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Work Package 6 - Task 6.1

Report on previous experiences with vaccine shortages in EU countries (and non-EU consortium member countries), and responses at national and European levels

(Deliverable D.6.1.)

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List of Acronyms

ECDC	European Center for Disease prevention and Control
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
ETAGE	European Technical Advisory Group of Experts on Immunisation
EU-JAV	European Joint Action on Vaccination
GDPR	General Data Protection Regulation
GVAP	Global Vaccine Action Plan
ISS	Istituto Superiore di Sanità (Italian National Institute of Health)
MH	Ministry of Health
MAH	Marketing Authorization Holder
NRA	National Regulatory Authority
PHA	Public Health Authority
SAGE	WHO | Strategic Advisory Group of Experts on Immunisation
SDG	Sustainable Development Goal
VPD	Vaccine Preventable Diseases
WHO	World Health Organization
WP	Work Package

Vaccine Acronyms

BCG	Bacille-Calmette-Guérin (Tuberculosis) vaccine
DT	Diphtheria and tetanus toxoid vaccine (paediatric formulation)
DTaP	Diphtheria and tetanus toxoid and acellular pertussis vaccine (paediatric formulation)
DTP	Diphtheria and tetanus toxoid and whole-cell pertussis vaccine (paediatric formulation)
HepA	Hepatitis A vaccine
HepB	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b vaccine
HPV	Human papillomavirus vaccine
IPV	Inactivated poliovirus vaccine
IIV3	Inactivated trivalent influenza vaccine
IIV4	Inactivated quadrivalent influenza vaccine
JE	Japanese encephalitis vaccine
MenACWY	Meningococcal conjugate vaccine, quadrivalent
MenB	Serogroup B meningococcal vaccine
MenC	Serogroup C meningococcal vaccine
MMR	Measles, mumps & rubella vaccine
MMRV	Measles, mumps, rubella & varicella vaccine
PCV13	Pneumococcal conjugate vaccine (13-valent)
PPSV23	Pneumococcal polysaccharide vaccine (23-valent)
ROTA	Rotavirus vaccine
Td	Tetanus & diphtheria vaccine (adult/adolescent formulation)
Tdap	Tetanus, diphtheria & acellular pertussis vaccine (adult/adolescent formulation)
TT	Tetanus toxoid vaccine
VAR	Varicella vaccine
YF	Yellow fever vaccine

Executive summary

Vaccines save millions of lives globally every year and are universally considered as one of the most successful and cost-effective public health interventions ever introduced. However, national immunisation programmes depend on an adequate supply of vaccines and many countries, globally and in the EU, are facing important challenges in this respect. Vaccines shortages are a serious public health issue as they can lead to missed opportunities for vaccination and a greater risk of occurrence of deadly vaccine-preventable disease.

Vaccine shortages have become more frequent globally and in Europe in recent years. The causes of vaccine shortages are complex, multifaceted, may vary by vaccine and country, and include supply, demand and information factors.

Prevention of vaccine shortages is a top priority globally and in the EU. The importance of vaccine security was highlighted during the 68th World Health Assembly (WHA) in May 2015, during which Member States were urged to "improve and sustain vaccine purchasing and delivery systems in order to promote the uninterrupted and affordable safe supply of all the necessary vaccines". In 2018, the EU Commission in its Council Recommendation on strengthened cooperation and coordination between EU countries, industry and other relevant stakeholders, against vaccine preventable diseases, included a reference to strengthening vaccine supply, procurement and stock management.

Work Package (WP) 6 "Vaccine supply and Preparedness" of the EU Joint Action on Vaccination (JAV), aims to define common basic principles for vaccine demand level of risks and develop a concept for how a data-warehouse for an EU-wide central repository for all consortium members (EU and non-EU) on vaccine supply and demand data can be designed. This report is a review of previous and ongoing vaccine shortages and stockouts in Europe, the main causes leading to the shortages, and actions undertaken (Task 6.1).

A survey was conducted among persons in charge of the national or subnational immunisation programme(s) or of vaccine supply/procurement in EU/EEA and consortium (EU-JAV) Member States (MS), to collect information on vaccine shortages and stockouts in the years 2016-2018 and responses at the national and European level. The survey was conducted from February to May 2019.

Twenty one countries participated in the survey (response rate 75%). Overall, 115 shortage and stockout episodes were reported in the three-year study period, 23 of which caused a disruption in immunization services. The most frequently involved vaccines were DT- and dT-containing combination vaccines, hepatitis B, hepatitis A, and BCG vaccines. The median duration of shortages/stockouts was five months (range <1 month-39 months).

Interruption in supply due to quality issues or to other reasons was the most frequently indicated cause of shortage, particularly for BCG and DT-containing vaccines, but also for HepB (adult), HepA (adult), HepA+HepB. Global shortage also played a major role in various vaccine shortage events, especially for BCG, DT-containing vaccines, hepatitis A, hepatitis B and rabies vaccines.

Most countries reported to procure vaccines at national level by the public sector. The preferred purchase mechanism is one based on competitive bidding and 13 countries purchase all or at least some vaccines from more than one manufacturer. Fourteen countries report using multiyear contracts for all vaccines. Sixteen countries stated that they keep stockpiles of vaccines. Only little more than half of countries surveyed reported having an immunization supply chain improvement plan and a vaccine supply manager at national level, to oversee the implementation of the plan. Similarly only about half of countries have recommendations or procedures in place to address shortage and stockout events. Most countries stated

that they regularly inform manufacturers about planned changes to immunization programmes and about VPD outbreaks.

Besides vaccines, the survey also identified the occurrence of shortages of biological products such as antitoxins and immunoglobulins. Overall, 25 shortages/stockouts were reported by 17 countries. The most frequently reported event was shortage/stockout of diphtheria antitoxin, reported by 12 countries.

In addition to the survey, the perspectives of two main stakeholders' (Vaccines Europe and the European Medicines Agency) were also collected.

In conclusion, results of the survey enable us to better describe vaccine shortages and stockouts in Europe, their impact and main causes. In addition, the survey results provide some insights into the procurement and tendering mechanisms used in EU-JAV countries and other EU/EEA countries. This information, together with information collected from the literature, and stakeholders' views, bring us to make the following general considerations and recommendations:

- More research is needed on the causes of vaccine shortages (including analysis of the economic and market–related causes) and on how the different causes interplay with each other.
- There is a need for all countries to have an immunization supply chain improvement plan, defining strategies to assure a stable and adequate vaccine supply for the immunisation programme in order to prevent shortages, and a vaccine supply manager at national level.
- Improved communication between public health authorities, manufacturers and regulatory agencies is needed. Mechanisms for an early and continuous dialogue between manufacturers and health authorities should be established to better anticipate the evolution of vaccine recommendations and more accurately forecast vaccine demand. Timely communication of shortages from MAHs to regulatory agencies and to public health authorities is needed. In case of vaccine shortages, communication by competent authorities to the public should not trigger undue concerns regarding the quality of vaccines.
- Procurement and tender mechanisms should be improved and take into consideration, among others, multisource suppliers, other factors besides price, and the length of contract.
- An EU platform for exchanging information on vaccine shortages and actions taken across countires would be helpful.
- In case of vaccine shortages, all countries should have procedures or recommendation in place regarding the use of alternative vaccines or vaccination schedules during the shortages. Such procedures could be developed in collaboration with National Immunisation Technical Advisory Groups (NITAGs).
- Coordinated actions are needed from all stakeholders to prevent and mitigate vaccine shortages.
- Shortages of biological products (the most concerning of which is diphtheria antitoxin, currently reported to be unavailable in several countries) deserve the same consideration as vaccine shortages.

Introduction

Vaccines save millions of lives globally every year and are universally considered as one of the most successful and cost-effective public health interventions ever introduced. However, national immunisation programmes depend on an adequate supply of vaccines and many countries, globally and in the EU, are facing important challenges in this respect (1). Vaccines shortages are a serious public health issue as they can lead to missed opportunities for vaccination and a greater risk of occurrence of deadly vaccine-preventable disease.

Vaccine shortages, and more generally shortages of medicines, have been a global issue for some time and have become more frequent globally and in Europe in recent years (2,3). A 2015 analysis of vaccine stockout indicators collected from the WHO-UNICEF Joint Reporting Form (JRF) and UNICEF's Vaccine Forecasting Tool, in the years from 2011 to 2015, reported that on average, one in every three WHO Member States experienced at least one stockout every year, of at least one vaccine for at least one month (1). One quarter of stockouts occurred in high-income countries. The vaccines most affected were Diphtheria-Tetanus-Pertussis (DTP) containing vaccines (often combined with hepatitis B and *Haemophilus influenzae* tybe b components), and Bacille Calmette-Guérin (BCG) vaccine, which respectively accounted for 43% and 31% of stockout events reported.

The most recent data from the European Region indicates that in 2017, 20 of 53 Member States reported 49 stockouts either at national or subnational levels, with a duration ranging from 1 to 12 months (4). The vaccines most commonly affected were DTP containing combinations and hepatitis B vaccines. Evidence also indicates that vaccine stockouts contributed to low or declining coverage rates in some Member States.

In response to stockouts, the WHO responded with advice to Member States to optimize current stocks, review and expand vaccine supply options, increase the country purchasing power, and adopt supply risk mitigation strategies (5).

The causes of vaccine shortages are complex, multifaceted and may vary by vaccine and country. Basically they occur when there is an imbalance in demand and supply. According to the Strategic Advisory Group of Experts on Immunisations, supply factors include production issues (such as batch failures and the high risks linked to vaccines, the complex and long vaccine production processes and quality requirements, and the tight production planning required), and the current limited supplier base for vaccines (which in turn is related, among others, to barriers to enter the market, business decisions based on product and market attractiveness, market strategies, mergers and acquisitions). Demand factors on the other hand relate principally to demand flexibility and predictability. Demand flexibility may be limited by complex and unharmonised registration procedures, limited interchangeability between products, and single-source procurement, while demand predictability may be affected by vaccine hesitancy, weak procurement systems with inadequate demand forecasting, and unexpected outbreaks. In addition to the above interrelated factors, information factors, related to supply and demand information and to timely communication between Agencies of Medicine, Public Health Authorities (PHAs) and industry, also play a role (6).

In response to the shortages, some EU/EEA countries have had to modify their vaccination programmes. For example, since 2015, nine EU Member States have had to adjust their immunisation policies to mitigate as much as possible the ongoing shortages of acellular pertussis vaccines (SAGE). Also recommendations have been issued by national public health authorities and by international organizations such as ECDC. For example, in 2017 temporary recommendations were issued in the UK in light of global shortages of hepatitis B vaccine, and ECDC developed recommendations in response to shortages of acellular pertussis and hepatitis A vaccines (7–9).

In general, responses to vaccine shortages have been short-term reactive responses such as the above. However, longer term activities targeting supply, demand and information factors are needed, together with a complete and centralised view of EU supply and demand for all vaccines and all Member States. The European Medicines Agency (EMA) publishes online information on medicine shortages (including vaccines) that affect or are likely to affect more than one EU Member State and that EMA has assessed, and provides a list of national registers in the EU/EEA Member States containing information on medicine shortages in these individual countries. However, since most shortages are dealt with at national level, the catalogue is not comprehensive (10).

Prevention of vaccine shortages is a top priority globally and in the EU. The importance of vaccine security defined as the "sustained, uninterrupted supply of affordable vaccines of assured quality" was highlighted during the 68th World Health Assembly (WHA) in May 2015, during which Member States were urged to "improve and sustain vaccine purchasing and delivery systems in order to promote the uninterrupted and affordable safe supply of all the necessary vaccines" (6).

The need to ensure a continuous uninterrupted availability of vaccines was also underlined at the 70th World Health Assembly of 2017 and the subsequent 2018 WHO report "Addressing the global shortage of, and access to, medicines and vaccines. Report by the Director General" (11).

In 2018, the EU Commission issued a Council Recommendation on strengthened cooperation and coordination between EU countries, industry and other relevant stakeholders, against Vaccine Preventable Diseases. The recommendation included, among others, a reference to strengthening vaccine supply, procurement and stock management (12).

In this context, the European Joint Action for Vaccines (EU-JAV, https://eu-jav.com) is a valuable opportunity to map the phenomenon across EU/EEA countries. The EU-JAV is a consortium of 20 European partners (18 EU/EEA member States and 2 non EU countries: Bosnia-Herzegovina and Serbia), coordinated by the National Institute of Health and Medical Research (Inserm, France) with the support of the French Ministry of Health and Solidarities, which aims to strengthen cooperation between European countries against vaccine-preventable diseases.

Work Package (WP) 6 "Vaccine supply and Preparedness" aims to define common basic principles for vaccine demand level of risks and develop a concept for how a data-warehouse for an EU-wide central repository for all consortium members (EU and non-EU) on vaccine supply and demand data can be designed. Task 6.1 of the WP follows the following objectives:

- Review previous experience about vaccine shortages and responses of EU countries (and non-EU consortium member countries);
- Develop guidelines on procedures to estimate vaccine needs and procurement in EU-MS in the short and long-term;
- Analyze and evaluate local financing mechanisms for purchase and stock of vaccines.

The present report is the deliverable for the first of the above objectives and describes recent and current shortages and stock-outs of vaccines and of other biological products in EU-JAV and other EU/EEA countries and how these were managed.

Materials and Methods

A survey was conducted among persons in charge of the national or subnational immunisation programme(s) or of vaccine supply/procurement in EU/EEA and consortium (EU-JAV) Member States (MS), to collect information on vaccine shortages and stockouts in the years 2016-2018 and responses at the national and European level.

Twenty-eight countries were invited to participate, including all 20 EU-JAV partners and eight EU/EEA countries not participating in the EU-JAV. EU-JAV countries include 18 EU/EEA and two non EU/EEA countries (Bosnia-Herzegovina and Serbia).

Regarding the 20 EU-JAV countries, we contacted by email participants of the WP6 workshop held at the EU-JAV Kick-off meeting (KOM) in Paris in September 2018. For countries who were not present at the KOM, we contacted the main contact persons retrieved from the general address list of EU-JAV partners. For the remaining EU countries, we contacted the nominated representatives of the Member States Committee for these countries and asked them to provide us with the contact details of the most relevant organisation or person whom we should contact to complete the survey. We asked for a single completed questionnaire for each country. Finally, we included a link to the survey and attached an information sheet to inform participants of the objectives of the survey and the way any personal data (contact details) would be handled.

The survey was launched on 27 February 2019 and participants were asked to complete the survey by 18 March 2019. The questionnaire was administered via the online tool, Surveymonkey® (https://www.surveymonkey.com/). Reminders were sent to countries who had not responded by the deadline and the last questionnaire was completed in May 2019. Participants could review and change their answers until closure of the survey in May.

For the purposes of the study, we used the draft definitions of shortages and stockouts discussed at an expert meeting convened by the World Health Organization (WHO) in 2016 (13). A “shortage” refers to a situation where the supply of vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition describes the situation in which demand exceeds supply at any point in the supply chain. A shortage may ultimately create a “stockout” at the point of service delivery to the patient, if the cause of the shortage cannot be resolved in a timely manner. A stockout refers to the complete absence of the vaccine at the point of service delivery to the patient.

Questionnaire

Following a review of the literature, a draft questionnaire was developed, made up of multiple-choice and open-ended questions, and pilot-tested for clarity and completeness by four EU-JAV consortium partners (Finland, Italy, Netherlands and Spain), between 24 January and 8 February 2019. Relevant comments and suggestions were integrated into the final version. The final questionnaire was divided into six sections:

1) General information (contact details). Questions 1-2.

2) Shortages and stock outs, current and in the last three years (Questions 3-4). This section collected information on recent shortages and stock outs of vaccines at the national and sub-national levels. Firstly, participants were asked if they had experienced any vaccine shortages/stockouts in their country in the last three years (from 2016 to 2018). In case of a positive answer, they were then asked to complete a Table to indicate which vaccines were affected by shortages/stockouts, at what administrative level (national, subnational) the shortages had occurred, the duration of each shortage/stockout event, and if any shortages were ongoing. In the same table, they were also asked to indicate if the shortage had caused a disruption of immunisation services (none, yes partial interruption, yes complete interruption).

3) Details of vaccine shortage/stockout events (12 questions per shortage episode: Questions 5-16 for Shortage N.1, Questions 17-28 for Shortage N.2, Questions 29-40 for Shortage N.3, and so on up to Shortage N.6: Questions 65-76). For each episode, we asked participating countries to provide further details, indicate any consequences of the shortage and any actions taken, by responding to 12 questions for each shortage/stockout episode experienced. In detail, we asked to specify:

- which factors had played a role in the shortage/stockout (more than one response was possible among: higher than expected demand for the vaccine due to an outbreak; higher than expected demand for the vaccine due to changes to vaccine schedule; higher than expected demand for the vaccine due to changes to targeted groups e.g. new targeted groups, widening of age cohorts targeted; higher than expected demand for the vaccine due to inaccurate forecasts; higher than expected demand due to safety concerns regarding other available products; interruption in production/supply due to quality issues; global shortage; poor stock management; lack of resources to purchase the vaccine; other, please specify)
- actions taken to address the shortage/stockout (more than one response was possible among: used available stockpiles of the vaccine; redistributed stockpile of the vaccine among regions or facilities; purchased additional doses of the vaccine from other supplier/manufacturer; imported vaccine not originally authorized in the EU; asked European institutions e.g. ECDC or other international organizations e.g. WHO for technical assistance; other please specify.)
- difficulties met in purchasing additional doses of vaccines from other suppliers, if applicable
- regulatory obstacles encountered in attempting to import doses of vaccine from other Member States, if applicable
- regulatory and other obstacles encountered in attempting to import vaccines not authorized in the EU, if applicable
- details on changes to the national immunisation programme caused by the shortage/stockout, i.e whether these changes involved the primary, booster, adolescent, adult or travel immunisation programmes, and details on the adjustments made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, changes in the timing of doses, boosting intervals, or age of dose administration, temporary suspension of the immunisation programme, prioritization of specific groups to whom to offer the vaccine)

4) Vaccine supply, procurement, purchase and stockpiling (Questions 77-101). In this section we collected information on vaccine procurement and purchase mechanisms used in each country, and on the existence of vaccine stockpiles. We also collected participants' opinions on a European centralized procurement system for vaccines, on a centralized stockpile, and on the creation of a data warehouse for EU-wide sharing of vaccine supply and demand data among dedicated stakeholders.

In detail, questions regarding vaccine procurement and purchase explored:

- the level at which vaccine procurement is carried out (competitive bidding, request for quotation, single-source procurement, or other, please specify)
- the existence of laws governing vaccine purchase systems
- needs estimation procedures used (including time period and level of estimation)
- whether vaccines are purchased from a single or multiple manufacturers
- whether it is possible to sign multi-year (>2 years) contracts with vaccine manufacturers
- any joint procurement mechanisms in place

- existence of an immunisation supply plan (i.e. a plan defining strategies to assure a stable and adequate vaccine supply for the immunisation programme and for public health preparedness, in order to avoid shortages)
- whether any vaccines are produced domestically (by a public health institution)
- existence of any procedures or recommendations to address shortages/stockouts (e.g. reporting procedures, recommendations regarding the use of alternative vaccines or vaccination schedules)
- whether at the procurement level, there is a dedicated vaccine supply chain manager.

Regarding stockpiles, we asked whether stockpiles of vaccines were available, at national or subnational levels, and, if so, for which vaccines, at what administrative level and for how many months of supply of the vaccine.

5) Communication (Questions 102-106)

In this section we collected information on:

- whether public health authorities communicate with vaccine manufacturers regarding planned changes of targeted groups, planned changes of vaccination schedule, planned introduction of new compulsory/recommended vaccines, and regarding occurrence of disease outbreaks (all of which could lead to increased demand for vaccines).
- whether legislation exists requiring that above expected changes to immunisation programme be communicated to manufacturers in advance
- who public health authorities inform in case of vaccine shortages/stockouts (European authorities, national authorities if regional or local procurement).

6) Shortages/stockouts of other biological products (Questions 107-113)
In this section we inquired about recent shortages and stock outs of other biological products besides vaccines, such as disease-specific immunoglobulins (IG) or serum antitoxins, at national and sub-national levels. Countries who had recently experienced such shortages were asked to briefly describe the main causes and issues involved and how these issues had been resolved. We also asked about current availability of the following products:

- Hepatitis B IG
- Varicella-zoster IG
- Rabies IG
- Tetanus IG
- Human normal IG
- Diphtheria antitoxin
- Botulinum antitoxin

As part of the validating process, once we received the completed questionnaires, a summary of results was sent to participants of each country to offer them the opportunity to check and validate the survey analysis and report back with comments or corrections.

Data collected data from each questionnaire/survey was analysed using MS Excel software. Variables were reported as absolute number and proportions. Results from open-ended questions were summarized.

Ethics

All persons who agreed to complete the survey were sent a privacy statement (according to GDPR 2018) and asked to provide permission to be contacted.

Results

Response rate and survey participants.

Between February and May 2019, 21 of 28 invited countries completed the survey (response rate 75%). Nineteen of 21 participating countries belong to the EU/EEA. Eighteen of 20 EU-JAV consortium countries (90%) participated (all except Belgium and Slovakia).

Table 1 lists the participating countries and institutions in each country. One country (Latvia) provided two responses from two different institutions (Latvian Centre for Disease Control and Latvian Agency of Medicine) which are in charge of vaccine procurement and supply. In this case, respondents were contacted and a joint answer was agreed upon.

Table 1. List of participating countries and affiliations of respondents by country. Survey on vaccine shortages and stockouts, EU-JAV and other EU/EEA countries, 2019.

Country	Affiliation of survey respondents
Bosnia HG*	Public Health Institute of Federation of Bosnia and Herzegovina (PHI)
Bulgaria*	Bulgarian Ministry of Health
Croatia*	Croatian Institute of Public Health (CIPH)
Denmark*	Statens Serum Institute (SSI)
Estonia	Estonian Health Insurance Fund
Finland*	National Institute for Health and Welfare (THL)
France*	Agence Nationale de sécurité du médicament et des produits de santé (ANSM)
Greece*	Hellenic Center for Disease Control and Prevention (HCDCP)
Hungary	National Public Health Centre
Ireland	HSE National Immunisation Office
Italy*	Ministry of Health
Latvia*	Centre for Disease prevention and Control of Latvia (CDPC) Agency of Medicines
Lithuania*	Ministry of Health
Malta*	Central Procurement Supplies Unit (CPSU)
Norway*	Norwegian Institute of Public Health (NIPH)
Romania*	Ministry of Health
Serbia*	Institute of Public Health of Serbia (IANPHI)
Slovenia*	National Institute of Public Health (NIJZ)
Spain*	Ministry of Health
Sweden*	Public Health Agency of Sweden
The Netherlands*	National Institute for Public Health and the Environment - Department for Vaccine Supply and prevention programmes (RIVM-DVP)

**countries participating in EU-JAV*

Shortages and stockouts: current and between 2016-2018

Nineteen of 21 participating countries reported at least one shortage/stockout events (all except Bulgaria and Estonia). Overall, 115 events were reported. Twenty-three of 67 shortages (34%) for which the information was given, were reported to have caused a disruption in immunization services.

Figure 1. Number of vaccines shortages and stockouts in EU JAV and other EU/EEA countries, 2016-2019.

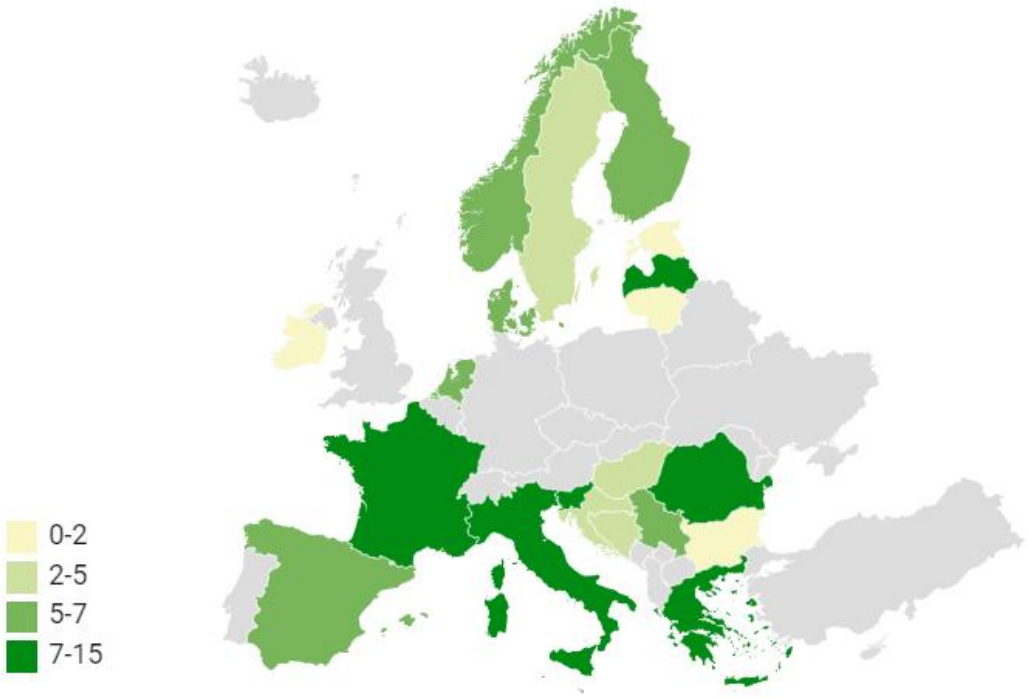

Figure 1 and Table 2 show the number and type of vaccine shortages and stockouts by country, from 2016-2019. The median number of shortage/stockout events reported by each country was 5, with a range from 0 (in Estonia and Bulgaria) to 15 (Italy). Five of 21 countries (Bosnia HG, Hungary, Sweden, Ireland and Lithuania) are in the lower 25th percentile with two shortage events or less reported for the specified observation period.

Six countries (France, Greece, Italy, Latvia, Romania and Slovenia) are in the upper 25% percentile, with each country reporting seven or more episodes of shortages/stockouts during the study period, and together accounting for over half of the total number of shortages (66/115; 57.4%) (Figure 1).

The majority of reported shortage/stockout events were shortages (67.0%; n=77/115), while the remaining 33.0% (n= 38/115) involved a stockout. In 32 of 38 stockouts, the stockout was preceded by a shortage.

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Table 2. Vaccine shortages and stockouts, EU-JAV and other EU/EEA countries, January 2016- February 2019

Country	N. of shortages	BCG	Cholera	DTaP	DT-IPV	DTaP-IPV	DTaP-IPV-Hib	DTaP-IPV-Hib-HepB	HepA (adults)	HepA (children)	HepB (adults)	HepB (children)	HepA+HepB	Hib	HPV	Influenza 3V	Influenza 4V	Men ACWY	Men B	Men C	MMR	MMRV	PVC 10	PPSV 23	Rabies	Rotavirus	TBE	Td	Tdap	Varicella	Yellow fever	Others*
Italy	15	x	x			x	x	x	x		x		x	x							x	x			x			x	x	x		
Greece	14	x				x	x	x	x	x	x	x			x			x			x	x		x				x			x	
France	12	x		x					x	x	x	x								x				x	x		x		x			
Latvia	10	x			x						x	x	x				x				x		x				x	x				
Slovenia	8								x	x	x				x									x		x		x				x
Romania	7			x		x		x			x	x									x				x							
Denmark	6								x	x	x		x			x									x							
Malta	6	x						x			x	x												x	x							
Spain	6	x							x		x														x			x	x			
Norway	5	x							x										x					x				x				
Serbia	5											x						x			x			x							x	
Netherlands	5	x			x	x					x														x							
Finland	5	x				x					x				x													x				
Croatia	3							x																				x	x			
Bosnia HG	2	x				x																										
Hungary	2						x				x																					
Sweden**	2															x	x															
Ireland	1	x																														
Lithuania	1														x																	
Bulgaria	0																															
Estonia	0																															
Total	**115**	**11**	**1**	**2**	**2**	**6**	**3**	**5**	**7**	**4**	**12**	**6**	**3**	**1**	**4**	**2**	**2**	**2**	**1**	**1**	**5**	**2**	**1**	**6**	**7**	**1**	**2**	**8**	**4**	**1**	**2**	**1**

**Tetanus monovalent*

*** A respondent from Sweden indicated that shortages of HepA, PPSV23 and Td had also occurred at subnational level but did not report these in the survey because details of the shortages were not available.*

As shown in Table 2, the most frequently reported shortages/stockouts were those involving DT- and Td-containing vaccines. These were reported by 14 countries and together accounted for 26.1% of events (n=30). These were followed by shortages/stockouts of Hepatitis B (n=18, 15.7% of shortages; 13 countries), Hepatitis A (n=11; 9.6%; 7 countries) and BCG vaccines (n=11, 9.6%: 11 countries). Rabies, PPSV23, MMR and HPV vaccines together accounted for most of the remaining shortages. Further details on vaccines involved in shortages/stockouts are shown in Table 2.

Figure 2. Vaccine shortage/stockout events by year of onset, EU-JAV and other EU/EEA countries, January 2016-February 2019

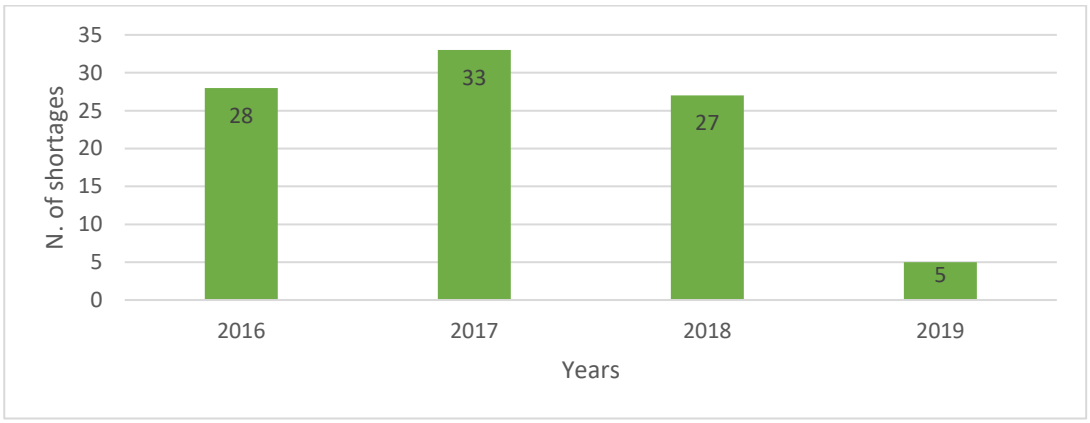
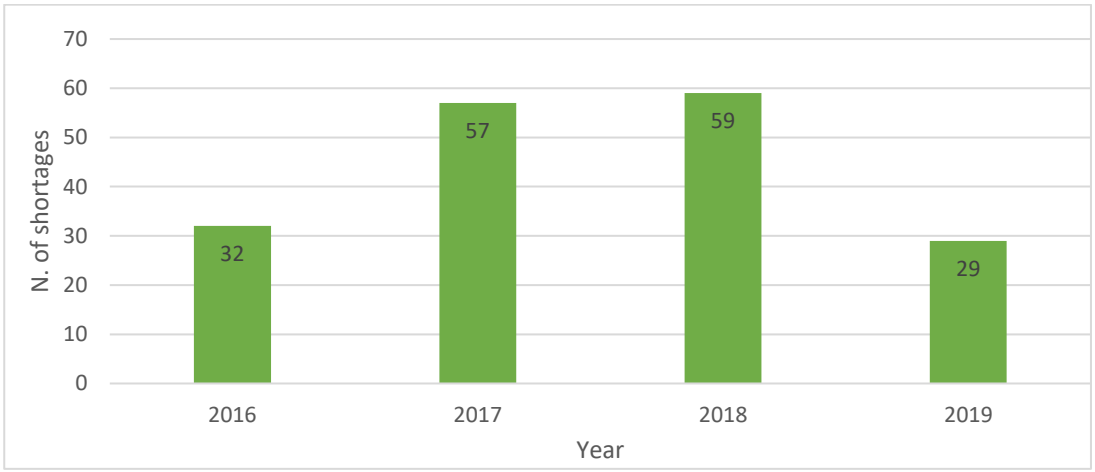


Figure 3. N. of ongoing vaccine shortage/stockout events, by year, EU-JAV and other EU/EEA countries, 2016-February 2019.



Administrative level at which shortage/stockout events occurred.

Participants were asked to indicate the administrative level at which each event had occurred. In 101 of 113 shortages (89.4%) for which the information was available), the shortage occurred at the national level and in 12 shortages (10.6%) the event occurred at subnational level (Table 3).

Table 3. Number of vaccine shortages and stockouts in EU-JAV and other EU/EEA countries, by vaccine and administrative level at which shortage occurred, January 2016-February 2019

Vaccines	N. shortage/stockout events				
	Administrative level			Total n. shortages (%)	N. countries
	National	Subnational	Unknown		
BCG	11			11 (9.6%)	11
Cholera	1			1 (0.9%)	1
DT- and Td-containing vaccines (DTaP, DTaP-IPV, DTaP-IPV/Hib, DTaP-IPV-Hib-HepB, DT-IPV, Tdap-IPV, Td-IPV, Tdap, td)	26	2	2	30 (26.1%)	14
Haemophilus influenzae type b (Hib)	1			1 (0.9%)	1
HEPA+HEPB	2	1		3 (2.6%)	3
Hepatitis A (HEPA) (adults & children)	11			11 (9.6%)	7
Hepatitis B (HEPB) (adults & children)	18			18 (15.7%)	13
Human papilloma virus (HPV)	4			4 (3.5%)	4
Influenza tri-/quadri-valent (IIV3/4)	2	2		4 (3.5%)	3
Measles-Mumps-Rubella (MMR)	3	2		5 (4.3%)	5
Measles-Mumps-Rubella-Varicella (MMRV)	1	1		2 (1.7%)	2
Meningococcal (ACWY, b, c)	3	1		4 (3.5%)	4
Pneumococcal (23-/10-valent)	7			7 (6.1%)	7
Rabies	6	1		7 (6.1%)	7
Rotavirus (Rota)	1			1 (0.9%)	1
Tick-borne encephalitis (TBE)	2			2 (1.7%)	2
Varicella		1		1 (0.9%)	1
Yellow fever (YF)	1	1		2 (1.7%)	2
Other *	1			1 (0.9%)	1
Total	**101**	**12**	**2**	**115**	**21**

*Tetanus monovalent

Duration of shortages.

Duration of shortages was reported for 93 out of 115 episodes (80.9%). The median duration was 5 months (IQ75: 2-20), ranging from less than one month (various vaccines) to 39 months (BCG vaccine in one country, DT-/Td-containing vaccines in two countries).

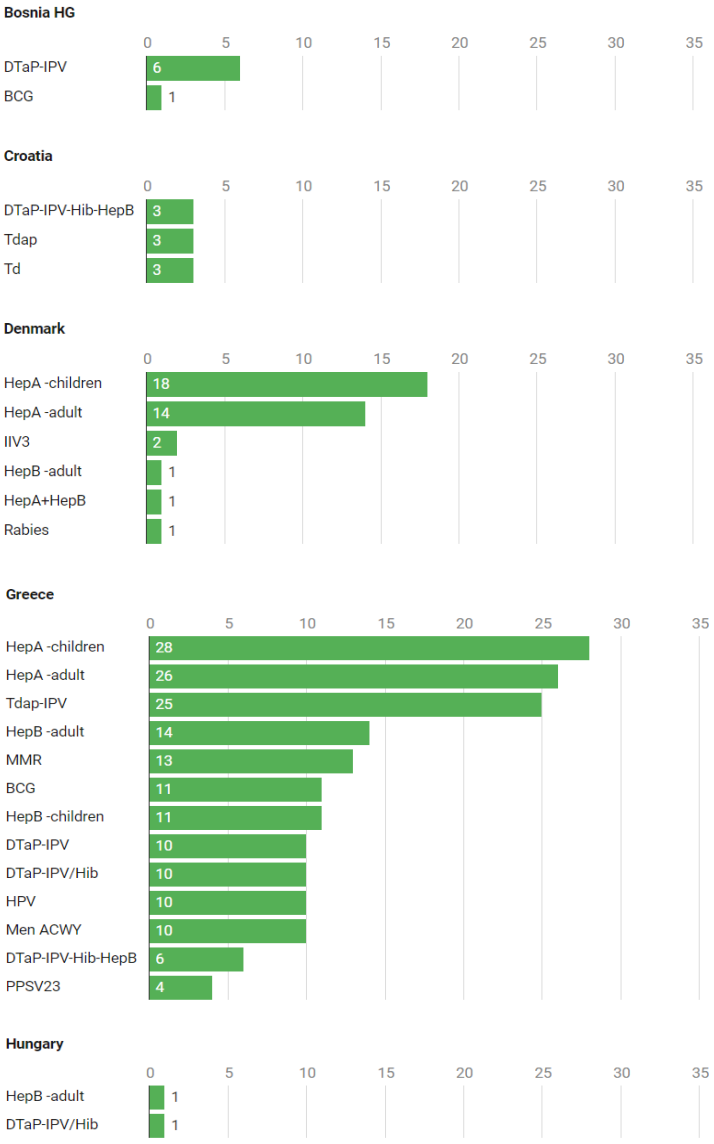
At the time of survey completion, there were ongoing shortages in the following six countries:

- France (Hep B paediatric formulation, Men C, PPSV23, YF)
- Greece (Hep A adults and Men ACWY)
- Italy (DT, Td and Tdap-containing vaccines, Hib, Hep B adults, Hep A adults, MMR, MMRV, varicella, Hep A-Hep B, rabies, cholera)
- Norway (Td)
- the Netherlands (Hepatitis B adults, Rabies)
- Spain (Rabies).

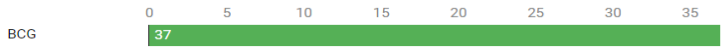
Overall, 18 shortage/stockout episodes (19.4%) lasted more than two years. The latter involved BCG vaccine and DT-containing vaccines. Figure 4 shows duration of vaccine shortages or stockouts by vaccine and country.

Figure 4. Duration (months) of vaccine shortages/stockouts, by vaccine and country, EU-JAV and other EU/EEA countries, 2016-2019.

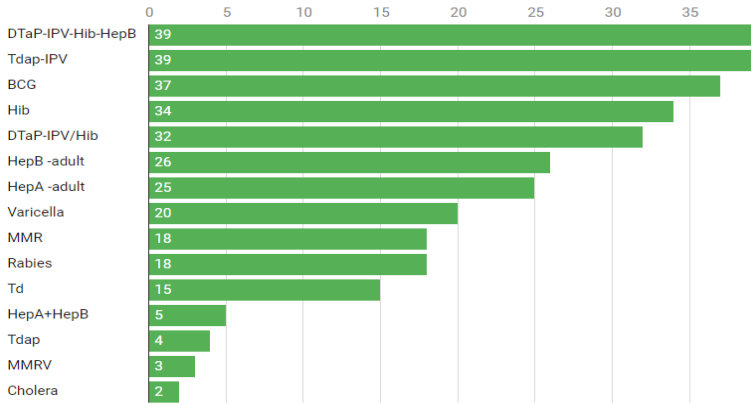
Note: In the graphs shown below, shortages are from at least one supplier and do not necessarily reflect availability of the vaccine in the country.



Ireland

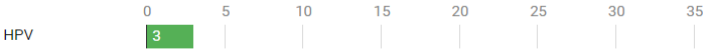


Italy

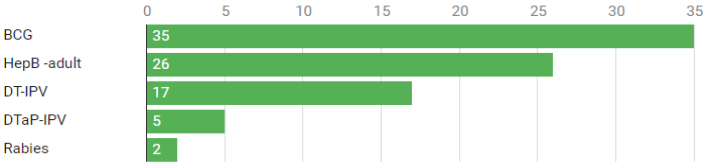


Latvia

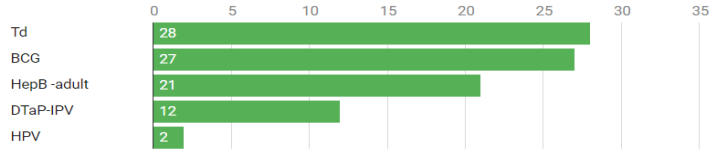
Lithuania



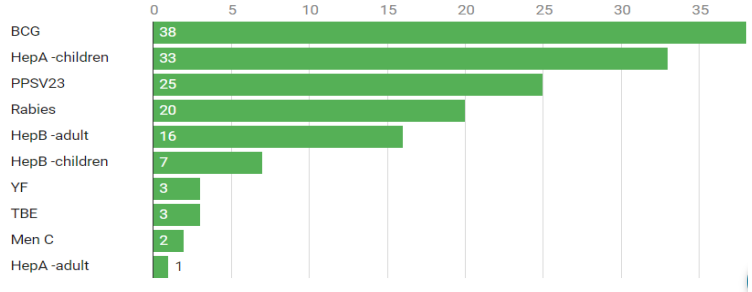
Netherlands

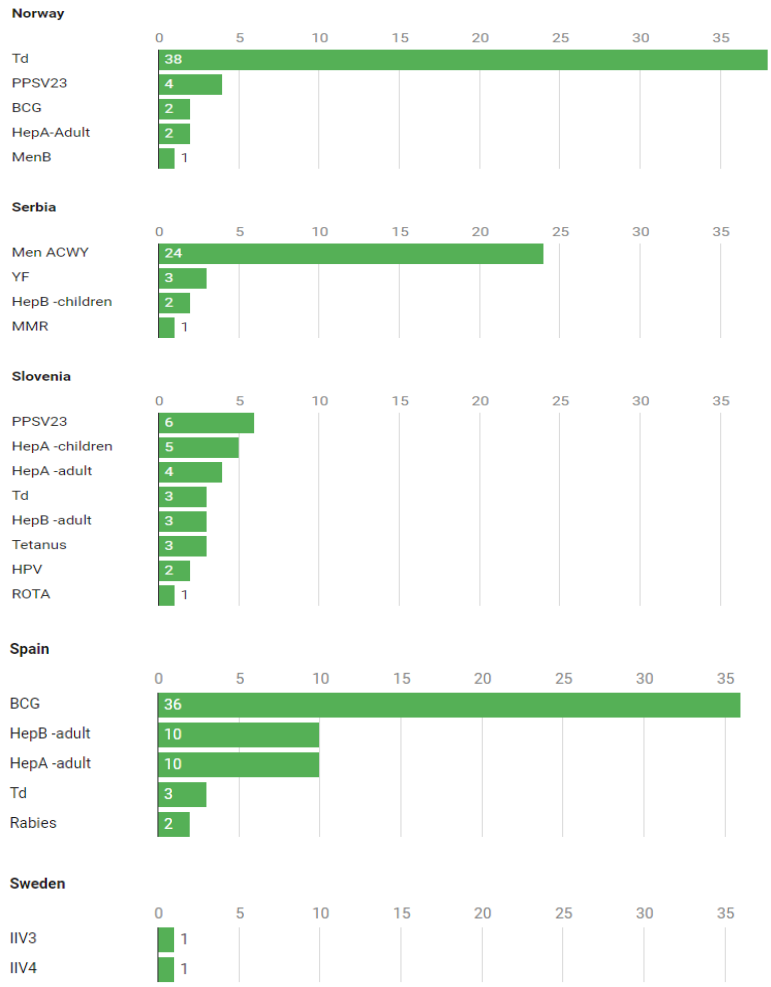


Finland



France





Changes made to national immunisation programme as a consequence of the shortage

In 28 of 91 shortage/stockout events for which the information was provided (30.8%), the shortage led to some change to the country's national immunisation programme (Table 4).

In 11 cases, shortages of Td, MenACWY, PPSV23, HepB (adult), HepA (adult), IIV3, IIV4 and YF vaccines made it necessary to introduce temporary changes to the adult immunisation programme or to prioritise risk groups. In seven cases, the primary immunisation programme for DT-containing vaccines, BCG, MMR and HepB paediatric vaccines was affected, in four cases temporary changes were made to the booster immunisation programme. In four cases travel immunisations (Td, Tdap and Rabies vaccines) were affected and in another three cases adolescent immunisation programme was involved by the changes. Finally, shortage of BCG in on country led to changes to the HCWs immunisation programme.

Table 4. Impact of shortages and stockouts on immunisation programme in EU-JAV and other EU/EEA countries 2016-2019

"Did the shortage/stockout cause any changes to the national immunisation programme?"*

Response	N. shortages	%
Yes	28	30.8
No	63	69.2
Total	***91***	***100.0***

*No response for 24 shortages

Details regarding the adjustments made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritisation of specific groups to whom to offer the vaccine) were mentioned only for three cases in which prioritization of risk groups was reported.

Reported causes of shortages

For each shortage event, participants were asked to indicate which factors played a role in the shortage. Figure 5 and Figure 5 show the factors which played a role in the reported shortages/stockouts, by frequency and vaccine.

The most frequently reported causes of shortages/stockouts were interruption in production and/or supply due to quality issues or to other reasons (n=39; 33.9%), followed by global shortage (n=35; 30.4%). Higher than expected demand due to changes to vaccine schedule, targeted groups or inaccurate forecasts accounted for 7.0 % of shortages. Higher than expected demands due to safety concerns regarding other available products was not reported for any of the shortages (Figure 5).

Figure 5. Factors that played a role in vaccine shortages in EU-JAV and other EU/EEA countries, 2016-2019 (N=115).

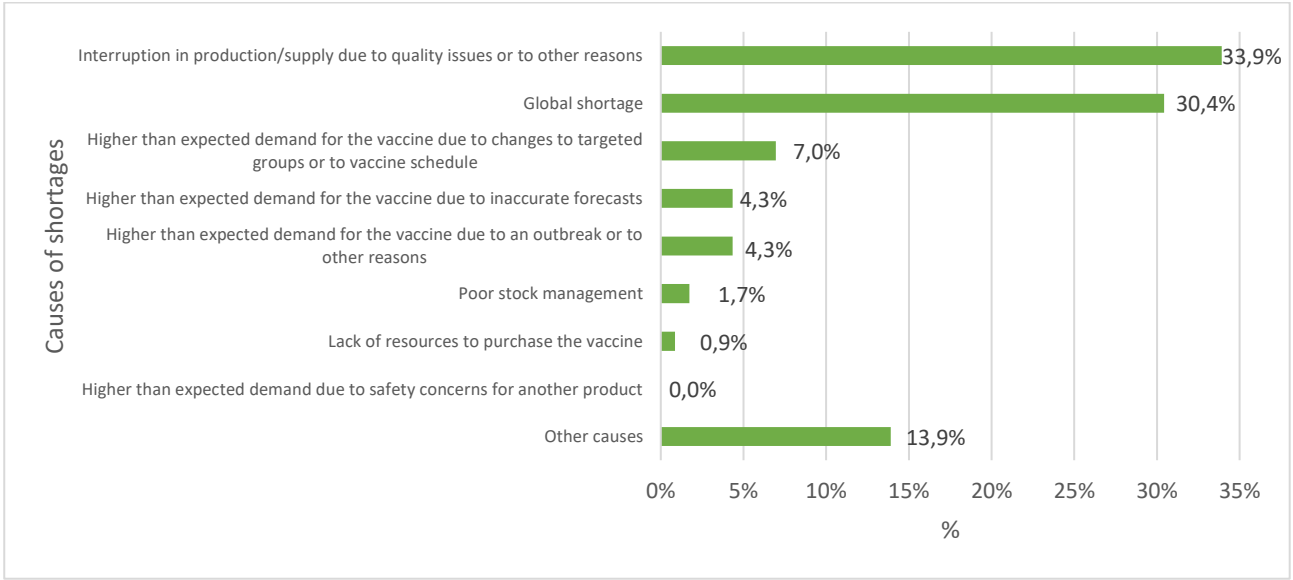


Table 5. Main factors playing a role in vaccine shortages/stockouts in EU-JAV and other EU/EEA countries, by vaccine, 2016-2019 (N=110)

VACCINE	CAUSE OF SHORTAGE/STOCKOUT	N. SHORTAGE/STOCKOUT EVENTS
BCG	Interruption in production/supply due to quality issues	6
	Global shortage	3
	Interruption in production/supply due to unspecified reason	3
	Higher than expected demand for the vaccine due to changes to targeted groups	1
DT-containing vaccine	Global shortage	9
	Interruption in production/supply due to quality issues	8
	Interruption in production/supply due to unspecified reason	6
	Delayed delivery of vaccine	3
	Higher than expected demand for the vaccine due to changes to vaccine schedule	3
	Higher than expected demand for the vaccine due to changes to targeted groups	2
	Procurement delays, legislation and procedures	2
	Lack of interest in the production of bivalent vaccine	1
HepA	Global shortage	6
	Interruption in production/supply due to quality issues	3
	Interruption in production/supply due to unspecified reason	1
	Higher than expected demand for the vaccine due to an outbreak	1
HepB	Global shortage	7
	Interruption in production/supply due to quality issues	3
	Interruption in production/supply due to unspecified reason	1
	Higher than expected demand for the vaccine due to inaccurate forecasts	1
	Delayed delivery of vaccine	1
	Lack of producer Good Manufacturing Practice (GMP)	1
	Unknown	1
HepA+HepB	Interruption in production/supply due to quality issues	2
	Global shortage	1
Pneumococcal	Global shortage	2
	Interruption in production/supply due to unspecified reason	2
	Lack of resources to purchase the vaccine	1
	The only registered supplier for this vaccine did not offer a vaccine on the tender since June of 2017	1
Rabies	Global shortage	3
	Interruption in production/supply due to quality issues	1
	Interruption in production/supply due to unspecified reason	1
	Poor stock management	1
Influenza tri-/quadri-valent	Higher than expected demand for the vaccine due to inaccurate forecasts	3
	Higher than expected demand for the vaccine due to unspecified reason	2
	Global shortage	1
Measles-Mumps-Rubella (MMR)	Higher than expected demand for the vaccine due to changes to targeted groups	1

VACCINE	CAUSE OF SHORTAGE/STOCKOUT	N. SHORTAGE/STOCKOUT EVENTS
	Interruption in production/supply due to unspecified reason	1
	Poor stock management	1
	Global shortage	1
	Higher than expected demand for the vaccine due to unspecified reason	1
Human papilloma virus (HPV)	Delayed delivery of vaccine	1
	Higher than expected demand for the vaccine due to changes to targeted groups	1
	Interruption in production/supply due to quality issues	1
Meningococcal	Global shortage	1
	Higher than expected demand for the vaccine due to inaccurate forecasts	1
Tetanus	Global shortage	1
	Interruption in production/supply due to quality issues	1
Tick-borne encephalitis	Higher than expected demand for the vaccine due to unspecified reason	1
Yellow fever	Only one supplier for this vaccine is present in the country and did not timely respond	1
Rotavirus	Interruption in production/supply due to quality issues	1
Total		**110**

Global shortage was reported by 13 countries and played a role in various vaccine shortage events, especially BCG vaccine, DTaP containing vaccines, hepatitis A and hepatitis B vaccines (especially the adult formulation) and rabies vaccine (

Table 5).

Interruption in production and supply was frequently indicated as a factor leading to shortages of BCG, DT-containing vaccines, and other vaccines (Table 5). Other less frequent factors were those related to an unexpected increase of demand due to changes to groups targeted by the immunisation programme (4.3%; n=5 shortage episodes) or to changes to vaccine schedule (2.6%; n=3 episodes).

Inaccurate forecasts led to insufficient supplies of vaccine doses in 4.3% (n=5) of shortage episodes. Increased demand due to occurrence of an outbreak was reported in only 2.6% (n=3) shortage episodes regarding MMR and HepA vaccine.

Only a very small proportion of reported episodes was caused by poor stock management or lack of resources and no country experienced a shortage as a result of a higher than expected demand due to safety concerns regarding other available products.

The following were “other factors” mentioned:

- delay of vaccine delivery (4.3%, n=5; Td, DTaP-IPV-Hib-HepB, Tdap, HepB paediatric , HPV)
- lack of suppliers (4.3%, n=5). In the latter case, respondents complained that their supply was dependent on only one supplier who either ceased the production (BCG, PPSV23), did not offer a vaccine on the tender (PPSV23), was not interested in the production of the vaccine (Td) or did not timely respond to the tender (YF).
- issues at the procurement level, in terms of delays (DTaP-IPV-Hib, n=1), legislation (DTaP-IPV-Hib, n=1), or by lack of reimbursement (Men ACWY, n=1).

Actions taken to address vaccine shortages/stockouts and issues encountered.

Participants were asked to specify what actions they undertook to address each vaccine shortage/stockout (Table 6)

Table 6. Actions taken to address vaccine shortages, EU-JAV and other EU/EEA countries, 2016-2019

Country	Actions undertaken						
	Purchased additional doses from other supplier/ manufacturer	Used stockpiles	Redistributed stockpile	Imported vaccine from Non-EU	Used different combinations	Asked European or other institutions for technical assistance	Other
BOSNIA HG	X			X			
CROATIA	X	X		X			X
DENMARK	X	X	X				X
FINLAND	X	X		X			X
FRANCE		X	X	X			
GREECE	X			X			X
HUNGARY		X					X
IRELAND		X					
ITALY	X	X		X	X		
LATVIA		X	X	X	X	X	X
LITHUANIA			X				X
NETHERLANDS	X	X		X			
MALTA	X	X					X
NORWAY	X	X					X
ROMANIA		X	X			X	
SERBIA	X		X			X	X
SLOVENIA	X						X
SPAIN	X		X	X		X	X
SWEDEN	X		X				
Total	**13**	**12**	**8**	**9**	**2**	**4**	**12**

Responses were provided for 94 of 115 episodes. The most frequent action undertaken was to purchase additional doses of the vaccine from other supplier/manufacturer (36 shortages in 13 countries), followed by the use of available stockpiles of vaccine (31 shortages in 12 countries).

Stockpile appeared to play a major role also at subnational level: in 20 shortages it was necessary to redistribute stock doses among regions and facilities. Of note, some countries reported that they imported a vaccine not originally authorized in the EU (mainly BCG vaccine but also hepatitis B and DT-containing vaccines. Additionally, one country reported having imported BCG vaccine through Bulgaria from Canada.

Finally, European institutions (e.g. ECDC) or other international organizations (e.g. WHO) were contacted for technical assistance only in five shortages in four countries.

Issues encountered in purchasing vaccine from other suppliers and importing vaccine doses

When asked which issues they found in purchasing vaccine doses from other suppliers/manufacturers, the main problem encountered (in 15 of 36 shortages, 41.7%) was that competitor manufacturers were also

experiencing shortages. Other countries reported that there were either few competitor manufacturers (and these were not able to comply with the request) or no competitors in the EU. One country reported that the competitor set inflexible prices. None of the countries reported as an issue the other two available multiple choices "resources were limited and we could not afford other purchases" and "the original manufacturer was not obliged to participate in the payment of the new purchase". Four countries reported that no issues were encountered with purchasing additional doses of vaccine. For example, Slovenia succeeded in finding another supplier and purchasing further doses of Td vaccines and also succeeded in importing doses of other vaccines such as HepA (adults), Hep A (paediatric) and monovalent Tetanus vaccines.

"Other" problems described regarded the fact that in some cases only a few doses of vaccine were requested (for example in Spain, BCG vaccine) because only specific risk groups needed to be vaccinated, but the only manufacturer of vaccines (not authorized in the EU) only had available multi-dose containers (100 doses/vial, 1,000 doses) of the vaccine. As a consequence, the country did not purchase the vaccine. A similar problem was found also by Norway when they attempted to purchase BCG from an alternative supplier but pack size (200 doses per pack) created some issues.

In one instance, one country managed to procure some more doses from another manufacturer (Denmark, HepB for adults) but the available doses were insufficient to cover the demand. Another issue described is that purchasing from suppliers not using open procurements can be very time consuming due to the legal aspects involved.

Regarding importation from other MS, this was done by 15 countries, for a total of 35 shortages. No issues were reported in the majority of cases, however, for 13 of 35 shortages respondents stated that they encountered some specific problems. The most frequent one (reported in 5 shortages) was that other countries were also experiencing shortages so that they could not provide them with additional doses. Another issue, reported in four shortages in a single country (Malta), was related to "*registration issues due to the need for parallel importation*". One respondent also noted that international regulatory aspects can be a major determinant because "*It is not clear how to pay vaccine purchased from state institution of other Member States. […] wholesalers provide the storage and distribution of vaccines. Therefore the extra tender would be necessary for distribution of additional Td doses purchased from other source, the tender can take time.*" National laws were invoked as a possible barrier to importation. For example, one country highlighted that inflexibility of national legislation makes importation much more difficult. The packaging language as a possible problem to the transfer of doses was cited only by one respondent. However, in that specific case, the country accepted to import vaccine doses packed for other countries in other languages. Lastly, two countries had problems related to importation of BCG vaccine and to quality approval. They reported that they were unable to import BCG from other countries due to the lack of Official Control Authority Batch Release (OCABR) for EU/EEA in accordance with European Directorate for the Quality of Medicines (EDQM) recommendations.

Finally, regarding importation of vaccines not authorised in the EU, several problems were encountered. In one country, the competent authority did not approve other available BCG vaccines so that they could not import it. One country succeeded in importing BCG vaccine from Japan through an agent in Sweden, by requesting a release to the EU market and by acquiring a special permit by the national medicines authority. However, although in this case they achieved the hoped for result, the survey respondent specified that this procedure would probably no longer be allowed.

Stockpiles

Available stockpiles were usedn in 31 shortages in 12 countries. This measure was used mainly in the case of DT-containing vaccine shortages (n=14), but also played a role in shortages of BCG (n=4), rabies (n=3), Hepatitis B (adults) (n=3), Hepatitis A (paediatric) (n=2) and pneumococcal vaccines (n=2). Stockpiles were also used for other three vaccines (HepA+HepB, HPV, TBE).

Finally, nine countries reported a redistribution stockpile of the vaccine among regions or facilities to address 20 vaccine shortages.

Vaccine procurement, purchase mechanisms, stockpiling, needs estimation, domestic production

Procurement

Vaccine procurement differs among the participating countries.

- 13 participants stated that in their countries vaccine procurement occurs exclusively at the national level (public sector)
- 1 participant stated that in their country (Italy) procurement occurs exclusively at subnational level
- In 1 country (Greece) vaccines are procured entirely by the private sector through marketing authorization holders, wholesalers and local pharmacies.
- 6 countries procure vaccines at more than one level. (Table 7). In detail:
  - In one country (Spain) vaccine procurement is carried out at national and subnational levels and through private sector. However, the latter accounts only for an estimated 5% of vaccines.
  - In one country (Sweden) vaccine procurement is carried out at national and subnational levels.
  - Participants in four countries (Slovenia, Netherlands, Estonia, and France) reported that in their country vaccines procurement occurs at both national (by public health authorities) and private sector levels, with the latter accounting for a variable proportion of total vaccines, from 30% (Slovenia) to 5% (Netherlands). One of four countries (Estonia) did not specify the proportion of vaccine doses procured in the private sector but reported that, while all vaccines included in the national immunisation programme are procured centrally (at national level), all other vaccines (e.g. travel vaccinations, most adult vaccinations) are provided in the private sector.

Purchase mechanisms

The most frequently reported purchase mechanism was competitive bidding, used by 19 countries. Among these countries, three reported having more one purchase mechanism, namely single-source procurement (3/3) and request for quotation (2/3).The remaining countries use other mechanisms: one country (Hungary) reported using “request for quotation”, and one country (Greece) responded “Other” also specifying that the mechanism used is ”marketing authorization holders/wholesalers/local pharmacies” i.e. retail-based market.

Supplier base

In eight countries, each vaccine is purchased from a single manufacturer (directly or indirectly through a wholesaler). On the contrary, in five countries, vaccines are always purchased from more than one manufacture. In the eight remaining countries at least some vaccines are purchased from more than one manufacturer.

Of the 13 countries who report purchasing all or some vaccines from more than one manufacturer:

- 4 countries (Denmark, Ireland, Serbia, and Finland) ensure a multiple-supplier base (Denmark only for flu vaccine) by requiring, for purchases made at national level, that a proportion of doses is purchased from each manufacturer participating in the tender.
- 4 countries (Spain, Sweden, Italy, France) purchase vaccines at the subnational level (regions/provinces/districts) and in this way ensure that as many manufactures as possible are engaged in the national vaccine supply.
- 5 countries have other mechanism in place. Of these, four countries use, for all or for some vaccines (e.g. flu and tick-borne encephalitis), framework agreements targeted for two or four providers, while in one country national procurement depends exclusively on private sector.

Multi-year contracts for provision of vaccines

Participants were asked to indicate whether it was possible in their country to sign multi-year (>2 years) contracts with vaccine manufacturers. In 14 of 21 countries multi-year contracts are the norm for all vaccines, three use multi-year contracts only for some vaccines, one uses only biannual contracts,two only annual contracts.

Table 7. Vaccine procurement, purchase mechanisms, stockpiling, needs estimation, domestic production in EU-JAV and other EU/EEA countries.

COUNTRY	Level of procurement			Purchase mechanism			Purchase from single/all manufacturer/supplier	Contracts >2 years possible	Vaccine needs estimation		Time period of estimation used	Domestic production of vaccines
	National level (public sector)	Subnational level (public sector)	Private sector (proportion)	Competitive bidding	Request for quotation	Single-source procurement			National level	Subnational level		
BOSNIA HG	X			X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		<1 year	No
BULGARIA	X			X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		1 year	BCG, Td, TT, DTwP
CROATIA	X			X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		2-3 years	No
DENMARK	X			X			At least some vaccines purchased from >1 manufacturer	Yes, for all vaccines	X		2-3 years	No
ESTONIA	X		X (vaccines not included in the NIP)	X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		2-3 years	No
FINLAND	X			X			Vaccines always purchased from >1 manufacturer	Yes, for all vaccines	X	X	2-3 years	No
FRANCE		X	X (Unknown)	X			At least some vaccines purchased from >1 manufacturer	No, only annual contract	Private sector		1 year	No
GREECE			X	Marketing authorization holders (MAHs) /wholesalers/ local pharmacies			Vaccines always purchased from >1 manufacturer	No central mechanisms exist. Market-driven procedures are followed by MAHs	-	-	1 year	No
HUNGARY	X			X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		2-3 years	Trivalent influenza vaccine (3Fluart)
IRELAND	X			X			At least some vaccines purchased from >1 manufacturer	Yes but only for some vaccines	X		4-5 years	No
ITALY		X		X		X	Vaccines always purchased from >1 manufacturer	Yes, for all vaccines		X	2-3 years	No

COUNTRY	Level of procurement			Purchase mechanism			Purchase from single/all manufacturer/supplier	Contracts >2 years possible	Vaccine needs estimation		Time period of estimation used	Domestic production of vaccines
	National level (public sector)	Subnational level (public sector)	Private sector (proportion)	Competitive bidding	Request for quotation	Single-source procurement			National level	Subnational level		
LATVIA	X			X			At least some vaccines purchased from >1 manufacturer	No, only biannual contract	X		2-3 years	No
LITHUANIA	X			X			Vaccines always purchased from a single manufacturer	No annual contract	X		1 year	No
MALTA	X			X*	X*	X *	Vaccines always purchased from >1 manufacturer	Yes but only for some vaccines	X		<1 year	No
NETHERLANDS	X		X (5%)	X	X	X	At least some vaccines purchased from >1 manufacturer	Yes, for all vaccines	X**		4-5 years	No
NORWAY	X			X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		4-5 years	No
ROMANIA	X			X			Vaccines always purchased from >1 manufacturer	Yes, for all vaccines	X		1 year	No
SERBIA	X			X			At least some vaccines purchased from >1 manufacturer	Yes but only for some vaccines	X		2-3 years	BCG, DT, Td, TT
SLOVENIA	X		X (30%)	X			Vaccines always purchased from a single manufacturer	Yes, for all vaccines	X		1 year	No
SPAIN	X	X	X	X			At least some vaccines purchased from >1 manufacturer	Yes, for all vaccines		X	2-3 years	No
SWEDEN***		X		X			At least some vaccines purchased from >1 manufacturer	Yes, for all vaccines	X	X	2-3 years	No

** Model depends on patency and product. most of the vaccines are purchased through competitive tender*
*** National level for vaccines included in the national immunisation programme; vaccine needs estimations for individual vaccinations are performed by private sector at travel clinics*
****Joint procurement of vaccines included in the NIP for all regions is implemented since 2019*

Vaccine needs estimation

Most countries (n=16) reported that they estimate vaccine needs at the national level, three countries do so at the subnational level and one country in the private sector. One country did not respond. In ten countries, vaccine needs estimates over two-three years, in six countries the time period considered is one year, in three countries it is 4-5 years and in two countries it is less than one year (Table 8).

Table 8 shows how vaccine needs are estimated in each country.

Table 8. Methods used to estimate vaccines needs in EU-JAV and other EU/EEA countries.

COUNTRY	VACCINE NEED ESTIMATION METHODS
BOSNIA HG	Continuous follow up. At each procurement cycle (normally 4 years) Population calculations and historic review are used.
BULGARIA	Based on population registers, according to data from the National Statistical Institute; the expected birth rate; the expected morbidity from communicable diseases; the annual plans of GPs; the immunization coverage achieved during the previous year.
CROATIA	Based on earlier consumption and size of birth cohort
DENMARK	It is estimated from experience from previous years and taking new recommendations into consideration
ESTONIA	National database for birth cohorts and statistics of vaccination coverage, NITAG's approval for detailed procurement plan, including estimation of risks for vaccination coverage, monthly usage reports.
FINLAND	WHO methodology
FRANCE	NA
GREECE	According to previous year's consumption
HUNGARY	Based on number of live births
IRELAND	Target cohort figures are taken from the Central Statistics Office
ITALY	For most vaccines, they are estimated at the regional level considering forecasts on the number of persons in the target cohorts and other population groups. For some vaccines (e.g. flu) the estimate is based on the number of doses administered in the previous year.
LATVIA	Vaccine needs are estimated by the Centre for Disease Prevention and Control of Latvia, by taking into account in general foreseen size of immunized cohorts in case of routine vaccination or average number of vaccine doses used (for instance, Td for adults or rabies vaccine). Number of estimated doses is justified in relation to immunization coverage.
LITHUANIA	Centre for Communicable diseases prevention and control estimate vaccine needs according to Lithuanian immunization Schedule and number of children in different age cohorts. There are national guidelines for vaccine needs estimation.
MALTA	Based on vaccination schedule and use in the NHS
NETHERLANDS	Birth cohorts versus vaccine uptake
NORWAY	Based upon age cohort and vaccination coverage
ROMANIA	Based on the request of the family doctors in correlation with epidemiological data
SERBIA	Needs estimation is based upon:-Target population (birth-cohort)-Number of doses in the schedule-Target immunization coverage (95%)-Wastage factor (5%)-Buffer stock – 15% of total vaccine needs for the supply period
SLOVENIA	Estimated by the National Institute of Public Health
SPAIN	Vaccine needs are estimated at sub-national level according to the population of each region and coverage.
SWEDEN	Based on age cohort for vaccines within the NIP, for other vaccines according to earlier consumption.

Domestic production of vaccine

Countries were asked if any vaccines are produced domestically by a public health institution. Three countries do so, in particular, Hungary produces trivalent influenza vaccine, Bulgaria produces BCG, Td, TT, and DTwP vaccines, and Serbia produces BCG, DT, Td, and TT. Of note, Bulgaria did not report shortages in the present survey (Table 9).

Stockpiles

Twenty of 21 participants (95%) responded to this question. Most (n=16; 71%) stated that their country keeps stockpiles of vaccines (Table 9). Eleven of 16 have stockpiles for all vaccines included in the national immunisation programme and/or with national marketing authorization in the country, while five countries have stockpile of only some vaccines. Four participants stated that their countries do not have stockpiles (Table 9).

All stockpiles (100%) are held at the national level (16/16 countries). The size of the stocks varies by country and vaccine. In general, 10 countries reported having enough stocks to provide supply for 3 to 6 months (Table 9).

Joint Procurement

Some Member States mentioned the framework contract for pandemic influenza (14). Three countries (Latvia, Estonia, and Lithuania) report being part of the Baltic countries initiative for cross-border joint procurements of various vaccines, including BCG, pneumococcal, hexavalent and rotavirus vaccines. One country (Ireland) stated that it is "*in the process of EU procurement for pandemic flu, BCG, PPD and botulism antitoxin*".

Immunisation supply plan, procedures to address shortages, supply chain manager

Immunisation Supply plan

Five countries reported having an immunisation supply plan although this is not always available as a specific document. Of sixteen countries who do not have an immunisation plan, seven address supply issues in their national vaccination plan (Table 9).

Table 9. Existence of Immunisation supply plans, procedures to address shortages, supply chain managers, and vaccine stockpiles in EU-JAV and other EU/EEA countries, 2019.

COUNTRY	IMMUNISATION SUPPLY PLAN	AVAILABILITY OF PROCEDURES OR RECOMMENDATION TO ADDRESS SHORTAGES	VACCINE SUPPLY CHAIN MANAGER	STOCKPILE			
				YES, ALL VACCINES (ADMIN. LEVEL)	YES, SOME VACCINES (ADMIN. LEVEL)	NO	DURATION OF SUPPLY (MONTHS)
BOSNIA HG	No, our national vaccine plan addresses supply issues	No	Yes	X (national)			3-6 months
BULGARIA	No	No	No		X (national)		3-6 months
CROATIA	Yes, 3-year Immunization programme; Health Care Act; Law on the Protection of the Population from Infectious Diseases	*Ad hoc* recommendations as needed	Yes	X (national)			3 months
DENMARK	Yes, sufficient stock of about 6 months	Yes, for childhood vaccines	Yes	X (national)			3-6 months
ESTONIA	No, our national vaccine plan addresses supply issues	Estonia has a national central warehouse for vaccines and has stocks for each vaccine. In case deliveries are delayed for a longer period of time (than amount available in national stock), there is ad hoc NITAG meeting to decide on possible alternatives	Yes	X (national)			3-6 months
FINLAND	No, our national vaccine plan addresses supply issues	Yes, mechanism of intervention import	Yes	X (national)			3-6 months
FRANCE	No, our national vaccine plan addresses supply issues	*Décret n° 2016-993 du 20 juillet 2016 relatif à la lutte contre les ruptures d'approvisionnement de médicaments LOI n°2016-41 du 26 janvier 2016 - art. 151*					
GREECE	No, our national vaccine plan addresses supply issues	Yes, Ministry of health circulars (www.moh.gov.gr), National Immunization Programme and modifications	No		X (national)		7-12 months
HUNGARY	No, our national vaccine plan addresses supply issues	In case of shortage of any vaccines the National Public Health Center decides on the issue.		X (national)			<3 months
IRELAND	No	No	Yes	X (national)			<3 months
ITALY	No	No	No			X	
LATVIA	No*	Ad hoc recommendations as needed. Previous experience is taken into account.	No**			X***	
LITHUANIA	No, our national vaccine plan addresses supply issues	No	No	X (national)			3-6 months
MALTA	No, our national vaccine plan addresses supply issues	We use alert systems that are published on the CPSU website and send via sms to HCP	Yes		X (national)		3-6 months
NETHERLANDS	Yes, safety stocks and other measures. Not available as a document.	Yes, RIVM has procedures in place to react to impending Shortages	Yes	X (national)			3-6 months

COUNTRY	IMMUNISATION SUPPLY PLAN	AVAILABILITY OF PROCEDURES OR RECOMMENDATION TO ADDRESS SHORTAGES	VACCINE SUPPLY CHAIN MANAGER	STOCKPILE			
				YES, ALL VACCINES (ADMIN. LEVEL)	YES, SOME VACCINES (ADMIN. LEVEL)	NO	DURATION OF SUPPLY (MONTHS)
NORWAY	Yes. Long term contracts and preparedness stock	Internal procedure	Yes	X (national)			3-6 months
ROMANIA	No	No	Yes	X (national)			<3 months
SERBIA	No, our national vaccine plan addresses supply issues	No	No			X	
SLOVENIA	Yes	Yes (from National Institute of Public Health)	Yes		X (national)		<3 months
SPAIN	No	No	No		X (national)		3-6 months
SWEDEN#	No	Joint document describing roles and responsibilities for key stakeholders. All shortages and stockouts should be reported to the Medical Products Agency of Sweden	Yes			X	

**Respondent reported there is a legislative framework which defines responsibilities of involved services (Center for Disease Prevention and Control, National Health Service) and suppliers*
*** Respondent reported that "functions of vaccine supply chain management are divided between two state institutions (Centre for Disease Prevention and Control of Latvia and National Health Service) and wholesalers (vaccine suppliers) according to legislative framework and trilateral contracts".*
**** According to contracts vaccine suppliers (wholesalers) are obliged to warn about the imminent shortage of vaccines no later than three months before stockout, but they are not obliged to keep a defined physical stockpile of vaccines in the country warehouses.*
 # From 2019 there is the immunisation supply plan for vaccines included in the NIP. Stockpiles for 3-month supply will be introduced for some vaccines from September 2019 on national level.

Procedures /recommendations in place to address shortages

We asked participants if, procedures or recommendations (e.g. reporting procedures, recommendations regarding the use of alternative vaccines or vaccination schedules) are available in their country, to address the vaccine shortages/stockouts. Thirteen of 21 countries (62%) reported having some type of procedure or recommendations in place; these are summarized in Table 9.

Dedicated supply chain manager

Countries were asked about the presence of a supply chain manager in their country. Thirteen countries, 68% (of which 12 procure vaccines at national level) responded that in their country there is a person responsible for management of the vaccine supply chain while six countries stated that this figure does not exist in their country. Two countries did not respond to the question.

EU centralized procurement and stockpiles

When asked if they would be in favour of a European centralized procurement system for vaccines, five respondents stated that they are in favour of EU procurement for all vaccines, four were favourable only for some vaccine or specific conditions (e.g. pandemic influenza vaccine). Seven respondents did not have any specific opinion about this topic while two respondents disagreed with this proposal.

Twelve participants were in favour of a European centralized stockpile of vaccines (seven for all vaccines and five only for certain vaccines). Three respondents were against a centralized stockpile. Of the remaining seven (22 respondents in total because there were two respondents from one country and they did not agree on this issue), five did not express any preference (don't know) and two did not respond.

Finally, participants were also asked about whether they would be in favour of developing a data warehouse for EU-wide sharing of vaccine supply and demand data among dedicated stakeholders. Eleven countries were in favour as opposed to three who disagreed with the proposal. Five participants did not express any preference (don't know) and two did not respond.

Communication

Participants were asked in which of a listed set of situations (all having the potential of increasing vaccine demand) does their country's public health authorities regularly communicate with vaccine manufacturers.

- 18 of 21 (86%)respondents indicated that public health authorities in their countries regularly inform manufacturers about every planned introduction of new compulsory/recommended vaccines
- 17 (81%) indicated that public health authorities communicate planned changes to vaccination schedule
- 14 (67%) informed vaccine manufacturers about occurrence of disease outbreaks
- 13 (62%) communicated with vaccine manufacturers regarding planned changes of targeted groups.

Two countries (Lithuania, Italy) reported to not regularly communicate with manufacturers.

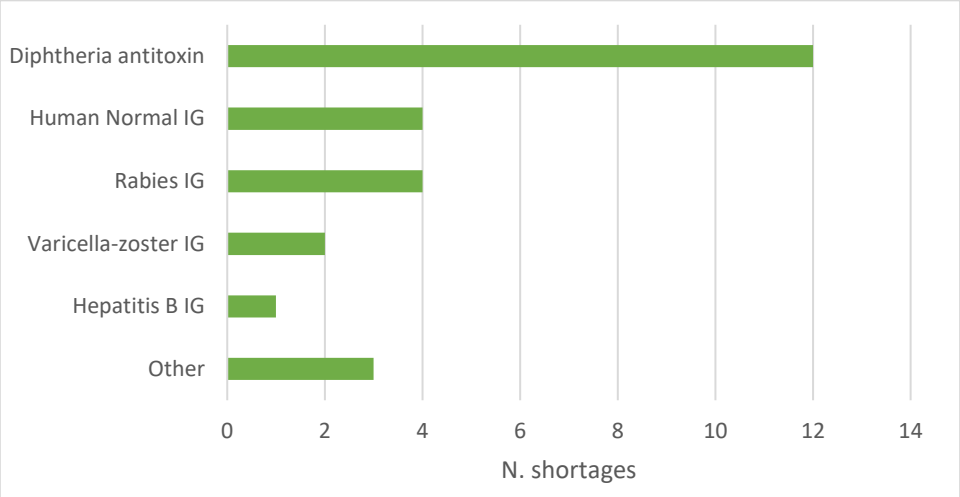
None of the 21 participants have legislation requiring that the above changes are communicated to MAHs in advance.

We also asked participants about institutions that are usually informed in case of vaccine shortages. Nineteen stated that national authorities (including Ministry of Health, Ministry of Social Affairs, Ministry of Human Capacities and health STM and Medicine Authority) are informed in case of regional or local procurement. Among the 19 respondent countries, two (Latvia, Lithuania) reported also to inform European institutions and two (Finland, Lithuania) reported to inform international organizations such as WHO or UNICEF.

Shortages/Stockouts of other biological products

Figure 6 shows reported shortages/stockouts of biological products in EU/EEA and consortium member countries in the three years considered. Overall 25 shortage/stockout episodes were reported by 17 countries. The most frequently reported event was shortage/stockout of diphtheria antitoxin, reported by 12 countries. No countries reported shortages of tetanus IGs.

Figure 6. Shortages and stockouts of biological products in EU-JAV) and other EU/EEA countries, 2016-2019



Among “Other shortages”, one country reported brief shortages of Botulinum toxin because of expiration of stock product and another country reported shortages of PPD and anti-Rhesus D IG

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Table 10. Reported shortages of biological products for infectious disease prophylaxis, their causes and actions taken, by country. EU-JAV and other EU/EEA countries, 2016-2019

COUNTRY	PRODUCT	CAUSES	ACTIONS
BOSNIA HG	Diphtheria antitoxin	Global shortage	Attempted to find a feasible supply. Have tried to find any producer. An Indian producer is identified. The product does not pass external activity testing. This is a problem not solved
BULGARIA	Human Normal IG	National production of Human Normal IG was stopped	None reported
CROATIA	Rabies IG	No one responded to the public tender	Informed the NRA (HALMED), which identified a wholesaler which imported rabies IG
DENMARK	Varicella-zoster IG	Products not licensed and therefore it can take time and a lot of effort to get products, especially if you need a new product	Working with other Nordic countries sharing information about products and producers
ESTONIA	Hepatitis B IG Varicella-Zoster IG Diphtheria antitoxin	Main issue has been to find balance between stocks and expected demand. These products are characteristically quite high priced, short expiry dates, without valid marketing authorization in Estonia, few suppliers and no good solution to estimate the actual usage. Therefore the stocks are quite low and if there are more than few cases at the same time, there could be a stock-out situation very quickly	Stocks are procured centrally in national level, there is a commission decision on how many vials are needed at subnational level for each case (stocks are divided to emergency medicine departments of two regional hospitals), compulsory timely reporting of each vial that has been used by the hospitals
FINLAND	Diphtheria antitoxin		Attempted to find a feasible supply. The problem is not solved.
FRANCE	Human Normal IG	Problem of the production site	Problem is still ongoing
GREECE	Human Normal IG	Restricted production due to restricted availability of raw material (human plasma).Not available at national level.	Ban of parallel export
HUNGARY	Diphtheria antitoxin	No product available on the European market.	We could not solve
IRELAND	Diphtheria antitoxin	Diphtheria Antitoxin has been short for a number of years.	Extended shelf life after testing in accredited laboratory showing continued potency
ITALY	Diphtheria antitoxin	Production interruption and few manufacturers available	Instead of measles and rubella Ig we use Human normal IG
LATVIA	Diphtheria antitoxin	Interruption in the supply chain	Product not authorised in Latvia. It is distributed on the basis of exceptional permits as unauthorised product from different manufacturers in Europe (e.g. Bulgaria) or in other countries (e.g. Russia)
LITHUANIA	Diphtheria antitoxin	We don't have any stock of diphtheria antitoxin. The main cause is that is not possible to procure at the moment.	None, no diphtheria cases since 2011
MALTA	None		
NETHERLANDS	Diphtheria antitoxin	Producer stopped producing	D-antitoxin - switched supplier
	PPD	PPD - production problems SSI/AJ Vaccines.	Bought non-registered product
	Anti-Rhesus D IG	Anti-Rhesus D IG - production problems	Switched supplier

COUNTRY	PRODUCT	CAUSES	ACTIONS
NORWAY	Diphtheria antitoxin	Difficult to procure because low demand for product. No supplier in EU. Indian manufacturer supplied through Swedish importer. Product had potency issues. Currently product is not part of stock. The shortage started when the existing product expired (2014).	Search was done and Scandinavian Biopharma Distribution was able to find a supplier (India). We received regulatory approval to import the product through Norwegian Medicines Agency. Problem is unsolved.
ROMANIA	Rabies IG Human Normal IG Diphtheria antitoxin	Lack of national/ European providers	Importation from other member state
SERBIA	None		
SLOVENIA	None		
SPAIN	Rabies IG Diphtheria antitoxin	Few competitor manufactures	Importing IG from other countries
SWEDEN	None		

Duration of shortages

Information on duration of shortage was available for 9 of 25 episodes. Duration of shortages varied by product and ranged from 2 months for Human Normal IG in two countries to 38 months for diphtheria antitoxin in three countries.

Ongoing shortages

Eight shortages of biological products were still ongoing at the time of survey completion. In particular:

- Italy (Diphtheria antitoxin)
- France (Human Normal IG)
- Netherlands (Diphtheria antitoxin)
- Greece (Human Normal IG)
- Bosnia HG (Diphtheria antitoxin)
- Lithuania (Diphtheria antitoxin)
- Hungary (Diphtheria antitoxin)
- Finland (Diphtheria antitoxin)

Main causes of shortages of other biological products

Participants were asked to describe the main causes and issues around each of the reported shortages of biological products, and how these were resolved. Questions were aimed at collecting opinions about shortages of biological products as a whole but, for some products, causes were product-specific. Eleven countries reported shortages of diphtheria antitoxin. Five countries were able to identify a cause that was specific to the shortage of this product. Respondents agreed upon the fact that the most relevant issue is related to a global shortage, production issues and a growing difficulty to procure the product. In fact, one respondent noted that the shortage started when the existing product expired and that so far there are no manufacturers within the EU. Most of the diphtheria antitoxin shortages across Europe indeed started in the same period, between 2016 and 2017.

Out of four countries that reported shortages of Human Normal IG, three countries were able to identify a cause. In two cases, shortages were the consequence of interruption of production at national level (Bulgaria) or of occurrence of issues at the production site (France) and lasted two months. In another country (Greece), it lasted 21 months and was the consequence of restricted production due to low availability of raw materials.

Regarding rabies IG shortages the main reported reason was common to other IG shortages, namely the lack of producers/manufacturers. Regarding varicella IG shortage, one country reported that these products were not licensed so that getting products require time and effort increasing the difficulty to procure them.

In the single case of HBV IG shortage, the main reported issues were that the products were high priced, with short expiry dates, no valid marketing authorization in the country and with few suppliers. As a consequence, the stocks are quite low and if there are more than a few cases at the same time, a stockout situation could develop very quickly.

Actions undertaken

Some actions undertaken were specific for diphtheria antitoxin and others were common to all the other products. The main actions implemented to mitigate diphtheria anti toxin shortages are described below:

- One country described attempts to import the product for preparedness scope from an Indian manufacturer, through a Swedish importer, after receiving regulatory approval by the National Medicine Agency;
- One country switched to another supplier;
- One country asked for permission of distribution of antitoxins authorised in another EU country or third country;
- Finally, one country extended the shelf life of available product after tests in an accredited laboratory.

Similarly, for the other IGs, there was a general attempt to import product from other countries, including non-EU countries or to find other wholesalers or suppliers. In some other cases countries had to modify their practices. For instance, in one country it was decided to use Human normal IG instead of measles and rubella IG. In other cases the problem could not be solved and in at least one case the shortage led to the interruption of the immunisation programme.

Current availability of biological products other than vaccines

The most frequently unavailable products were diphtheria antitoxin and rabies IG, reported respectively by five and four countries. No country reported unavailability of varicella-zoster IG (Table 11).

Table 11. N. of countries in which biological products other than vaccines are unavailable. EU-JAV and other EU countries.

Product	N. of countries
Diphtheria antitoxin	7
Rabies IG	4
Human Normal IG	3
Hepatitis B IG	2
Tetanus IG	2
Varicella-zoster IG	0

EU central stockpile for biological products other than vaccines

Eighteen participants stated that they would be in favour of a European central stockpile for biological products other than vaccines, either for all biological products (10 countries) or only for diphtheria antitoxin (8 countries). One country specified that they would agree to a European stockpile of all biological products that are difficult to purchase but no specifications were provided. Lastly, three remaining respondents did not answer the question or did not express an opinion.

Stakeholders' Views

In view of the important role that stakeholders such a Vaccines Europe (VE) and the European Medicines Agency (EMA) play in the prevention and management of vaccine availability issues, we gathered their perspectives on the main problems leading to shortages, on what is being done and on what should be done to avoid or mitigate them. Stakeholders' views were collected through an email questionnaire sent to Vaccines Europe and seven vaccine manufacturers (*GlaxoSmithKline, Pfizer, Sanofi Pasteur, MSD, Astra Zeneca, Abbott, Seqirus*), a face-to-face meeting with Vaccines Europe representatives, and an email questionnaire sent to EMA representatives.

Vaccines Europe

According to Vaccines Europe (VE), one of the main factors to be addressed to prevent or mitigate vaccine shortages are the complex and diverse regulatory requirements in EU/EEA and worldwide. Vaccines are highly technical biological products with complex and lengthy manufacturing, control, and release processes. The majority of vaccines have very long production lead times (i.e. time from the start of the production of the antigen until release of the finished product by the manufacturers) ranging from 18 to 24 months and complex multivalent vaccines (e.g. pertussis-containing vaccines, meningococcal and pneumococcal conjugated vaccines) can have production lead times up to 36+ months. Only very few vaccines have slightly shorter production lead times ranging from 12 to 18 months (e.g. monovalent hepatitis B vaccines). Regulatory aspects significantly impact on three steps of the vaccine supply chain which, according to VE, are susceptible of improvements: quality control tests; post-approval changes (PACs); packaging and labelling requirements.

Quality control tests. According to VE, quality control tests represent 70 per cent of vaccine production time: on each lot, between 100 and more than 1000 quality control tests are performed by the manufacturer. Furthermore, before distribution, each lot is systematically controlled by official Medicines Control Laboratories (OMCLs) which results in dual (or multiple) testing.
According to VE, repetitive quality controls and retesting might play an important role in shortages by delaying availability of lots, increasing the risk to reject compliant batches due to "out-of-specifications", losing some compliant lots, reducing the number of doses and remaining shelf-life at the time of the final release to market entry, leading to high consumption of biological reagents and resulting in unnecessary use of animal testing. VE proposes that the European Directorate for the Quality of medicine and Healthcare (EDQM) should pursue efforts towards elimination of animal testing, optimize OMCL testing strategies, procedures and guidelines, harmonize methods within the EU OMCL network and between EU and non EU countries, and build systems and procedures in favor of reliance of EU batch testing. They also suggest that the European Commission should set/extend Mutual Recognition Agreements (MRA) to batch release by EU OMCLs and selected non-EU NCLs (e.g. U.S. and Canada).
Post-approval changes (PACs). Vaccine manufacturers are pushed to innovate and improve their products in order to deliver effective and safe products, as by the EU Good Manufacturing Practices (GMP). However, each change must be authorized by Regulatory agencies, such as EMA (for centralized procedure) or national agencies. While acknowledging the importance of PACs, VE considers that PACs add complexity to the vaccine life-cycle management for several reasons, because of the wide number of variations needed to be submitted every year worldwide, the diverse regulatory requirements and the long lead times for regulatory approval (6 months for EMA but up to 4 years worldwide)
According to VE, risk-based approaches, global convergence of regulatory requirements, processes and procedures, and Mutual Recognition Agreements (MRAs) for inspections of vaccine facilities and approvals of PACs should be developed for optimizing vaccine supply.

Packaging and labelling requirements. Country-specific packaging and labelling requirements are another factor which may contribute to shortages. Due to a combination of factors such as the market size, limited vaccine shelf life (1 to 3 years), cold chain requirements or conditions imposed by tenders, vaccines may have to be delivered in small volumes (sometimes a few thousand doses) of country-specific packs. Packaging lines therefore have to continuously be stopped to allow changes of label, leaflet and carton. Indeed, as soon as vaccine syringes or vials are labelled or packed in a country-specific format, they can no longer be transferred to another country without repackaging unless prior documented agreement from authorities of the new destination country is obtained. In addition, due to the small size of vaccine packs to facilitate cold chain distribution and storage, the use of multilingual packs (which is only possible when product information is exactly the same) is limited to 2 or 3 languages. A solution proposed by VE would be to use electronic leaflets. These could be introduced on top of the paper leaflet to facilitate the transfer of vaccine for a period of time and to demonstrate the feasibility and absence of negative impact on patient information.
According to VE, besides regulatory issues, accurate prediction of demand and appropriate procurement practices are critical to secure supply. Because of the long production lead times for vaccines, and the time needed to build and license a new production facility (5-10 years), a quick response by industry to unexpected changes of demand is not always feasible. Capacity is adapted to the demand forecast at the time of construction planning, and an unexpected and significant increase of demand, particularly if at global level, cannot always be faced by existing facilities capacity.

Better anticipation of demand is therefore needed globally, according to VE. This can be achieved by early and continuous dialogue between industry and national competent authorities, including National Immunization Technical Advisory Groups (NITAGs), (in compliance with competition laws) regarding vaccine recommendations, and improving procurement practices. Ideally, to help manufacturers ensure an accurate production, estimates of vaccine needs should be made for five or more years and not less than 2-3 years

Regarding purchasing models, according to VE, procurement practices that value multiple suppliers to stay in the market may secure a more sustainable supply. Also, VE considers that contracts are often driven by the lowest price or price-only selection criteria and this can increase the downward pressure on commodisation of the vaccine market, leading to reduced investments and the survival of mainly larger companies. Some other aspects of procurement may also exacerbate vaccine shortages, according to VE. For example, tenders may not recognize the long lead times, and may have rigid supply requirements that cannot always be fulfilled. Therefore, VE is of the opinion that procurement practices should be adapted to enable better manufacturing planning and reduce risks both to the purchaser and the manufacturer, e.g. longer lead times for the production and delivery of products, longer contract duration and split tenders for interchangeable vaccines.

Regarding a common EU vaccine stockpiling mechanisms to mitigate shortages, VE states that this may be useful to address certain situations of shortages in the EU but underlined some critical aspects. First of all, although stockpiles are useful in short-term fluctuations they should not to be intended as the ultimate solution. Secondly, stockpiles would not solve the fragmentation of the EU (in terms of languages and regulatory) that would make the transfer of doses difficult because of leaflets and packages in different languages, different presentations, different pack sizes, etc.

VE supports early notification of shortages when they occur, but point out that it is not always possible to recognize potential supply shortages early on (for several reasons, e.g. manufacturing problems can occur at any stage, quick demand increase) and that when these are detected, manufacturers need to conduct investigations to understand the implications. Also there is no common definition of shortages and no mechanism for supranational communication of shortages for nationally approved products. In regard to the

latter point, industry is in favor of informing national competent authorities as soon as EMA is informed, provided that this can be done without creating additional administrative burden for the manufacturers, i.e. via a single EU portal for shortage notification. However, VE expressed several concerns regarding public communication by authorities following a notification of shortages by a manufacturer. Public communication may lead to a "stockpiling" behavior by supply chain partners that may worsen the shortage and can rise unjustified concerns about vaccine quality. Also, it is important that any communication prepared by competent authorities be shared with the manufacturer before its publication so that the manufacturer can be prepared to address any potential questions.

When supply is constrained, there may be a need to temporary review vaccine recommendations to ensure the continuity of the vaccination program. VE recommendation is that, during periods of constrained supply, ECDC continues to provide rapid risk assessment reports to Member States, in order to support decision-making on priority groups to receive vaccines and temporary vaccination calendars. This could, for example, lead to delaying booster doses and to deferring vaccination of other target groups.

European Medicines Agency

The European Medicines Agency (EMA) agrees that shortages or problems with availability of medicines are increasingly affecting the EU. The Agency recognizes the causes of shortages identified by industry, which include long lead times in production, reduced manufacturing capacity, limited number of sites manufacturing vaccines, reactive use of quality risk management in supply chain planning, and capacity not matching demand due to imperfect planning.

EMA has been active in identifying actions to prevent vaccine shortages for a number of years. A reflection paper was drafted in 2012 highlighting the need for manufacturers to be more proactive and develop supply chain resilience. Since 2016, EMA together with the Heads of Medicines Agencies (HMA) (a network of the heads of the National Competent Authorities whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area), established a Task Force looking at the availability of authorised medicines, including vaccines. The aim of the Task Force is to lay the foundations for an improved and harmonised EU approach in addressing the problems of medicines' availability issues, including vaccines. Specifically the Task Force's mission is to develop and coordinate actions for better prevention, identification, management of and communication on issues that can affect the availability of medicines across Europe.

Because the causes of shortages are multifactorial, according to EMA/HMA, there is no single solution and coordinated actions are needed from all stakeholders. A multi–stakeholder workshop was therefore organised and took place in November 2018, to find ways to better address availability issues and to prevent shortages (15).

The Task Force recently published two documents, both of which underwent extensive consultation with stakeholder groups, including at a multi-stakeholder workshop in November 2018:

1) a guidance for marketing authorisation holders on reporting of shortages in the EU, and

2) a good practice guidance for communication to the public on medicines' availability issues.

The first document provides guidance to the pharmaceutical industry, a key player in addressing shortages, on the detection and early notification of impending shortages of medicines to competent authorities in the EU/EEA. So far, the detection and coordination of the management of shortages in the Union (EEA) has not been consistent because of the absence of a common definition. Also, it was not possible to make

comparisons across countries because of differences in reporting requirements of shortages. The guidance clarifies when a notification should be made and to whom, and provides a common definition of the term 'shortages', agreed at EU level, which should enable a more harmonised and timely approach in the detection and management of issues with the supply of medicines. The new proposed definition for notification and detection of shortages by MAHs, agreed by EMA, HMA and stakeholders, is "a shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level". A proposed template for shortage notification by companies, which specifies the information that should be included in notifications, is also included in the guidance. The guidance and template will be implemented in a pilot phase, which is currently planned to start in the last quarter of 2019 (16).

The second document is addressed to EU national competent authorities (NCA) and EMA and lays out principles and examples of good practices for communicating timely, accurate and up-to-date information on shortages to the public, including patients and healthcare professionals.

Regarding the issues related to the transfer of vaccine doses between countries to mitigate/limit the impact of supply disruption in case of vaccine shortages, EMA states that it should be possible for vaccines to be transferred from one Member State to another. A bit more problematic is the transfer from outside the EU to the EU and vice versa as quality specifications may differ from one region to another so an assessment might be needed. Transfer of vaccines authorised in centralised procedure is deemed to be easier, as labelling information and authorized presentations are fully harmonized, albeit some differences remain, most notably language requirements, national blue box requirements (additional information placed on outer packaging) and sometimes differences in local representative listed in the package leaflet.

Regarding the possibility of introducing a common single pack across Europe, EMA points out that Article 63(3) of Directive 2001/83/EC already allows the granting of an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet (for centralised products can be agreed at EU level). Furthermore, it allows a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State (even for centralised products has to be agreed at national level at each 'importing' country).

Any introduction of "common single pack across Europe" or even common primary packaging (which could also provide some increased flexibility for supply) would require agreement among MS for more systematic exemptions from language requirements for certain products. If such approach was to be explored, vaccines could be a suitable product category to consider, as they are not self-administered, are products of high public-health importance and often face shortage issues.

Replacing the conventional paper leaflet with an e-leaflet is currently not foreseen by the EU pharmaceutical legislation. An e-leaflet would only be acceptable in addition to the paper format. Options for more widespread use of electronic product information are currently being explored.

Regarding feasible solutions to simplify post-approval changes (PACs), EMA points out that change management protocols provide significant flexibility to MAHs especially for biological medicinal products as the strategy is being approved before the data is generated. This is followed by a minor variation that allows changes to be assessed within 30 days, so can be timely implemented.

Grouping of different changes and work sharing for different medicinal products are being widely used at European level for vaccines to assess and timely implement the same changes in multiple vaccines approved in different regulatory framework: Centralised, Art 58, MRP/DCP and nationally.

EMA also underlines that the agency is working with other regions within the International Council for Harmonisation of Technical requirements for Pharmaceuticals for Human Use (ICH), which brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. The ICH works on harmonisation on the technical and regulatory requirements across regions on pharmaceutical product lifecycle management (ICH Q12). In addition, WHO has a suggested classification of post authorisation changes as guidance for third countries that are based and closely aligned with the EU risk-based approach and classification of changes in post authorization (17). An example of a specific regulatory procedure for vaccines is the Influenza vaccines specific guidance annual strain update variation (18).

Regarding the possibility of setting/extending Mutual Recognition Agreements for inspections of vaccine facilities by EMA and FDA, EMA stated that the current EU-US MRA foresees an extension to vaccine manufacturers by 15 July 2022 and that in order to support the inclusion of vaccines for human use and plasma derived pharmaceuticals within the product coverage, the experience gained through joint inspections will be considered. MRAs are trade agreements covering conformity assessment, i.e. that each party's testing and the testing regime for a particular product is recognised. It does not extend to recognising each other's product approvals as this would be an erosion of national sovereignty and for the EU would undermine the single market.

"Approval of PACs" would not be possible in a MRA with the EU. However, reliance on assessments of PACs by Stringent Regulatory Authorities does take place in large parts of the world already without MRAs e.g. the take up of the Certificate of Pharmaceutical Product scheme as well as other reliance initiatives that are ongoing e.g. International Pharmaceutical Regulator's Forum and other multilateral arrangements.
Regarding batch release by EU OMCLs and selected non-EU NCLs, this is not conformity testing as envisaged by the MRAs because this is an additional independent public health measure by an OMCL to confirm the quality of a vaccine before use on the national territory. It seems that legislative change in the EU would be required to allow for the recognition of OMCL testing in MRAs or other reliance initiative

Discussion

The present survey confirms that vaccine shortages and stockouts are common events in EU/EEA countries. Overall, 19 out of 21 participating countries experienced 115 shortage and stockout events in the three-year study period, of which 38 were stockouts. In six countries, some of the reported shortages were ongoing at the time of survey completion. In addition, there are ongoing shortages of other biological products, especially diphtheria antitoxin.

Results from our study seem to differ somewhat from data collected annually through the UNICEF/WHO Joint Reporting Form (unpublished data provided by WHO-Regional Office for Europe), according to which, 73 stockout events occurred in 18 EU/EEA countries (plus Switzerland and San Marino) in the period 2016-2018. However, these differences can be explained mainly by two factors: the JRF collects data only on stockouts (not shortages) that lasted at least one month and, the countries from which data was collected by the JRF in 2016-2018 do not perfectly match those that participated in our survey. More specifically, the JRF collected data from 10 countries that did not participate in our study. In addition, the JRF analysis focuses on selected vaccines common to all national immunization schedules, and stockout events are defined by antigen (19).

It should be noted that the shortages reported in our study may involve either a single manufacturer or all manufacturers producing a specific vaccines. Therefore, they do not necessarily lead to stockouts nor impact vaccination delivery. A country experiencing a shortage from one manufacturer may succeed in using available stockpiles or purchasing vaccines from other suppliers and in so doing, avoid immunisation service disruptions even if the shortage is still ongoing. For instance, in the Netherlands, a DT-containing vaccine shortage lasted 49 months but it did not have an impact on vaccine delivery because the country succeeded in ensuring a stable vaccine supply.

The number of shortage/stockout episodes, their causes and impact on the population varied between countries. However, almost all participating countries reported at least one shortage and most shortages occurred at national level. Italy and Greece were the countries that reported most shortage/stockout events, followed by France and Latvia. Only two countries did not report any shortages in the three years considered. The number of ongoing shortages almost doubled in 2018 with respect to 2016 although the number of new shortages in each year remained constant in the three years considered. The survey confirmed that vaccine shortages had a relevant impact on vaccine services, in terms of changes to the vaccination schedule and also in terms of time resources spent to find adequate solutions to mitigate the shortages.

The vaccines most frequently affected by the shortages in the three year study period were DT-containing vaccines, followed by hepatitis B and BCG vaccines. These results are consistent with global and European data which also show that DTP vaccines are the vaccines most often involved in stockouts (1) (4).

DT-containing vaccines accounted for about one quarter of shortages in 14 countries and most were due to global shortage. These vaccines represent a wide group of different vaccine combinations and a shortage of one component can potentially lead to shortages of many combination vaccines. According to a global market study a critical issue when it comes to these vaccines is that they are often combined with acellular pertussis (aP) vaccine and aP-containing vaccines have a small supplier base (one to four manufacturers per vaccine) (20). A 2015 ECDC risk assessment showed that shortages of acellular pertussis vaccine (which does not exist as a stand-alone vaccine) in the EU/EEA, deeply affected availability of all pertussis combination vaccines (such as DTaP, dTap ETC) and immunization programmes in nine countries. Our survey confirms these results and show that nine of 27 countries who experienced a shortage of DT containing vaccines had to change their immunization programmes (mostly primary and booster programmes) to mitigate the impact of the shortage (8,9).

Hepatitis B and A vaccines were respectively the second and fourth most frequently affected vaccines for number of shortage/stockout events, most of which due to global shortage. Hepatitis B vaccine is included in all EU/EEA national immunization programmes while hepatitis A vaccine is frequently recommended to risk groups. In Europe, hepatitis A and B vaccine shortages are occurring since several years (21). A 2017 ECDC assessment confirms that there is limited supply availability of HepA vaccine since several years and that this has hindered implementation of control measures in some countries experiencing outbreaks (22). Of note, in our survey, only one respondent considered outbreaks as the cause of hepatitis A vaccine shortage. In the RRA, the limited supply of hep A vaccine in EU/EEA was attributed mainly to past and ongoing production issues with MAHs along with increased demand.

Supply issues of Bacille Calmette-Guérin (BCG) vaccine are being reported globally since several years (23,24). In the EU/EEA, BCG vaccination is mandatory in four countries (Bulgaria, Czech Republic, Hungary and Poland), generally recommended in 11 and recommended in some specific conditions in seven (25). Our results on BCG shortages are consistent with a 2014 web-based survey about the state of BCG immunization implementation in Europe which showed that shortages of this vaccine occurred in eight European countries which were using BCG vaccine produced by SSI in Denmark (26). Our results indicate that BCG shortage was due to production problems of one large supplier (Statens Serum Institut of Denmark – SSI) and the limited number of manufacturers with authorized products (6,27). As of November 2018, two manufacturers were authorized in Europe (AJ vaccines and SSI) and approved in 16 European countries (28). However, SSI interrupted BCG production in 2015, leaving only one manufacturer to meet BCG demand in Europe (23). Bulgaria and Serbia also produce BCG vaccine but their products are not authorized by EMA.

In our survey, the most commonly reported causes of vaccine shortages were production issues and global shortage. Interruption of production occurred in shortages of several vaccines reported by 12 countries. We did not ask respondents to specify the reason for the interruption but it is well-known that vaccine production is complex and at higher risk of production failures, including “out of specification batches” with respect to other manufactured drugs. In addition, when these situations occur, production capacity cannot be increased quickly because of the complexity of vaccine production and the long lead times, leading to insufficient availability of vaccine doses. Production issues has been cited by other authors as a leading cause of drug shortages in European countries (2).

Global shortage was a factor in one third of shortages, in agreement with data from WHO/Unicef JRF which found that this was the main cause of vaccine stockouts in high income countries (such as most EU countries) (29). However, the root causes behind global shortage are often not specified. As in the cases described above (BCG, hepatitis, DTP-containing vaccines), global shortage can be the result of various interrelated factors, including interruption of production due to quality issues, lack of raw material, and a limited supplier base. The latter is cited as a relevant problem for vaccines since in the last decade industry consolidation has led to fewer vaccine manufacturers (21). Economic and market-related factors are likely to be at the root of this. Entering the market is a business decision, and low market prices, especially for older vaccines, may lead to either manufacturers not entering the market in the first place or withdrawing from the market because of low profits.

The literature confirms that causes of vaccine shortages are complex and interrelated, vary by product and country, and include supply, demand and information issues (6,27). Also, the consulted stakeholders agree that the causes of shortages are multifactorial and that there is no single solution. Although industry representatives highlighted the complex regulatory requirements and lack of harmonisation, especially regarding PACs, as one of the major causes of delays and shortages, EMA does not seem to fully share this opinion and points out that change management protocols provide significant flexibility to MAHs especially

for biological medicinal products. A recent study also found little evidence for the existence of an association between complex regulatory requirements for post-approval changes and shortages (27). The latter study does recognize, however, that the regulatory complexity of PACs on a global scale can be an aggravating factor in some cases.

According to survey results, vaccine procurement in EU/EEA and other EU-JAV countries is almost entirely performed by the public sector at national level. A higher number of shortage/stockout events was reported by the one country that procures vaccine exclusively at subnational level and by the one country that procures vaccines through the private sector. Although it is not possible to establish a correlation between procurement level and number of shortages, our findings suggest that future research could better investigate the relationship between procurement mechanism and resilience to shortages. Regarding purchase mechanisms, most survey participants reported that they prefer a competitive bidding based on price. This is not unexpected as this mechanism favours market competition and lowers vaccine prices. According to vaccine manufacturers, price-only biddings do not favour the most effective and safe vaccine but only the cheapest and does not incentivise R&D efforts. This view seems to be shared by other experts who suggest that a tendering system should take into account other factors than just price (30,31).

Our results show that in eight of 21 countries, vaccines are always purchased from a single supplier and most countries report signing contracts having a duration of more than two years. Single source procurement may increase the risk of shortages should one manufacturer experience production problems (21). However, our results do not provide evidence in this regard. According to Vaccines Europe, single supplier tender with multi-years contracts could introduce market distortion, by preventing competitors to access the market for a long period of time and eventually lead them to quit the market.

A recently experimented type of procurement is joint procurement, used for pandemic influenza vaccine by 20 European countries (14). Only five respondents to our survey expressed a favourable opinion on joint EU procurement for all vaccines and another four countries are favourable to joint procurement of at least some vaccines. One respondent pointed out that the joint procurement initiative for pandemic flu "*… has cost loads of time and energy, whereas it has not resulted in a better result than expected in a one-on-one situation. Especially the long lead time and compromises in the procurement strategy were bottle necks.*"

Similarly, seven countries stated that they are in favour of a European centralized stockpile for all vaccines and five for some vaccines. One country highlighted that *"If all countries would have stocks and proper forecasting, there would be fewer problems. This is a more promising option".* Another country specified that "*… there are too many regulatory and legal hurdles that would make this effective […] very labor intensive to update and maintain. Limited gain. We believe though it may be relevant for rare diseases."* Industry also does not believe that stockpiling is the ultimate solution since the reasons for shortages are many and varied. In addition, a centralised stockpile would be difficult to create in the EU because, although in theory the EU is a single market, it is operationally fragmented (e.g. different languages, different vaccine presentations, different pack size requirements). Finally, among other issues, long term stockpiling would require significant harmonisation of regulatory requirements.

As specified in the GVAP, there is a need for all countries to have an immunization supply chain improvement plan and a vaccine supply manager at national level, to oversee the implementation of the plan (32). Our results show that these recommendations have been implemented only in little more than half of countries surveyed. Of note, the four countries which experienced the highest number of shortages reported not having a vaccine supply chain manager. The degree to which these two factors contribute to the occurrence of shortages and stockouts is not clear, but to align European countries to WHO policy might constitute a further step towards vaccine security.

We also explored whether countries have recommendations or procedures in place to address shortage and stockout events; these were reported by only about half of countries. It is fundamental that in case of vaccine shortages, all countries be ready to make recommendations in a timely manner to mitigate shortages.

Timely communication between supply and demand is a well-known factor in the prevention of vaccine shortages(6). Two communication flows need to be considered: 1) communication from public health authorities to manufacturers of ongoing outbreaks and changes to vaccine policies and strategies that have to be translated into precise supply needs 2) communication of impending shortages from manufacturers to public health authorities, including national regulatory agencies, and to EMA. Our results indicate that most EU countries regularly inform MAHs about planned changes to immunization programmes and, to a slightly lesser extent, about VPDs outbreaks. However, it is not known how much time in advance they do so. In consideration of vaccines' long lead times, it is important that this information starts to circulate early so that manufacturers can scale up production accordingly.

Similarly, manufacturers should inform public health authorities in a timely manner about anticipated shortages so that reactive measures can be implemented (21). Currently, manufacturers in Europe are obliged to communicate vaccine shortages at least two months before they occur to EMA and/or to National Agency of Medicines (33).

Strengths and limitations of the study.

To our knowledge, this is the first survey to collect detailed information on vaccine shortages in EU/EEA countries. Previous studies (1,29) were focused only on vaccine stockouts in high-income countries as a whole or in the European WHO region. Our survey collected information also on vaccine shortages, country procurement systems and stockpiles. The high response rate represents an important achievement and suggests that vaccines shortages is perceived as a relevant issue to national authorities.

One of the limits of the study is that participants may have interpreted the definition of shortages and stockouts differently. We used the definitions of shortages and stockouts proposed by the WHO. However, some participants reported shortages from only one manufacturer, which did not affect vaccination services, while others may have reported only stockout events which they routinely report to WHO through the Joint Reporting Form. Also, in our definition we did not specify a minimum duration for shortages/stockouts to be reported so as to increase the sensitivity of our research and collect as much information as possible. However, this may also have introduced different interpretations of shortage and stockout among respondents (34). There are several different definitions of vaccine shortages and ongoing efforts at European level to agree on a common definition (13). The EMA and HMA taskforce on availability of authorized medicine have recently developed a proposal for a definition to be used by MAHs for reporting of shortages of medicinal products (including vaccines) in the EU/EEA (35).

Another limit is due to the fact that survey respondents working at national level may not be completely informed of all shortages occurring in their country (or of specific details of each shortage) when vaccine procurement occurs at subnational level. Finally, although the response rate was very high overall, some questions were not fully addressed by some respondents. This might be due to the complexity of retrieving the information but also to the length of the survey which, in cases where countries had encountered many shortages, was very long and time-consuming.

Conclusion and Recommendations

Vaccine shortages are a relevant problem in EU/EEA. Results of the survey described in this report enable us to better characterize the entity of the problem, the impact of vaccine shortages and stockouts in EU/EEA, and their main causes. In addition, the survey results provide some insights into the procurement and tendering mechanisms used in EU-JAV countries and other EU/EEA countries and aspects of vaccine needs estimation. This information, together with information collected from the literature, and stakeholders' views, bring us to make the following general considerations and recommendations:

- More research is needed on the causes of vaccine shortages (including analysis of the economic and market–related causes) and on how the different causes interplay with each other.
- There is a need for all countries to have an immunization supply chain improvement plan, defining strategies to assure a stable and adequate vaccine supply for the immunisation programme in order to prevent shortages, and a vaccine supply manager at national level.
- Improved communication between public health authorities, manufacturers and regulatory agencies is needed. Mechanisms for an early and continuous dialogue between manufacturers and health authorities should be established to better anticipate the evolution of vaccine recommendations and more accurately forecast vaccine demand. Timely communication of shortages from MAHs to regulatory agencies and to public health authorities is needed. In case of vaccine shortages, communication by competent authorities to the public should not trigger undue concerns regarding the quality of vaccines.
- Procurement and tender mechanisms should be improved and take into consideration, among others, multisource suppliers, other factors besides price, and the length of contract.
- An EU platform for exchanging information on vaccine shortages and actions taken across countries would be helpful.
- In case of vaccine shortages, all countries should have procedures or recommendation in place regarding the use of alternative vaccines or vaccination schedules during the shortages. Such procedures could be developed in collaboration with National Immunisation Technical Advisory Groups (NITAGs).
- Coordinated actions are needed from all stakeholders to prevent and mitigate vaccine shortages.
- Shortages of biological products (the most concerning of which is diphtheria antitoxin, currently reported to be unavailable in several countries) deserve the same consideration as vaccine shortages.

References

1. Lydon P, Gasca A, Dumolard L, Urfer D, Senouci K. Vaccine stockouts around the world: Are essential vaccines always available when needed? Vaccine [Internet]. 2017 Apr 19 [cited 2019 Jan 17];35(17):2121–6. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X17300452

2. Pauwels K, Huys I, Casteels M, Simoens S. Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC Health Serv Res [Internet]. 2014 Dec 26 [cited 2019 Jul 31];14(1):438. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-14-438

3. Strategic Advisory Group of Experts (SAGE) on Immunization. 2014 Assessment report of the Global Vaccine Action Plan [Internet]. 2015 [cited 2019 Mar 11]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/SAGE_DoV_GVAP_Assessment_report_2014_English.pdf?ua=1

4. World Health Organizzation (WHO) Regional Office for Europe. European Vaccine Action Plan 2015-2020 Midterm report [Internet]. 2016 [cited 2019 Jul 9]. Available from: http://www.euro.who.int/pubrequest

5. Benes O. Dealing with vaccine shortages: current situation and ongoing activities Impact of shortages and solutions set up by countries Vaccine-preventable Diseases and Immunization VPI/DCE World Health Organization Regional Office for Europe [Internet]. Meeting of the Strategic Advisory Group of Experts on Immunization. 2016 [cited 2019 Jan 27]. Available from: https://www.who.int/immunization/sage/meetings/2016/april/2_Benes_shortages_SAGE_Apr2016.pdf

6. Strategic Advisory Group of Experts (SAGE). Pre-empting and responding to vaccine supply shortages [Internet]. 2016 [cited 2019 Jul 26]. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/.

7. Public Health England. Hepatitis B: vaccine recommendations during supply constraints - GOV.UK [Internet]. 2017 [cited 2019 Jul 31]. Available from: https://www.gov.uk/government/publications/hepatitis-b-vaccine-recommendations-during-supply-constraints

8. European Center for Diseases prevention and Control (ECDC). Rapid risk assessement: Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA [Internet]. 2015 [cited 2019 Jul 28]. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/vaccine-shortage-rapid-risk-assessment-october-2015.pdf

9. European Center for Diseases prevention and Control (ECDC). Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA (first update) [Internet]. 2016 [cited 2019 Jul 28]. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/RRA-shortage-of-aP-containing-vaccines.pdf

10. European Medicines Agency (EMA). Shortages catalogue [Internet]. [cited 2019 Jul 31]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue

11. World Health Organization (WHO). Addressing the global shortage of, and access to, medicines and vaccines [Internet]. 2018 [cited 2019 Feb 27]. Available from: http://www.unsgaccessmeds.org/final-report,

12. The Council of the European Union. COUNCIL RECOMMENDATION of 7 December 2018 on strengthened cooperation against vaccine-preventable diseases [Internet]. 2018 [cited 2019 Jul 31]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018H1228(01)&from=GA

13. Hedman L. Meeting Report: Technical Definitions of Shortages and Stockouts of Medicines and Vaccines [Internet]. 2016 [cited 2019 Jan 15]. Available from: http://www.who.int/about/licensing/copyright_form/en/index.html

14. European Commission. Framework contracts for pandemic influenza vaccines [Internet]. 2019 [cited 2019 Jul 26]. Available from: https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/ev_20190328_memo_en.pdf

15. Heads of Medicines Agencies (HMA). HMA/EMA Joint Task Force on Availability of authorised medicines for human and veterinary use (TF AAM) [Internet]. [cited 2019 Jul 30]. Available from: https://www.hma.eu/522.html

16. European Medicines Agency (EMA). Medicine shortages: EU network takes steps to improve reporting and communication [Internet]. [cited 2019 Jul 8]. Available from: www.ema.europa.eu/contact

17. World Health Organization (WHO). Annex 3 WHO guidelines on variations to a prequalified product [Internet]. [cited 2019 Jul 30]. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1

18. European Medicines Agency (EMA). Guideline on influenza vaccines-submission and procedural requirements [Internet]. 2017 [cited 2019 Jul 30]. Available from: www.ema.europa.eu/contact

19. World Health Organization (WHO), UNICEF. WHO/UNICEF Joint Reporting Process [Internet]. WHO. World Health Organization; 2013 [cited 2019 Jul 30]. Available from: https://www.who.int/immunization/monitoring_surveillance/routine/reporting/reporting/en/

20. World Health Organization (WHO), Market Information for Acces to vaccines (MI4A). Global market study Diphteria and Tetanus-containing vaccines [Internet]. 2019 [cited 2019 Jul 26]. Available from: www.who.int/immunization/diseases/tetanus/WHO_UNICEF_Joint_communique_on_TT_to_Td_Replacement_Final28June2018.pdf

21. Viral Hepatitis Prevention Board (VHPB). Survey on Hepatitis vaccine shortage among VHPB advisors [Internet]. 2018 [cited 2019 Jul 28]. Available from: http://www.vhpb.org/files/html/Meetings_and_publications/Presentations/LISB41.pdf

22. European Center for Disease Prevention and Control (ECDC). Hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men [Internet]. 2017 [cited 2019 Jul 26]. Available from: https://ecdc.europa.eu/sites/portal/files/documents/RRA hep A outbreak EU EEA in MSM third update 28 June 2017_0.pdf

23. Cernuschi T, Malvolti S, Nickels E, Friede M. Bacillus Calmette-Guérin (BCG) vaccine: A global assessment of demand and supply balance. Vaccine [Internet]. 2018 Jan 25 [cited 2019 Mar 6];36(4):498–506. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X17317486

24. du Preez K, Seddon JA, Schaaf HS, Hesseling AC, Starke JR, Osman M, et al. Global shortages of BCG vaccine and tuberculous meningitis in children. Lancet Glob Heal [Internet]. 2019 Jan 1 [cited 2019 Jul 8];7(1):e28–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30554756

25. European Center for Disease prevention and Control (ECDC). Vaccine Scheduler | ECDC [Internet]. [cited 2019 Jul 26]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=14&SelectedCountryIdByDisease=-1

26. Kontturi A, Santiago N, Tebruegge M, Von Both U, Salo E, Ritz N, et al. The impact of Bacille Calmette-Gu erin shortage on immunisation practice and policies in Europe e A Paediatric Tuberculosis Network European Trials Group (ptbnet) survey *. Tuberculosis [Internet]. 2016 [cited 2019 Jul 8];101:125–9. Available from: http://dx.doi.org/10.1016/j.tube.2016.08.005

27. The Economist Intelligence Unit Supported by the Parenteral Drug Association. Medicine and vaccine shortages: What is the role of global regulatory complexity for post approval changes? Econ [Internet]. 2018 [cited 2019 Jul 26]; Available from: http://graphics.eiu.com/upload/topic-pages/medicine-shortages/Medicine-and-vaccine-shortages-EIU.pdf

28. European Medicines Agency (EMA). BCG vaccine (freeze-dried): List of nationally authorised medicinal products [Internet]. [cited 2019 Jul 28]. Available from: www.ema.europa.eu/contact

29. World Health Organizzation (WHO). Global Vaccine Action Plan Monitoring - Secretariat annual report 2018 [Internet]. 2018 [cited 2019 Jul 29]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/web_gvap_secretariat_report_2018.pdf

30. The Economist Intelligence Unit. Addressing medicine shortages in Europe. Econ [Internet]. 2017 [cited 2019 Jul 31]; Available from: http://graphics.eiu.com/upload/topic-pages/medicine-shortages/Addressing-medicine-shortages-in-Europe-EIU.pdf

31. Kanavos P, Seeley L, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium [Internet]. 2009. Available from: http://ec.europa.eu/DocsRoom/documents/7607/attachments/1/translations/en/renditions/pdf

32. World Health Organizzation (WHO). Global Vaccine Action Plan (GVAP) report 2017. Subchapter 5: Stock outs [Internet]. [cited 2019 Jul 28]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/gvap_2017_secretariat_report_stockouts.pdf

33. European Commission. Paper on the obligation of continuous supply to tackle the problem of shortages of medicines [Internet]. 2018 [cited 2019 Jul 31]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159381.pdf

34. Cuddy B, Hansen AB. Improving reporting and monitoring: EU-wide shortage definition and metrics [Internet]. 2018 [cited 2019 Jul 30]. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-improving-reporting-monitoring-eu-wide-shortage-definition-metrics-b-cuddy-hansen_en.pdf

35. European Medicines Agency (EMA). Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA) [Internet]. 2019 [cited 2019 Jul 31]. Available from: www.ema.europa.eu/contact

Appendix 1. Questionnaire

WP6- Task 6.1.
Survey on vaccine procurement, shortages and response at the national and EU/EEA level

Definitions of vaccines shortages and stockouts

In order to have a common understanding of the terms shortage and stockout we report below the definitions provided for these terms by the "WHO Meeting Report: Technical Definitions of Shortages and Stockouts of Medicines and Vaccines", held on 5 October 2016.

Shortage: The supply of medicines, health products, and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas.

Stockout: The complete absence of the medicine, health product or vaccine at the point of service delivery to the patient.

1) General information

Please fill in this form with your personal details

1. Personal information

Country: _____
Name of the Respondent: _____
Affiliation: _____
E-mail _____
Office Telephone N.: _____

2. Can we contact you if we have questions about your responses?

☐ Yes
☐ No

2) Shortage and/or stockouts current and in the last three years.

This section collects information on recent shortages and stockouts at the national and sub- national levels in your country (current and in the last 3 years).

3. Have you experienced any vaccine shortages/stockouts in your country in the last three years? (2016-2018)

☐ Yes
☐ No

If you did not experience any vaccine shortages/stockouts in the last three years, please skip to Section 5 (Question 77)

4. If Yes, for which of the following products? Please fill in the table below with additional details regarding each shortage/stockout

Vaccine	**Shortage? (Yes/No)**	**If Yes, specify at which level (national/ subnational)**	**Stock-out? (Yes/No)**	**If Yes, specify at which level (national/ subnational)**	**Dates? (from MM/YYYY to MM/YYYY/Ongoing)**	**Did the Shortage/Stock-out cause a disruption of immunisation services? (Yes, total interruption of the immunisation programme for the vaccine /Yes, partial interruption or changes to vaccination programmes or schedules/None)**
BCG						
DTaP-IPV-Hib-HepB						
DTaP-IPV/Hib						
DTaP-IPV						
DTaP						
Tdap						
Tdap-IPV						
Td						
Haemophilus Influenzae type B (Hib)						
Measles-Mumps-Rubella (MMR)						
Measles-Mumps-Rubella-Varicella (MMRV)						
Varicella						
Hepatitis B (HBV) (adult)						
Hepatitis B (children)						
Hepatitis A (HAV) (adult)						
Hepatitis A (children)						
HAV+HBV						
Human papilloma virus (HPV)						
Influenza trivalent						
Influenza quadrivalent						
Influenza intranasal (LAIV)						
Meningococcal B						
Meningococcal C						
Meningococcal ACWY						
Pneumococcal 13-valent						
Pneumococcal 10-valent						

Pneumococcal 23-valent						
Rotavirus						
Rabies						
Cholera						
Typhoid fever oral						
Typhoid fever parenteral						
Tick-borne encephalitis						
Yellow fever						
Japanese encephalitis						
Other (to be specified below)						

If you selected "other", please specify which vaccine: _____

3) Details of vaccine shortage/stockout events

This section aims to investigate which factor(s) played a role in each of the shortage/stockout events reported and how your country responded. If your country experienced more than 6 shortage/stockout events, please let us know by adding a comment at the end of Shortage /stockout episode 6 (Question 76).

Shortage/stockout episode 1

5. Please specify vaccine: _____
6. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

☐ Higher than expected demand for the vaccine due to an outbreak
☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
☐ Higher than expected demand for the vaccine due to inaccurate forecasts
☐ Interruption in production/supply due to quality issues
☐ Global shortage
☐ Poor stock management
☐ Lack of resources to purchase the vaccine
☐ Higher than expected demand due to safety concerns regarding other available products
☐ Other, please specify_____

7. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please upload any available documents (see next question) or provide a web link.

_____
_____

8. You can upload any available document here below.

9. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

- ☐ Used available stockpiles of the vaccine
- ☐ Redistributed stockpile of the vaccine among regions or facilities
- ☐ Purchased additional doses of the vaccine from other supplier/manufacturer
- ☐ Imported vaccine not originally authorized in the EU
- ☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
- ☐ Other, please specify: _____

10. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

- ☐ Did not attempt to purchase from other manufacturers
- ☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
- ☐ Competitor manufacturers set inflexible prices
- ☐ Original manufacturer was not obliged to participate in the payment of the new purchase
- ☐ Competitor manufacturers were also experiencing shortages
- ☐ There were few competitor manufacturers so that they were not able to comply with the request
- ☐ There were no competitor manufacturers
- ☐ None of the above
- ☐ Other, please specify: _____

11. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

- ☐ Yes
- ☐ No
- ☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____

_____

12. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

- ☐ Yes
- ☐ No
- ☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____

_____

13. Did the shortage/stockout cause any changes to the national immunisation programme?

- ☐ No
- ☐ Yes

14. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

- ☐ primary immunisation programme (first two years of life)
- ☐ booster immunisation programme
- ☐ adolescent immunisation programme
- ☐ adult immunisation programme
- ☐ travel immunisations
- ☐ other, please specify

_____
_____

15. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____
_____
_____
_____

16. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____
_____
_____
_____

Shortage/stockout episode 2

17. Please specify vaccine: _____

18. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

- ☐ Higher than expected demand for the vaccine due to an outbreak
- ☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
- ☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
- ☐ Higher than expected demand for the vaccine due to inaccurate forecasts
- ☐ Interruption in production/supply due to quality issues
- ☐ Global shortage
- ☐ Poor stock management
- ☐ Lack of resources to purchase the vaccine
- ☐ Higher than expected demand due to safety concerns regarding other available products
- ☐ Other, please specify_____

19. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please

upload any available documents (see next question) or provide a web link.

_____

_____

20. You can upload any available document here below.

21. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

- ☐ Used available stockpiles of the vaccine
- ☐ Redistributed stockpile of the vaccine among regions or facilities
- ☐ Purchased additional doses of the vaccine from other supplier/manufacturer
- ☐ Imported vaccine not originally authorized in the EU
- ☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
- ☐ Other, please specify: _____

22. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

- ☐ Did not attempt to purchase from other manufacturers
- ☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
- ☐ Competitor manufacturers set inflexible prices
- ☐ Original manufacturer was not obliged to participate in the payment of the new purchase
- ☐ Competitor manufacturers were also experiencing shortages
- ☐ There were few competitor manufacturers so that they were not able to comply with the request
- ☐ There were no competitor manufacturers
- ☐ None of the above
- ☐ Other, please specify: _____

23. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

- ☐ Yes
- ☐ No
- ☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____

_____

24. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

- ☐ Yes

☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____
_____

25. Did the shortage/stockout cause any changes to the national immunisation programme?

☐ No
☐ Yes

26. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

☐ primary immunisation programme (first two years of life)
☐ booster immunisation programme
☐ adolescent immunisation programme
☐ adult immunisation programme
☐ travel immunisations
☐ other, please specify

_____
_____

27. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____
_____
_____
_____
_____
_____
_____
_____

28. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____
_____
_____
_____
_____
_____
_____
_____

Shortage/stockout episode 3

29. Please specify vaccine: _____

30. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

- ☐ Higher than expected demand for the vaccine due to an outbreak
- ☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
- ☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
- ☐ Higher than expected demand for the vaccine due to inaccurate forecasts
- ☐ Interruption in production/supply due to quality issues
- ☐ Global shortage
- ☐ Poor stock management
- ☐ Lack of resources to purchase the vaccine
- ☐ Higher than expected demand due to safety concerns regarding other available products
- ☐ Other, please specify_____

31. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please upload any available documents (see next question) or provide a web link.

_____
_____

32. You can upload any available document here below.

33. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

- ☐ Used available stockpiles of the vaccine
- ☐ Redistributed stockpile of the vaccine among regions or facilities
- ☐ Purchased additional doses of the vaccine from other supplier/manufacturer
- ☐ Imported vaccine not originally authorized in the EU
- ☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
- ☐ Other, please specify: _____

34. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

- ☐ Did not attempt to purchase from other manufacturers
- ☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
- ☐ Competitor manufacturers set inflexible prices
- ☐ Original manufacturer was not obliged to participate in the payment of the new purchase
- ☐ Competitor manufacturers were also experiencing shortages

☐ There were few competitor manufacturers so that they were not able to comply with the request
☐ There were no competitor manufacturers
☐ None of the above
☐ Other, please specify: _____

35. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____
_____

36. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____
_____

37. Did the shortage/stockout cause any changes to the national immunisation programme?

☐ No
☐ Yes

38. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

☐ primary immunisation programme (first two years of life)
☐ booster immunisation programme
☐ adolescent immunisation programme
☐ adult immunisation programme
☐ travel immunisations
☐ other, please specify

_____
_____

39. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____
_____
_____
_____
_____
_____
_____
_____

40. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____
_____
_____
_____
_____
_____
_____
_____

Shortage/stockout episode 4

41. Please specify vaccine:_____

42. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

- ☐ Higher than expected demand for the vaccine due to an outbreak
- ☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
- ☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
- ☐ Higher than expected demand for the vaccine due to inaccurate forecasts
- ☐ Interruption in production/supply due to quality issues
- ☐ Global shortage
- ☐ Poor stock management
- ☐ Lack of resources to purchase the vaccine
- ☐ Higher than expected demand due to safety concerns regarding other available products
- ☐ Other, please specify_____

43. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please upload any available documents (see next question) or provide a web link.

_____
_____

44. You can upload any available document here below.

45. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

☐ Used available stockpiles of the vaccine
☐ Redistributed stockpile of the vaccine among regions or facilities
☐ Purchased additional doses of the vaccine from other supplier/manufacturer
☐ Imported vaccine not originally authorized in the EU
☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
☐ Other, please specify: _____

46. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

☐ Did not attempt to purchase from other manufacturers
☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
☐ Competitor manufacturers set inflexible prices
☐ Original manufacturer was not obliged to participate in the payment of the new purchase
☐ Competitor manufacturers were also experiencing shortages
☐ There were few competitor manufacturers so that they were not able to comply with the request
☐ There were no competitor manufacturers
☐ None of the above
☐ Other, please specify: _____

47. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:
_____
_____

48. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:
_____
_____

49. Did the shortage/stockout cause any changes to the national immunisation programme?

☐ No
☐ Yes

50. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

☐ primary immunisation programme (first two years of life)
☐ booster immunisation programme
☐ adolescent immunisation programme
☐ adult immunisation programme
☐ travel immunisations
☐ other, please specify

_____
_____

51. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____
_____
_____
_____
_____
_____
_____
_____

52. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____
_____
_____
_____
_____
_____
_____
_____

Shortage/stockout episode 5

53. Please specify vaccine: _____

54. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

☐ Higher than expected demand for the vaccine due to an outbreak

☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
☐ Higher than expected demand for the vaccine due to inaccurate forecasts
☐ Interruption in production/supply due to quality issues
☐ Global shortage
☐ Poor stock management
☐ Lack of resources to purchase the vaccine
☐ Higher than expected demand due to safety concerns regarding other available products
☐ Other, please specify_____

55. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please upload any available documents (see next question) or provide a web link.

_____
_____

56. You can upload any available document here below.

57. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

☐ Used available stockpiles of the vaccine
☐ Redistributed stockpile of the vaccine among regions or facilities
☐ Purchased additional doses of the vaccine from other supplier/manufacturer
☐ Imported vaccine not originally authorized in the EU
☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
☐ Other, please specify: _____

58. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

☐ Did not attempt to purchase from other manufacturers
☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
☐ Competitor manufacturers set inflexible prices
☐ Original manufacturer was not obliged to participate in the payment of the new purchase
☐ Competitor manufacturers were also experiencing shortages
☐ There were few competitor manufacturers so that they were not able to comply with the request
☐ There were no competitor manufacturers
☐ None of the above
☐ Other, please specify: _____

59. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____
_____

60. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:

_____
_____

61. Did the shortage/stockout cause any changes to the national immunisation programme?

☐ No
☐ Yes

62. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

☐ primary immunisation programme (first two years of life)
☐ booster immunisation programme
☐ adolescent immunisation programme
☐ adult immunisation programme
☐ travel immunisations
☐ other, please specify

_____
_____

63. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____
_____
_____
_____
_____
_____
_____
_____

64. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____
_____
_____
_____
_____
_____
_____
_____

Shortage/stockout episode 6

65. Please specify vaccine: _____

66. Which factors played a role in the shortage? (more than one response is possible, click all that apply)

☐ Higher than expected demand for the vaccine due to an outbreak
☐ Higher than expected demand for the vaccine due to changes to the vaccine schedule
☐ Higher than expected demand for the vaccine due to changes to targeted groups (e.g. new targeted groups, widening of age cohorts targeted)
☐ Higher than expected demand for the vaccine due to inaccurate forecasts
☐ Interruption in production/supply due to quality issues
☐ Global shortage
☐ Poor stock management
☐ Lack of resources to purchase the vaccine
☐ Higher than expected demand due to safety concerns regarding other available products
☐ Other, please specify_____

67. Have any reports/journal articles/risk assessments (national or EU) /recommendations been published regarding the shortage/stockout, including the response to the shortage? If Yes, please upload any available documents (see next question) or provide a web link.

_____
_____

68. You can upload any available document here below.

69. What actions, if any, did you undertake to address the vaccine shortage/stockout? (more than one response is possible)

☐ Used available stockpiles of the vaccine
☐ Redistributed stockpile of the vaccine among regions or facilities
☐ Purchased additional doses of the vaccine from other supplier/manufacturer
☐ Imported vaccine not originally authorized in the EU

☐ Asked European institutions (e.g. ECDC) or other international organizations (e.g. WHO) for technical assistance
☐ Other, please specify: _____

70. If you attempted to purchase additional doses of the vaccine from other suppliers/manufacturers, which, if any, of the following problems did you encounter? (one or more replies are possible)

☐ Did not attempt to purchase from other manufacturers
☐ Resources were limited (e.g. because of a fixed budget) and we could not afford other purchases
☐ Competitor manufacturers set inflexible prices
☐ Original manufacturer was not obliged to participate in the payment of the new purchase
☐ Competitor manufacturers were also experiencing shortages
☐ There were few competitor manufacturers so that they were not able to comply with the request
☐ There were no competitor manufacturers
☐ None of the above
☐ Other, please specify: _____

71. If you attempted to import doses of the vaccine from other Member States, did you encounter any regulatory obstacles that made importation difficult or impossible?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:
_____
_____

72. If you attempted to import vaccines not authorized in the EU, did you encounter any regulatory or other obstacles?

☐ Yes
☐ No
☐ Not applicable, did not attempt to import vaccine

If Yes, please specify what problems occurred:
_____
_____

73. Did the shortage/stockout cause any changes to the national immunisation programme?

☐ No
☐ Yes

74. If yes, please specify for which of the following immunisation programmes (more than one reply is possible)

- ☐ primary immunisation programme (first two years of life)
- ☐ booster immunisation programme
- ☐ adolescent immunisation programme
- ☐ adult immunisation programme
- ☐ travel immunisations
- ☐ other, please specify

_____

_____

75. If yes, please specify in detail what adjustments were made (e.g. use of alternative vaccination schedules or of alternative vaccines or formulations, timing of doses, boosting intervals, age of dose administration, temporary suspension of immunisation programme, prioritization of specific groups to whom to offer the vaccine)

_____

_____

_____

_____

_____

_____

_____

_____

76. Please, use the space below if you wish to add any other relevant information regarding actions undertaken and consequences of the shortage.

_____

_____

_____

_____

_____

_____

_____

_____

4) Vaccine supply, procurement, purchase and stockpiling

77. At what level is vaccine procurement carried out in your country? (more than one reply is possible)

- ☐ National level (public sector)
- ☐ Subnational level (public sector)
- ☐ Private sector, specify proportion of total vaccinations _____

** Private sector defined as "comprising all health care providers who exist outside of the public sector, whether their aim is for philanthropic or commercial purpose" (WHO, 28 November 2017)*

78. Which purchase mechanism/s* does your country use?

- ☐ Competitive bidding
- ☐ Request for quotation

☐ Sole-source procurement
☐ Other, please specify_____

*please refer to WHO webpage "Procurement mechanisms and systems" for definitions at: https://www.who.int/immunisation/programmes_systems/procurement/mechanisms_systems/pooled_procurement/en/

79. For vaccines that are produced by more than one manufacturer, does your country purchase the vaccines from a single manufacturer or from all manufacturers that produce them?

☐ Yes, vaccines are always purchased from more than one manufacture
☐ Yes, at least some vaccines are purchased from more than one manufacture
☐ No, vaccines are always purchased from a single manufacturer

80. If "Yes", what mechanism, if any, is in place in your country to assure that vaccines are not purchased from a single manufacturer??

☐ Purchase is made at subnational level by individual regions/provinces/districts
☐ Purchase is made at national level but it is required that a proportion of vaccines be purchased from each manufacturer that produces the vaccine
☐ Other, please specify
_____
_____
_____
_____

81. Are vaccine needs routinely estimated at:

☐ National level (government agency)
☐ Subnational level
☐ Private sector (please specify)
☐ Other (please specify)

82. What time period of estimation is used?

☐ < 1 year
☐ 1 year
☐ 2-3 years
☐ 4-5 years
☐ >5 years

83. How are vaccine needs estimated in your country?

_____
_____

84. Does your country produce its own supply of vaccine? (therefore, not relying solely on pharmaceutical companies)

☐ No
☐ Yes, specify which vaccine(s): _____

85. Does your country have any joint procurement mechanisms with other countries?

☐ No
☐ Yes, specify for which vaccines and with which countries
_____
_____

86. Are there laws in your country related to the systems of purchasing vaccines?

☐ No
☐ Yes, please specify _____

87. Please upload any available document:

88. Does your country have an immunisation supply plan (i.e. a plan defining strategy to assure a stable and adequate vaccine supply for the immunisation programme and for public health preparedness, in order to avoid shortages).

☐ Yes, please specify and if possible, provide a web link of available documents or upload any available document (Q89) _____
☐ No
☐ No, but we have a national vaccine plan that addresses supply issues

89. Please upload document or provide web link of available documents:
_____

90. In case of shortages/stockouts, are procedures or recommendations (e.g. reporting procedures, recommendations regarding the use of alternative vaccines or vaccination schedules) available in your country to address the shortages/stockouts?

☐ No
☐ Yes, please provide details and if possible, provide a web link of available documents or upload any available document (Q91)_____

91. Please upload document or provide web link of available documents:
_____

92. At the procurement level, is there a dedicated vaccine supply chain manager?

☐ No
☐ Yes

93. Does your country have a stockpile of vaccines?

☐ Yes for all vaccines
☐ Yes only for some vaccines
☐ No

94. If yes, please specify which vaccines
_____

95. If yes, at what level?

- ☐ National (central) level
- ☐ Subnational level

96. If yes, the stockpile is equivalent to how many months of supply?

- ☐ <3 months
- ☐ 3-6 months
- ☐ 7-12 months
- ☐ >12 months

97. In your country, is it possible to sign multi-year (>2 years) contracts with vaccine manufacturers?

- ☐ No, only annual contracts
- ☐ No, only biannual contracts
- ☐ Yes but only for some vaccines
- ☐ Yes, for all vaccines

98. Would you be in favour of a European centralized procurement system for vaccines?

- ☐ Yes, for all vaccines
- ☐ Yes, only for certain vaccines
- ☐ Yes, only in certain conditions (e.g. pandemic)
- ☐ No
- ☐ Don't Know

99. Would you be in favour of a European centralized stockpile of vaccine?

- ☐ Yes, for all vaccines
- ☐ Yes, only for certain vaccines
- ☐ Yes, only in certain conditions (e.g. pandemic)
- ☐ No
- ☐ Don't know

100. Would you be in favour of a data warehouse for EU-wide sharing of vaccine supply and demand data among dedicated stakeholders?

- ☐ Yes
- ☐ No
- ☐ Don't know

101. Please, use this space if you wish to add any other relevant information regarding aspects of vaccine supply, procurement, purchase and stockpiling

_____
_____
_____
_____

5) Communication

This section aims to investigate communication issues between public health authorities and manufacturers

102. For which of the following situations does your country regularly communicate with vaccine manufacturers?

- ☐ Planned changes of targeted groups
- ☐ Planned changes of vaccination schedule
- ☐ Planned introduction of new compulsory/recommended vaccines
- ☐ Disease outbreaks
- ☐ No communication
- ☐ Other, please specify _____

103. In your country, does legislation exist requiring that above changes are communicated to manufacturers in advance?

- ☐ Yes
- ☐ No

104. In case of shortage/stockout, who do you inform?

- ☐ European authorities
- ☐ National authorities (if subnational shortage)
- ☐ Other, specify _____

105. Please describe briefly the above answer

_____
_____
_____

106. Please, use this space if you wish to add any other relevant information regarding "Communication"

_____
_____
_____

6) Shortages/stockouts of other biological products

107. Have you experienced any shortages of other biological products (e.g. measles Immunoglobulins or diphtheria antitoxin) in your country in the last three years?

- ☐ Yes
- ☐ No

108. If yes, for which of the following products and for how long?

Vaccine	Did you experience any shortage? (Yes/No)	Did you experience any stockout? (Yes/No)	If Yes, specify at which level (national/subnational)	Dates? (from MM/YYYY to MM/YYYY or Ongoing)
Hepatitis B IG				
Varicella-zoster IG				
Rabies IG				
Tetanus IG				
Human normal IG				
Diphtheria antitoxin				
Other, please specify				

*IG= Immunoglobulins

109. If you experienced immunoglobulins or antitoxin serum shortage, please describe briefly main causes and issues.

_____
_____
_____

110. How did you solve the above issue/s?

_____
_____
_____
_____

111. Are these products available in your country?

Vaccine	Is it available in your country? (Yes/No)
Hepatitis B IG	
Varicella-zoster IG	
Rabies IG	
Tetanus IG	
Human normal IG	
Diphtheria antitoxin	
Other, specify	

112. Some of the above-mentioned products are potentially lifesaving treatment if delivered promptly. Nevertheless, some countries reported substantial delays and issues when trying to import some of these products e.g. diphtheria antitoxin. Would you be in favour of a European central stockpile for these products?

☐ Yes, for all
☐ Yes, but only for some of them (Specify: _____)
☐ No

113. Please, use this space if you wish to add any other relevant information regarding shortages/stockouts of other biological products.

_____
_____
_____