies to decrease pertussis transmission to infants. Pediatrics. 2015 Jun;135(6):e1475-82.
16. Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, et al. Antibody Responses After Primary Immunization in Infants Born to Women Receiving a Pertussis-containing Vaccine During Pregnancy: Single Arm Observational Study With a Historical Comparator. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015 Sep 15.
17. Cherry JD. The Effect of Tdap Vaccination of Pregnant Women on the Subsequent Antibody Responses of Their Infants. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015 Sep 15.
18. John T, Voysey M, Yu LM, McCarthy N, Baudin M, Richard P, et al. Immunogenicity of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine compared to standard-dose diphtheria, tetanus, acellular pertussis when used as a pre-school booster in UK children: A 5-year follow-up of a randomised controlled study. Vaccine. 2015 Aug 26;33(36):4579-85.
19. Collins CL, Salt P, McCarthy N, Chantler T, Lane L, Hemme F, et al. Immunogenicity and safety of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine as a pre-school booster in UK children. Vaccine. 2004 Oct 22;22(31-32):4262-9.