



Are vaccine shortages a relevant public health issue in Europe? Results from a survey conducted in the framework of the EU Joint Action on Vaccination



Antonietta Filia^{a,*}, Maria Cristina Rota^a, Adriano Grossi^{a,b}, Domenico Martinelli^{c,d}, Rosa Prato^{c,d}, Giovanni Rezza^a

^a Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

^b Section of Hygiene and Preventive Medicine, Università Cattolica del Sacro Cuore, Rome, Italy

^c Department of Medical and Surgical Sciences, University of Foggia, Italy

^d Department of Hygiene, Policlinico Riuniti University Hospital of Foggia, Italy

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ABSTRACT

National immunisation programmes require an adequate supply of vaccines to function properly but many countries, globally and in Europe, have reported vaccine shortages. A comprehensive view of vaccine shortages and stockouts in the EU/EEA is missing in the published literature.

This study was conducted in the framework of the European Joint Action on Vaccination (EU-JAV). Twenty-eight countries, including 20 EU-JAV consortium member states and an additional 8 EU/EEA countries, were invited to participate in a survey aimed at collecting information on vaccine shortages and stock-outs experienced from 2016 to 2019, their main causes, actions taken, and other aspects of vaccine supply. Twenty-one countries completed the survey (response rate 75%), of which 19 reported at least one shortage/stock-out event. Overall, 115 events were reported, 28 of which led to a change in the national immunisation programme. The most frequently involved vaccines were DT- and dT-containing combination vaccines, hepatitis B, hepatitis A, and BCG vaccines. The median duration of shortages/stock-outs was five months (range <1 month–39 months). Interruption in supply and global shortage were the most frequently indicated causes. Only about half of countries reported having an immunization supply chain improvement plan. Similarly, only about half of countries had recommendations or procedures in place to address shortages/stockouts. The survey also identified the occurrence of shortages/stockouts of other biological products (e.g. diphtheria antitoxin in 12 countries). Public health strategies to assure a stable and adequate vaccine supply for immunization programmes require coordinated actions from all stakeholders, harmonized definitions, strengthening of reporting and monitoring systems, the presence of an immunization supply chain improvement plan in all countries, and procedures or recommendations in place regarding the use of alternative vaccines or vaccination schedules in case of shortages/stockouts.

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1. Introduction

Vaccines save millions of lives globally every year and are considered as one of the most successful and cost-effective public health interventions ever introduced. However, vaccination programmes depend on an adequate supply of vaccines, and vaccine shortages have been reported globally and in the European Region [1–5]. Vaccines shortages are a serious public health issue as they

can lead to missed opportunities for vaccination, low or declining coverage rates and a greater risk of occurrence of deadly vaccine-preventable diseases.

Since 1998, the World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF) jointly collect, through the Joint Reporting Form on Immunization (JRF), various global immunization data, including vaccine stockout performance indicators, from 194 Member States (MS) [6]. The JRF focuses on vaccine stockout events that occurred in the preceding year and that lasted at least one month at national level. In 2016, 38% of WHO MS, representing 34% of the world's birth cohort, reported stockouts for at least one vaccine and for an average

* Corresponding author at: Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

E-mail address: antonietta.filia@iss.it (A. Filia).

duration of 51 days. Stockouts occurred in countries of all income levels, including 20% of high income countries, although middle income countries were the most affected; 23% of stockouts occurred in European countries [3]. Since 2019, the WHO publishes an annual Global Vaccine Market Report which includes data on JRF stockout indicators for the previous year [7,8]. In 2018, 69 countries worldwide reported a national stockout of one or more vaccines (46% of 149 total reporting countries) [7].

In the WHO European Region, the most recent published data on vaccine stockouts, based on JRF reports, indicates that in 2017, 20 of 53 MS reported 49 stockouts, either at national or sub-national levels, with a duration ranging from one to 12 months. Vaccine stockouts contributed to low or declining coverage rates in two MS [4]. More recently, another WHO EURO document assesses the magnitude of shortages of essential medicines (including vaccines) that occurred in 2018, but these data are aggregated and not limited to vaccines [9]. A comprehensive view of vaccine shortages and stockouts in the EU/EEA is missing in the published literature.

Prevention of vaccine shortages is a top priority globally and in Europe. The need to ensure a continuous uninterrupted availability of vaccines was highlighted during the 68th World Health Assembly (WHA) in May 2015, during which MS 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” [10]. In 2016, the WHA adopted resolution 69.25 to address the global shortage of medicines and vaccines [11,12,13].

The European Joint Action on Vaccination (EU-JAV) (www.eu-jav.com) is a consortium of 20 European partners (18 EU/EEA MS and 2 non-EU countries: Bosnia-Herzegovina and Serbia), coordinated by the French National Institute of Health and Medical Research (Inserm), with the support of the French Ministry of Health and Solidarities and funded by the European Commission. The consortium aims to strengthen cooperation between consortium member countries against vaccine-preventable diseases. One of the aims of the project is to strengthen vaccine supply and preparedness in these countries. In this context we aimed to describe recent shortages and stockouts of vaccines in JAV countries, the main causes leading to the shortages and stockouts, and how these were managed. We also aimed to explore other relevant information not included in published WHO reports, including procurement methods used and MS opinions on centralized procurement and stockpiling. Finally, we collected information on shortages and stockouts of other biological products such as disease-specific immunoglobulins (IG) or serum antitoxins, which are also not included in the WHO reports.

2. Methods

2.1. Study

A survey was conducted from February to May 2019, via the online tool SurveyMonkey® (<https://www.surveymonkey.com/>), among persons in charge of the national or subnational immunization programme(s) or of vaccine supply/procurement in EU/EEA and consortium MS of the EU-JAV, to collect information on vaccine shortages and stockouts from 1 January 2016 to 31 May 2019 and responses at national and European levels.

Twenty-eight countries were invited to participate, including all 20 EU-JAV partners and eight EU/EEA countries not participating in the EU-JAV consortium. We contacted by email the main contact persons of all EU-JAV countries and the nominated representatives of the Member States Committee for non-EU-JAV countries and asked them to provide us with the contact details of the most

relevant organisation or person in charge of vaccine supply at national level. We asked for a single completed questionnaire for each country.

2.2. Questionnaire

The questionnaire was developed following a review of the literature on vaccine shortages and was pilot-tested for clarity and completeness by four EU-JAV consortium partners. It consisted in multiple-choice and open-ended questions, divided into six sections: 1) contact details, 2) vaccine shortages and stockouts that occurred from 2016 to 2018 and those ongoing at the time of survey completion (May 2019); information on the types of vaccines affected, the administrative level (national, subnational) in which these had occurred, the duration of each event, and any disruption of immunization services, 3) details of each vaccine shortage/stockout event, including causal factors, actions taken (use of or redistribution of available stockpiles, purchase/importation of additional doses), regulatory and other difficulties/obstacles encountered in attempting to import doses from other MS, and changes to the national immunization programme caused by the shortage/stockout, 4) vaccine procurement and purchase mechanisms, existence of vaccine stockpiling, opinions on centralized procurement systems and stockpiles, and on creation of a data warehouse for EU-wide sharing of vaccine supply and demand data among dedicated stakeholders, 5) communication between public health authorities, vaccine manufacturers, on planned changes of targeted groups and of vaccination schedules, introduction of new compulsory/recommended vaccines, and occurrence of disease outbreaks, and 6) shortages/stockouts of other biological products such as disease-specific immunoglobulins (IG) or serum antitoxins.

2.3. Definitions

For the purposes of the study, we used the draft definitions of shortages and stockouts developed by the WHO in 2016 [13–14]. A “shortage” refers to a situation where the supply of vaccines identified as essential by the health system is considered 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. The definitions were used to better determine the entity of the problem of vaccine supply in EU/EEA, by quantifying both shortages and stockouts, but not to evaluate separately shortages and stockouts.

2.4. Data management and analysis

Data was collected into a secure database, stored at the Istituto Superiore di Sanità and made accessible only to principal investigators. A descriptive analysis was performed using Excel Microsoft for tables and graphs.

2.5. Ethical statement

An attached information sheet informed participants of the objectives of the survey and the way any personal data (contact details) were handled. 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.

3. Results

Between February and May 2019, 21 of 28 invited countries completed the survey (response rate 75%): nineteen EU/EEA countries, Bosnia-Herzegovina and Serbia. Nineteen of 21 participating countries reported at least one shortage/stockout event (all except Bulgaria and Estonia). Overall, 115 events were reported. The number of new events per year is shown in Fig. 1; for 22 episodes (19.1%), the year of onset was not known

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 reported two events or less in the specified observation period (Fig. 2); six countries reported seven or more episodes, together accounting for over half of the total number of shortages/stockouts (66/115; 57.4%).

Table 1 shows the number and type of vaccine shortages and stockouts by country, from 2016 to 2019. The majority of reported events were shortages (67.0%; n = 77/115), while the remaining 33.0% (n = 38/115) involved a stockout.

The most frequently reported shortages/stockouts were those involving Diphtheria-Tetanus (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 Bacillus Calmette-Guérin (BCG) vaccines (n = 11, 9.6%; 11 countries). Rabies, Pneumococcal Polysaccharide vaccine (PPSV23), Measles-Mumps-Rubella (MMR) and Human Papillomavirus (HPV) vaccines together accounted for most of the remaining shortages/stockouts.

The shortage/stockout events occurred at the national level in 101 (89.4%) of 113 events for which the information was available, and at subnational level in 12 events (10.6%).

Duration of shortages/stockouts was reported for 93 out of 115 episodes (80.9%). The median duration was 5 months (IQR: 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). Eighteen shortage/stockout episodes (19.4%) lasted more than two years; these involved BCG and DT-containing vaccines. At the time of survey completion, there were ongoing shortages/stockouts in six countries.

In 28 of 91 shortage/stockout events for which the information was provided (30.8%), these led to some temporary changes to the country’s national immunization programmes, including the primary and booster immunization programmes, immunization of high risk groups, immunization of healthcare workers, and travel immunizations. Reported changes included the use of alternative schedules or vaccine formulations, changes to the timing of doses or boosters, prioritisation of specific groups, and temporary

suspension of travel immunizations (yellow fever and rabies vaccination).

3.1. Reported causes of shortages/stockouts

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 or targeted groups, inaccurate forecasts, or due to occurrence of an outbreak/other reasons accounted respectively for 7.0%, 4.3% and 4.3% of events (Fig. 3).

Global shortage was reported by 13 countries and played a role in shortage/stockout events of BCG vaccine, DT-containing vaccines, hepatitis A and B vaccines (especially the adult formulation) and rabies vaccine. Interruption in production and supply was frequently indicated as a factor leading to shortages/stockouts of BCG, DT-containing vaccines, and other vaccines.

Other factors, reported in 13.9% of shortages/stockouts (Fig. 3), included delay of vaccine delivery (4.3%), lack of suppliers (4.3%), and in a few cases, issues at the procurement level, in terms of delays, legislation, or lack of reimbursement. Regarding lack of suppliers, 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).

3.2. Actions taken to address vaccine shortages/stockouts

As shown in Table 2, the most frequent action undertaken to address vaccine shortage/stockout 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). In 20 episodes, it was necessary to redistribute stock doses among regions and facilities. Finally, European institutions (e.g. ECDC) or other international organizations (e.g. WHO) were contacted for technical assistance only in five shortages/stockouts in four countries.

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

Nine of 13 countries who responded to this question reported some issues in purchasing additional 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. Some countries reported that there were

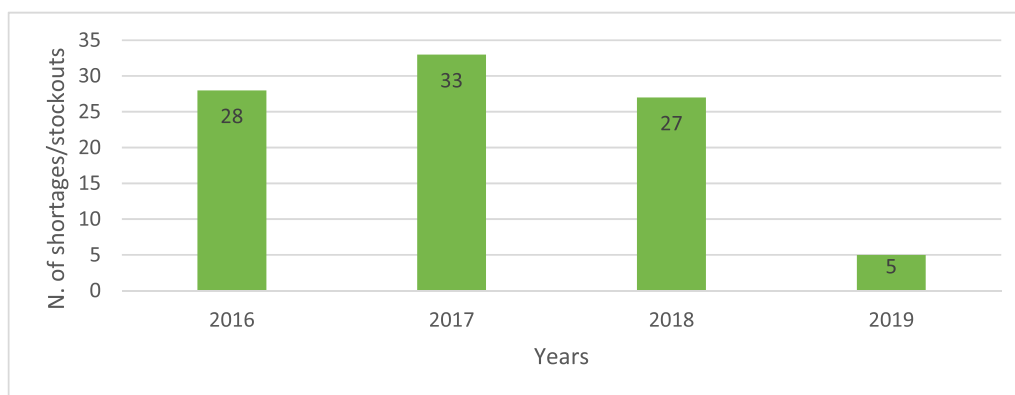


Fig. 1. Vaccine shortage/stockout events by year of onset, EU-JAV and other EU/EEA countries, January 2016–May 2019.

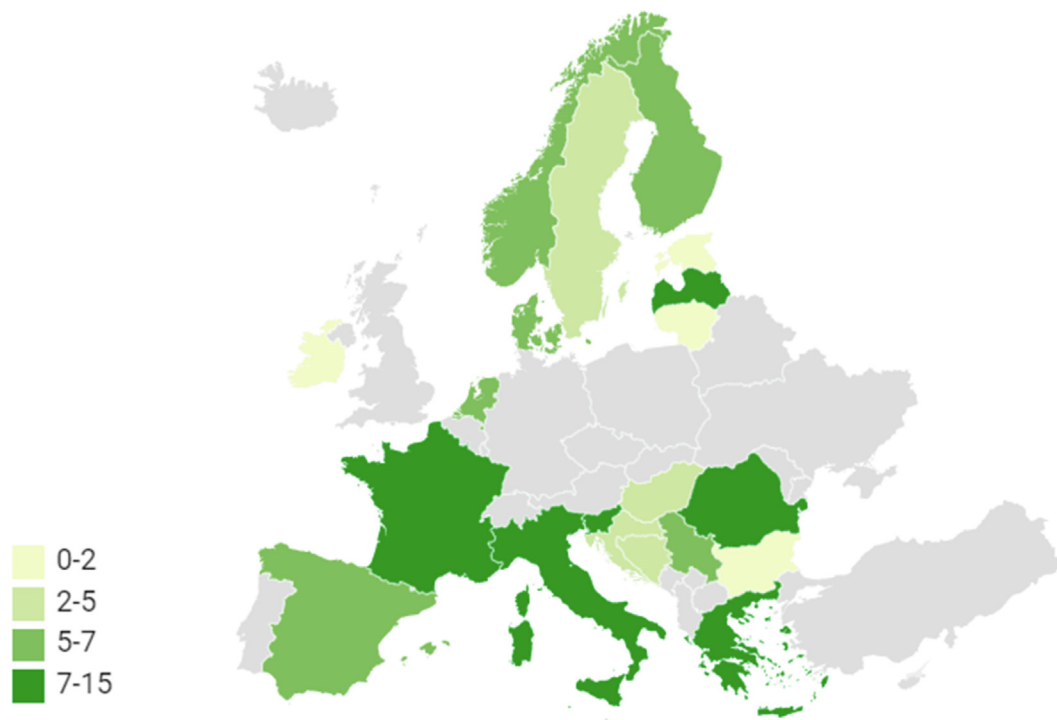


Fig. 2. Number of vaccines shortages and stock-outs in EU JAV and other EU/EEA countries, 2016–2019.

either few competitor manufacturers (and these were not able to comply with the request) or no competitors in the EU.

Regarding importation from other MS, this was done by 15 countries, for 35 shortages/stockouts. For 13 of 35 shortages/stockouts, respondents stated that they encountered some specific problems, including that other countries were also experiencing shortages/stockouts so that they could not provide them with additional doses, international regulatory aspects regarding the payment of vaccine purchased from other countries (in particular from wholesalers), the time needed for the tender of additional doses purchased from another source, inflexibility of national legislation, quality approval, and issues with the packaging language. Several problems were described regarding importation of vaccines not authorised in the EU.

3.4. Vaccine procurement and purchase mechanisms

Thirteen countries reported that they procure vaccines at national level by the public sector. In the remaining countries, vaccines are procured either exclusively at subnational level (one country) or entirely by the private sector (one country). Six countries procure vaccines at more than one level (national and subnational levels, public and private sector levels).

The most frequently reported purchase mechanism is one based on competitive bidding, used by 19 countries. Three of 19 countries reported having more than one purchase mechanism (including single-source procurement and request for quotation). The remaining countries use other mechanisms. Thirteen countries purchased all or at least some vaccines from more than one manufacturer. Fourteen countries report using multiyear contracts for all vaccines.

3.5. Stockpiles

Available national stockpiles were used in 31 shortages/stockouts in 12 countries. This measure was used mainly in the case

of DT-containing vaccines ($n = 14$), but also played a role with 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 (Hepatitis A + B, HPV, Tick-borne encephalitis). Finally, nine countries reported a redistribution of stockpiles of the vaccine among regions or facilities.

3.6. Immunization supply plan, procedures to address shortages, supply chain manager

Five countries reported having an immunization supply plan although this is not always available as a specific document. Of sixteen countries who do not have an immunization plan, seven address supply issues in their national vaccination plan (Table 3).

Thirteen of 21 countries (62%) reported having some type of procedure or recommendations in place, regarding the use of alternative vaccines or vaccination schedules to address the vaccine shortages/stockouts.

Thirteen countries, 68% (of which 12 procure vaccines at national level) reported that in their country there is a dedicated supply chain manager while six countries stated that this figure does not exist in their country. Two countries did not respond to the question.

3.7. Communication

Participants were asked in which of a listed set of situations having the potential to increase vaccine demand do their country's public health authorities regularly communicate with vaccine manufacturers. Eighteen of 21 (86%) respondents indicated that they regularly inform manufacturers about any planned introduction of new compulsory/recommended vaccines, 17 (81%) communicate planned changes to the vaccination schedule, 14 (67%) about occurrence of disease outbreaks and 13 (62%) about planned changes of targeted groups. Two countries reported not regularly communicating with manufacturers. None of the participants

Table 1
Vaccine shortages and stockouts, EU-JAV and other EU/EEA countries, January 2016– May 2019.

Country	N. of shortages/stockouts	BCG	Cholera	DT-Containing*	HepA (adults)	HepA (children)	HepB (adults)	HepB (children)	HepA + HepB	Hib	HPV	Influenza 3 V	Influenza 4 V	Men ACWY	Men B	Men C	MMR	MMRV	PVC 10	PPSV 23	Rabies	Rotavirus	TBE	Varicella	Yellow fever	Others**
Italy	15			X	X	X	X	X	X	X							X	X			X					
Greece	14	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			X					
Latvia	8	X	X	X	X	X	X	X	X	X							X	X			X					
Romania	8			X	X	X	X	X	X	X							X	X			X					
Denmark	7			X	X	X	X	X	X	X							X	X			X					
Malta	6			X	X	X	X	X	X	X							X	X			X					
Spain	6	X	X	X	X	X	X	X	X	X							X	X			X					
Norway	5	X	X	X	X	X	X	X	X	X							X	X			X					
Netherlands	5			X	X	X	X	X	X	X							X	X			X					
Finland	5	X	X	X	X	X	X	X	X	X							X	X			X					
Croatia	3	X	X	X	X	X	X	X	X	X							X	X			X					
Bosnia HG	2	X	X	X	X	X	X	X	X	X							X	X			X					
Hungary	2			X	X	X	X	X	X	X							X	X			X					
Sweden***	2			X	X	X	X	X	X	X							X	X			X					
Ireland	1			X	X	X	X	X	X	X							X	X			X					
Lithuania	1			X	X	X	X	X	X	X							X	X			X					
Bulgaria	0																									
Estonia	0																									
Total	115	11	1	30	7	4	12	6	3	1	4	2	2	2	1	1	5	2	1	6	7	1	2	1	2	1

*DT-containing vaccines include: DtaP, DT-IPV, DTaP-IPV, DTaP-IPV-Hib, DTaP-IPV-Hib-HepB, Td, Tdap

**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.

reported having legislation in their country requiring that the above changes be communicated to marketing authorization holders (MAH) in advance.

We also asked participants about institutions that are usually informed in case of vaccine shortages. Nineteen stated that national authorities (e.g. Ministry of Health) are informed in case of regional or local procurement. Among the 19 countries, two reported also informing European institutions of the shortages/stockouts, and two reported informing international organizations such as WHO or UNICEF.

3.8. Opinions on European centralized procurement of vaccines, stockpiles, and EU-wide sharing of vaccine supply and demand data

Five respondents stated that they are in favour of a European centralized procurement system for all vaccines, four only for some vaccines or specific conditions (e.g. pandemic influenza vaccine). The remaining participants either did not have a specific opinion (seven countries) or disagreed with the proposal (two countries).

Twelve participants were in favour of a European centralized stockpile of vaccines (seven for all vaccines, five only for certain vaccines), three were against. Of the remaining respondents, five did not express any preference and two did not respond.

Eleven countries were in favour of developing a data warehouse for EU-wide sharing of vaccine supply and demand data among dedicated stakeholders, while three disagreed with the proposal. The remaining participants either did not express a preference or did not respond.

3.9. Shortages/stockouts of other biological products

Overall, 25 shortage or stockout episodes of other biological products were reported by 17 countries. The most frequently reported event involved diphtheria antitoxin, reported by 12 countries (Table 3). Duration of shortages/stockouts varied by product and ranged from two months (Human Normal IG) to 38 months (diphtheria antitoxin). Eight shortages/stockouts of biological products were still ongoing at the time of survey completion, of which six involved diphtheria antitoxin and two human normal IG. Rabies IG was reported to be unavailable in four countries.

4. Discussion

This article describes the vaccine supply situation in EU/EEA countries from 2016 to 2019, and confirms that vaccine shortages and stockouts are common events in EU/EEA. Overall, 19 out of 21 participating countries experienced 115 shortage/stockout events in the study period, of which about one third were stockouts. It is important to note that the survey was conducted before the COVID-19 pandemic, therefore COVID-19 vaccines are not considered.

Shortages reported in our study involved either a single manufacturer or all manufacturers producing a specific vaccine and did not necessarily lead to stockouts, nor affect vaccination delivery. A country experiencing a shortage from one manufacturer may have succeeded in using available stockpiles or purchasing vaccines from other suppliers and in so doing, avoided immunization service disruptions even if the shortage was still ongoing.

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/stockout event, most of these occurred at national level, and many had a relevant impact on vaccine services, in terms of changes to

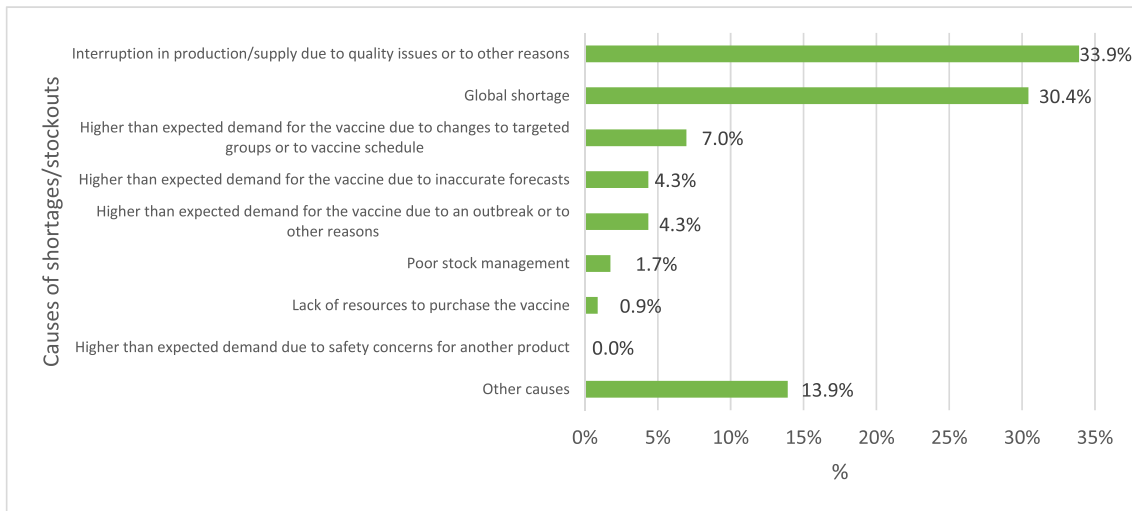


Fig. 3. Factors that played a role in vaccine shortages and stockouts in EU-JAV and other EU/EEA countries, 2016–2019 (N = 115).

Table 2
Actions taken to address vaccine shortages/stockouts, 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

Table 3
Shortages and stockouts of biological products in EU-JAV and other EU/EEA countries, 2016–2019.

Biological product	N. countries reporting shortages
Diphtheria antitoxin	12
Human normal IG	4
Rabies IG	4
Varicella-zoster IG	2
Hepatitis B IG	1
Tetanus IG	0
Botulinum antitoxin	1
Purified-protein derivative (PPD) tuberculin antigen	1
anti-Rhesus D IG	1

the vaccination schedule and in terms of time resources spent to find adequate mitigation solutions.

The vaccines most frequently affected were DT-containing vaccines, followed by hepatitis B and BCG vaccines. DT-containing vaccines accounted for about one quarter of shortage/stockout events, most of which 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) [15]. A 2015 European Center for Disease Control (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) and immunization programmes

in nine countries [16,17]. Our survey confirms these results and show that nine of 14 countries who experienced a shortage of DT-containing vaccines had to make temporary changes to their immunization programmes to mitigate the impact of the shortage.

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. According to a 2017 rapid risk assessment by the ECDC, of a multi-country outbreak of hepatitis A among men who have sex with men, limited supply availability of HepA vaccine in EU/EEA since several years hindered implementation of control measures in some countries experiencing outbreaks [18]. In the assessment, the limited supply of vaccine was attributed mainly to past and ongoing production issues of MAHs along with increased demand.

Supply issues of BCG vaccine have been reported globally in recent years [19,20]. In the EU/EEA, BCG vaccination is mandatory in four countries, generally recommended in 11 and recommended in some specific conditions in seven [21]. Our results indicate that BCG shortage in EU/EEA was due to production problems of one large supplier (Statens Serum Institut of Denmark – SSI) and the limited number of manufacturers with authorized products [5,22,23]. As of November 2018, only two manufacturers were authorized in Europe (AJVaccines and SSI) and approved in 16 European countries [24]. However, SSI interrupted BCG production in 2015, leaving only one manufacturer to meet BCG demand in Europe [19]. Bulgaria and Serbia also produce BCG vaccine but their products are not authorized by EMA.

Global data indicate that reported causes of vaccine shortages vary by vaccine and by country, are complex, multifaceted, and arise when there is an imbalance in demand and supply. Supply factors including production issues and the limited supplier base for vaccines, are closely interrelated with demand factors. Information factors, including timely communication between regulatory agencies, public health authorities and manufacturers also play a role [5]. In our survey, the most commonly reported causes of vaccine shortages/stockouts were production issues and global shortage. Regarding production issues, 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].

Regarding global shortage, this was a factor in one third of shortages/stockouts, in agreement with data from WHO/UNICEF which found that this was the main cause of vaccine stockouts in high income countries (such as most EU countries) [29]. The root causes behind global shortage are often not specified. There may be 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 [23]. 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 manufacturers either not entering the market in the first place or withdrawing from the market because of low profits.

Our survey indicates that most MS procure vaccines at national level by the public sector. When asked about their opinions about a European centralized procurement system for vaccine, only two

countries indicated that they would not be in favour of this. The ongoing COVID-19 pandemic has indeed highlighted some of the advantages of centralized procurement during a cross-border health threat. The common EU Vaccines Strategy ensured access to all MS to a diversified portfolio of several COVID-19 vaccines, from several suppliers, at a fair price, at the same time avoiding that MS compete with each other for fewer doses from fewer producers [25].

According to our results, the GVAP recommendations for all countries to have an immunization supply chain improvement plan and a vaccine supply manager to oversee the implementation of the plan [3] have been scarcely implemented. 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. Furthermore, it is fundamental that in case of vaccine shortages/stockouts, all countries be ready to make recommendations in a timely manner; however, only about half of countries in our survey reported having recommendations or procedures in place to address shortage and stockout events.

Timely communication between supply and demand is a well-known factor in the prevention of vaccine shortages [26]. 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. According to Article 81 of Directive 2001/83/EC, in Europe, manufacturers are obliged to communicate upcoming shortages (of medicines, including vaccines), at least two months before the interruption of supply, to the European Medicines Agency (EMA) and/or to National Agency of Medicines [26,27]. EMA publishes online information on vaccines shortages that affect or are likely to affect more than one EU MS. A recent WHO-Europe report suggests the need to improve advance notification of shortages to allow risk assessment and corrective actions to be taken [9]. The report indicates that notification systems should highlight not just stock levels but issues across the supply management process including problems with the manufacturing level, with procurement and with regulatory factors.

5. Strengths and limitations of the study

To our knowledge, this is the first survey to collect detailed information on vaccine shortages and stockouts in EU/EEA countries. Previous studies [1,7,8,28] were focused only on vaccine stockouts, in high-income countries as a whole or in the European WHO region.

This study had some limitations. Although the response rate was high, not all EU/EEA countries participated so our study probably underestimates the extent of vaccine shortages in EU/EEA. Another possible limitation is that, although we provided definitions to be used for the purposes of the survey, we cannot exclude that the definitions used for reporting a shortage or stockout at national level might be different across the participating countries,

as highlighted by various published reports [5,9,10,29]. There are ongoing efforts at European level to agree on a common definition of medicine shortages, including vaccines [9].

Finally, some survey respondents working at national level may not be completely informed of all shortages occurring in their country, for example when vaccine procurement occurs at subnational level.

6. Conclusion

Vaccine shortages are a relevant problem in EU/EEA. This survey enabled us to better characterize their entity and impact in EU/EEA, their main causes, and underlines that more research is needed on the root causes of vaccine shortages (including analysis of the economic and market-related causes) and on how these interplay with each other. Public health strategies to assure a stable and adequate vaccine supply require coordinated actions from all stakeholders, including harmonization of definitions used, strengthening of reporting and monitoring systems, presence of an immunization supply chain improvement plan in all countries, and procedures or recommendations regarding the use of alternative vaccines or vaccination schedules. Finally, shortages of biological products, the most concerning of which is diphtheria antitoxin, deserve the same consideration as vaccine shortages.

CRedit authorship contribution statement

Antonietta Filia: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing-original draft, Review and editing. **Maria Cristina Rota:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing review and editing. **Adriano Grossidata:** Data curation, Formal analysis, Writing original draft. **Domenico Martinelli:** Conceptualization, Methodology, Writing review and editing. **Rosa Prato:** Conceptualization, Methodology, Writing review and editing. **Giovanni Rezza:** Funding acquisition, Supervision, Writing review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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