

Pre-empting and responding to vaccine supply shortages

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EXECUTIVE SUMMARY

Introduction & situation

Vaccine Security, defined as the “sustained, uninterrupted supply of affordable vaccines of assured quality”¹, is recognised as a key component of successful national immunisation programmes. This area is getting more and more attention at all levels, particularly as several countries are having difficulties accessing some vaccines in the quantity they need.

Indeed, over the past couple of years, many countries, across regions and income groups, have reported shortages of vaccines. WHO EURO conducted a survey on shortages in September 2015 to which 77% of countries² replied that they had experienced a shortage of supply³ of at least one vaccine since the beginning of the year. In the Americas, PAHO reported that in 2015 the availability of yellow fever vaccine was just enough to cover 40% of the regional demand.⁴ In December 2014, UNICEF expected the mismatch between its demand and supply awards for the BCG vaccine to reach a deficiency of 71 million doses.⁵ The same issue has been reported for several vaccines, many considered traditional vaccines, including yellow fever, BCG, DTP, acellular pertussis (aP) containing vaccines and IPV.

Shortages of vaccines for outbreak response, such as meningococcal C and W containing vaccines have also been reported. In July 2015, WHO sounded the alarm over insufficient stockpiles of vaccines as the threat of epidemics caused by serogroups W and C appeared to be increasing. Meningitis C was identified as contributing to a meningitis outbreak in Niger in 2015.⁶

Other biological products, such as snake antivenom and diphtheria antitoxin, have also been in short supply for several years.^{7,8}

These shortages sometimes cause critical disruptions in timely immunisation services. Based on JRF data, in 2014 50 countries reported stockouts of two vaccines at national level for at least one month. More concerning is that in 33 countries⁹, district level stockouts led to an interruption of vaccination services. While stockout issues have been reported across all income groups, Middle Income Countries (MICs) seem particularly affected: 60% of all 50 countries reporting national level vaccine stockouts in 2014 were MICs. Also, more upper MICs and higher-income countries reported national level stockouts in 2014 than in 2013.¹⁰

Countries are therefore urging WHO to provide more information and assistance in order to better understand the vaccine supply situation, mitigate the effects of current shortages and prevent future ones. However, a comprehensive and global view of vaccine supply as well as vaccine shortages is missing, particularly for vaccines not supported by external development assistance.

¹ UNICEF definition, http://www.unicef.org/supply/files/RFP_501959.pdf.

² 20 out of 26 countries that returned the questionnaire.

³ Defined as “not being able to access the appropriate number of doses at the national level for planned activities”.

⁴ PAHO revolving Fund, Vaccines Supply Shortages, Challenges & Opportunities. DCVMN 16th International Annual General meeting.

Bangkok, Thailand. October 2015. Accessible at: http://www.dcvmn.org/IMG/pdf/dcvmn_2015_paho_presentationv2_for_publishing.pdf.

⁵ UNICEF Supply Division, BCG vaccine: Current Supply & Demand Outlook. December 2014. Accessible at:

http://www.unicef.org/supply/files/BCG_Supply_Status_December_2014.pdf.

⁶ WHO, Rapidly growing outbreak of meningococcal disease in Niger. May 2015. Accessible at: Rapidly growing outbreak of meningococcal disease in Niger.

⁷ WHO, WHO highlights critical need for life-saving antivenoms. May 2010. Accessible at:

http://www.who.int/mediacentre/news/notes/2010/antivenoms_20100504/en/.

⁸ ECDC, Diphtheria case highlights shortage of antitoxin in EU. June 2015. Accessible at:

http://ecdc.europa.eu/en/press/news/layouts/forms/News_DispForm.aspx?ID=1239&List=8db7286c-fe2d-476c-9133-18ff4cb1b568&Source=http%3A%2F%2Fecdc.europa.eu%2Fen%2Fpress%2Fnews%2Fpages%2Fnews.aspx.

⁹ Corresponding to 86% of countries that registered a district level stockout.

¹⁰ GVAP Secretariat, Global Vaccine Action Plan Monitoring, Evaluation & Accountability, Secretariat Annual Report 2015. 2015. Accessible at: http://www.who.int/immunisation/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf.

The importance of vaccine security and access to timely supply was highlighted at the 68th World Health Assembly (WHA) in May 2015, with the adoption of a resolution on the Global Vaccine Action Plan (GVAP) that urged Member States to “*improve and sustain vaccine purchasing and delivery systems in order to promote the uninterrupted and affordable safe supply of all the necessary vaccines*”.¹¹ The resolution also urged WHO to address factors that can detrimentally impact vaccine availability, through technical support to countries and specific programmes supporting and monitoring accessibility of quality vaccines at affordable prices.

Vaccines are not the only medical products at risk of shortages, and several medicines on the WHO Model Lists of Essential Medicines¹² have also been in short supply in recent years. There is insufficient information to measure the magnitude of the problem at global level, but at national level, data collected have shown the depth of the issue. In the US, for instance, drug shortage reports have listed 300 products in shortages in 2013, double that registered in 2010.¹³ Given the necessity to maintain access to essential medicines, a report was presented at the WHO Executive Board in January 2016¹⁴, detailing actions that could be explored at national and global levels in order to better pre-empt and respond to drug shortages.

Shortages versus stockouts

There are no well-established definitions of vaccine shortages. For the purpose of this work, and in order to distinguish between “shortage” and “stockout”, the following definitions have been used:

- Vaccine shortage: there is a vaccine shortage when a vaccine cannot be obtained by a country in sufficient amount to meet its needs. The lack of vaccine availability can be global (several countries impacted) or local (one country cannot acquire the volume it needs).
- Vaccine stockout: there is a stockout of vaccine when stocks at the national or district levels have been depleted.¹⁵

This means that a shortage may or may not lead to a stockout, if the country has enough doses in stock to bridge the lack of supply for some time. Stockouts of vaccines are also not necessarily related to a vaccine shortage, but may also be caused by poor use of available doses within the country (e.g. poor stock management or supply chain issues). According to a root cause analysis conducted by UNICEF in the 90 countries procuring vaccines through the Supply Division in 2014, only 10% of stockouts were due to global shortages.¹⁵

Main identified causes behind vaccine shortages

There are several causes behind shortages and they may vary from one vaccine to another and from country to country. They can be divided into three categories:

- **Supply:** Supply factors relate to the production of vaccines as well as market conditions (such as the number of products available and the number of manufacturers active on each vaccine market). Supply factors influence availability of vaccines.
- **Demand:** Demand factors relate to the flexibility and predictability of demand. Demand predictability relies on the capacity of a country to accurately forecast its demand and to have the appropriate measures in place for this demand to materialise. Demand flexibility relies on processes being in place to ensure that a country is able to secure the supply it needs. Demand factors influence access to timely supply.

¹¹ 68th World Health Assembly 2015, Resolution WHA68.6, Global Vaccine Action Plan. May 2015. Accessible at: http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R6-en.pdf.

¹² Lists are accessible at: <http://www.who.int/medicines/publications/essentialmedicines/en/>.

¹³ International Pharmaceutical Federation (FIP), Report of the International Summit on Medicine Shortage. Toronto, Canada, June 2013. Accessible at: <http://apps.who.int/medicinedocs/documents/s20979en/s20979en.pdf>.

¹⁴ WHO Executive Board, Addressing the global shortages of medicines, and the safety and accessibility of children’s medication, report by the Secretariat. EB138/41. Geneva, Switzerland. December 2015 http://apps.who.int/gb/ebwha/pdf_files/EB138/B138_41-en.pdf.

¹⁵ GVAP Secretariat, Global Vaccine Action Plan Monitoring, Evaluation & Accountability, Secretariat Annual Report 2015. 2015. Accessible at: http://www.who.int/immunisation/global_vaccine_action_plan/gvap_secretariat_report_2015.pdf.

- **Information:** Information factors relate to the lack of information available at the global level on supply and demand, which may contribute to a misalignment of supply and demand. Information factors influence the quality of communication and data availability to take sound, informed decisions from both the demand and supply sides.

More information on these causes is available in Annex 1.

Actions taken to mitigate impact of vaccine shortages and pre-empt future shortages

As there is no centralised information available on vaccine shortages and the mechanisms that countries have set up to cope with them, it is difficult to have a bird-eye view of the situation. Some specific information and data-collection exercises conducted in Europe have permitted a clearer view of actions taken at country level. In this area, responses are usually very reactive and intend to mitigate as much as possible the impact of short supply on service delivery. The current shortage situation is also generating ideas for longer term actions that countries, groups of countries and global organisations could set up to better respond to and pre-empt these shortages.

Actions by countries

In some countries and groups of countries, work has been undertaken to respond to and prevent shortages, sometimes with the support of regional or international partners. However, most countries find themselves unable to cope with and respond to these shortages. In June 2015, the European Technical Advisory Group of Experts on Immunisation (ETAGE) stated that “some Member States appear to have very limited or inadequate mechanisms in place to respond to fluctuations in vaccine supply, and little or no resilience in the face of vaccine supply interruptions. Further efforts are urged to support these countries in developing appropriate mechanisms to ensure sustainability of vaccine supplies and avoid vaccine stockouts”.¹⁶

Some countries are taking action to limit the impact of shortages. For instance, since 2015, nine Member States of the European Union / European Economic Area (EU/EEA) have adjusted their immunisation policies due to shortage of the aP vaccine. Measures have included¹⁷:

- Temporary suspension of the primary immunisation doses (e.g. Bulgaria)
- Changes to the primary immunisation schedule age of dose administration (e.g. Romania, Hungary)
- Modification of the vaccine formulation used as pre-school booster (e.g. Belgium, France)
- Delayed introduction of a new antigen in the primary immunisation schedule (e.g. Norway)
- Prioritisation of vaccine formulation for the primary immunisation schedule (e.g. Spain, Sweden)
- Use of acellular pertussis-containing vaccines not originally authorised in the EU

Actions by groups of countries & regions

Countries with existing regional common institutions are exploring possibilities to reinforce vaccine security at the regional level.

In the Americas, the PAHO Revolving Fund has become an example to other international organizations and WHO regions of an effective mechanism to ensure an uninterrupted supply of affordable, quality vaccines in the complex global vaccine market.

In the Association of Southeast Asian Nations (ASEAN), Member States are working together to explore opportunities for cooperation to improve vaccine security in the region. Several workshops

¹⁶ WHO, meeting report of the 15th meeting of the European Technical Advisory Group of Experts on Immunisation (ETAGE). Copenhagen, Denmark. September 2015. Accessible at: http://www.euro.who.int/_data/assets/pdf_file/0008/295559/ETAGE-2015-Report.pdf

¹⁷ European Centre for Disease Prevention and Control. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA – 8 October 2015. Stockholm: ECDC; 2015.

are being organised with Member States to assess feasibility and potential impact of areas such as “collaborative systems”, “human resources development”, “common price policy & pooled procurement” and “improved communication & coordination”.¹⁸

In the European Union, the Commission, in cooperation with the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), and WHO, is working with Member States to identify possible policy interventions in order to address problems related to vaccine supply. Measures proposed are *inter alia* aiming at strengthening mutual assistance of Member States in case of urgent vaccine needs or strengthening vaccine supply infrastructure in Member States.

More information on the work done in the European Union is available in Annex 2.

Actions by global partners

Several actors at the global level are implementing solutions in a collaborative manner. Activities include mitigation efforts, but also procurement planning, information-sharing mechanisms and longer term actions to support healthy markets.

Partners, including WHO, PAHO and UNICEF, are supporting countries in their mitigation efforts and working collaboratively to find adapted solutions. For instance, in 2015 WHO and UNICEF worked together to increase the supply base of BCG, through fast-tracking prequalification of a new product and through working to secure additional quantities from existing manufacturers. As a result, UNICEF is expecting supply to be sufficient in 2016 to meet both suppressed 2015 demand carried over to 2016, as well as total forecast demand through 2016-2018.¹⁹ The WHO Prequalification team²⁰ has also worked with individual countries to support fast-tracked national registration of new products (e.g. BCG in South Africa).

Longer-term activities vary from one organisation to another, spanning from activities targeting demand factors (policy, introduction, forecasting, vaccine delivery, supply management and tendering) to activities on supply factors (industry incentives, product development and market strategies) and information & communication factors. However, many activities implemented by international organisations focus on very specific groups of countries, with markets targeting Gavi-countries receiving the most support. Indeed, partners collaborate through Gavi, the Vaccine Alliance, to ensure that needs of the poorest countries are correctly matched by an adequate supply of vaccines. With that aim, the Alliance plays an important role in strengthening vaccine markets. For instance, efforts to strengthen the DTwP-HepB-Hib market have contributed to the “healthy market” that exists today, with a good supplier base of eight manufacturers with prequalified products.²¹

On information sharing, UNICEF offers comprehensive supply and demand information for the products and countries it serves, through “Market Updates” regularly published on the UNICEF website.²² However, a complete and centralised view of global supply and demand for all vaccines and all countries does not exist at this stage.

More information on long-term actions and areas of work of several global key partners is available in Annex 3.

¹⁸ ASEAN. Executive Summary: Workshop among ASEAN Countries on Opportunities for Regional Vaccine Security. Phuket, Thailand. October 2014.

¹⁹ UNICEF, Q and A: Update on BCG vaccine market – February 2016. Accessible at: http://www.unicef.org/supply/index_90306.html.

²⁰ WHO system for the prequalification of vaccines. Accessible at: http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/.

²¹ List of WHO prequalified vaccines accessible at: https://extranet.who.int/gavi/PQ_Web/.

²² UNICEF, Vaccines Supply and Market Overview. Accessible at: http://www.unicef.org/supply/index_vaccines.html.

Annex 1: main identified causes behind shortages²³

CATEGORY	SUB-CATEGORY	FACTORS	DESCRIPTION & EXAMPLES
SUPPLY	Production issues	Batch failures and high risks linked to biological products	<ul style="list-style-type: none"> • Biologics are natural products so production with consistent accuracy is more complex than for manufactured drugs, leading to a higher risk of production failure (including “out of specification” batches). Variability of in-vivo control testing may have an impact on lead time and/or increasing batch losses.
		Complex & long production processes and quality controls	<ul style="list-style-type: none"> • Long production and capacity lead times: up to 1-2 years per lot and 3-5 years for a new facility. • Tight quality controls (QC): complex production process also relates to complex QC testing, which in some cases may delay availability or rapid access of vaccines. The weight of control steps can take up to 70% of production time. • Regulatory systems: national regulatory agencies (NRAs) in producing countries are not all functional (36 out of 44 countries in 2014 had a functional NRA). Regulatory requirements may vary by country. Sometimes also a high workload on the NRA can delay availability of supply (e.g. in India).
		Tight production planning	<ul style="list-style-type: none"> • Leaner production practices (“just-in-time” to reduce inventory and waste): leads to stronger consequences when something fails on the production line and limits the capacity to answer to rapid increases in demand. Production is also more at risk in case of decreased availability of quality raw material or substances. • Scaling up production: complex production process makes rapid scaling up of production difficult. • Product prioritization: if a manufacturer decides to switch a production line from a vaccine to another (e.g. to respond to an outbreak), there is a risk that another vaccine may not be produced (e.g. bottlenecks at filling or packaging stages). • Renovation of facilities: they are costly, take time and interrupt production. It may not be possible to produce enough doses in advance to bridge the time until the line becomes productive again. • <i>Example of seasonal influenza</i>: demand in Europe is not as high as expected, leading manufacturers to consider lowering their production. However, in case of an outbreak, capacities to respond will be reduced .
	Limited supplier base	Entry barriers (high sunk costs, R&D investments, technical know-how, GMP, investment risks, ...)	<ul style="list-style-type: none"> • High sunk costs: building new production lines and acquiring appropriate technical equipment is very expensive. New plants can cost several hundred millions to build. • R&D investments: R&D investments are costly. E.g. R&D costs for rotavirus vaccines have been estimated at \$150-508 million for Merck and GSK’s products. These amounts do not account for other failed R&D investments. • Technical know-how: to maintain quality of production, it is important that manufacturers follow Good Manufacturing Practice (GMP – latest WHO guidelines on GMP for biological products were updated in October 2015). In some countries (particularly developing countries), there may be limited capacity to develop, enforce and sustain further GMP.
		Decisions based on product and market	<ul style="list-style-type: none"> • Market segmentation (developed vs developing countries): manufacturers from developed countries tend to focus efforts on expensive new vaccines and manufacturers from developing countries to focus more on traditional vaccines. • Pressure on price and the issue of sustainability: manufacturers may decide not to invest (e.g. to renovate manufacturing

²³ Note that this is a working document that is still under development and review.

SUPPLY		attractiveness (e.g. profitability, certainty, ...) and ROI	<p>facilities) in products with high uncertainty or low Return on Investments (ROI). Some manufacturers find themselves unable to compete with manufacturers located in places with very low costs, including low labour costs. Driving prices down too much may lead certain manufacturers to take the decision to exit the market.</p> <ul style="list-style-type: none"> • Competing against drugs: in large multinationals, vaccines may have to compete against drugs for attention and resources and need to prove that they are a good investment.
		Market strategies	<ul style="list-style-type: none"> • Preference for most profitable markets: some products might be developed to target high-income markets first and may not be adapted to low income settings (e.g. to be used out of the cold chain). In case of limited production available, manufacturers may decide to focus first on high-income markets. In the case of BCG, allocation of production to immunisation programmes may enter in competition with use as a bladder-cancer treatment. • Unknown political incentives: they may affect decisions to allocate doses to a country rather than another. • Cannibalisation between vaccines: when newer combination vaccines enter the market, manufacturers may decide to redistribute production capacity to the newest vaccine and phase out the older vaccine, thus reducing the supply base of the older vaccine for countries that have not switched to the newer combination (eg. introduction of DTwP-HepB-Hib reducing availability of DTwP ; short supply of DTaP-Hib-IPV in 2015 while the hexavalent remained available) .
		Mergers & acquisitions (concentration)	<ul style="list-style-type: none"> • Concentrated markets with limited number of players: the nature of vaccine manufacturing costs, supply, and risk generates long-run market equilibrium with one or very few vaccine suppliers at any point in time. In markets with a limited number of manufacturers, a reduction in produced quantity from one manufacturer may quickly lead to “domino shortages”, as demand can only shift to a limited set of alternative products. These products may not be available in sufficient quantities to cover the resulting increase in demand (e.g. HepA vaccines in France in 2015-2016, with “domino shortages” of Havrix (GSK), then Avaxim (Sanofi Pasteur) and then putting Vaqta 50 (Merck) at risk of shortage as well). • Reduction in number of producing countries: as the market concentrates, the number of producing countries decreases (from 60 in 1990 to 44 in 2014). This market situation also limits profit possibilities for small manufacturers who are not strong enough to compete with large multinational manufacturers for market shares.
		Local production	<ul style="list-style-type: none"> • Relying on local production: several countries rely on local production for their local needs of traditional vaccines. Relying on small local production plants may increase the risk of shortages for the country if a production issue occurs or if the demand suddenly increases (lack of flexibility to respond to fluctuation in production or demand). • Investments in public sector manufacturing may be more at risk of sustainability: these investments are more likely to be at risk of sustainability as they often survive on subsidies. In the past, out of 11 countries with public and private investments in local manufacturing, only 2-3 have been considered successful. • <i>Example of BCG</i>: for many years, production of BCG has relied on local manufacturing. For instance, there are currently 4 manufacturers of the DCVMN (Developing Countries Vaccine Manufactures Network) producing BCG, with only 1 aiming at the global market with a prequalified product (Serum Institute of India) and 3 publicly supported companies with local capacity only (production capacity < 10M doses).
DEMAND	Little demand flexibility	Safety concerns	<ul style="list-style-type: none"> • Product quality: countries tend to prefer products that are WHO prequalified or that are produced and/or used in high-income countries (HICs). In 2015, 95% of vaccines registered by countries in the V3P database were either WHO prequalified vaccines or were produced in HICs.

DEMAND			<ul style="list-style-type: none"> Confidence and good relationships with one manufacturer: when a country trusts a manufacturer it may be inclined to continue working with this manufacturer, especially if there has been no safety issue with the product(s) purchased. Relying on only one manufacturer creates dependence and increases the risk of shortage if the manufacturer cannot deliver the product (production issues, cessation of production, ...). Reactivity to respond to a shortage is reduced.
		Inefficient and un-harmonized registration procedures	<ul style="list-style-type: none"> Complex registration procedures: countries asking for stringent procedures (e.g. high fees, lengthy paperwork, translation, local clinical trials, inspection, ...) might deter manufacturers from registering their products, particularly in small or less attractive markets/countries... Varying product specifications across countries also limits supply flexibility. Lack of functional NRAs: in 2015, on 194 WHO Member States, only 60 had a functional NRA. Lengthy registration processes: impact expedited access to vaccines. Few products registered: issues with registration processes may partially explain the fact that there are few products registered in each country at any point in time.
		Limited evidence on product interchangeability	<ul style="list-style-type: none"> Limited interchangeability between products: traditional vaccines may be used interchangeably but in general there are few studies showing interchangeability of vaccines. Therefore, once a product is added to the immunisation programme it is not easy for the country to switch to another product. It limits access to alternative products if one product becomes in short supply.
		Single award tenders	<ul style="list-style-type: none"> Single-source procurement: tenders are often awarded to only one manufacturer/product. It means that a country relies on only one supplier for each vaccine, which increases the risk of shortages if availability of this product decreases. It also increases delays to find an alternative solution if a shortage occurs. <i>Example of UNICEF on multiple-award tenders:</i> UNICEF clearly states in its procurement principles that it procures from multiple suppliers for each vaccine presentation in order to strengthen security of supply.
		Low elasticity of demand resources	<ul style="list-style-type: none"> Budget constraints: immunisation budgets are usually fixed at the national level and may not be extended to cover for economic factors impacting the purchase of vaccines, such as volatile exchange rate. This can have dramatic consequences for access (e.g. in South Africa, the Rand lost more than 50% of its value against the US dollar between 2011 and 2015). Lack of flexibility of donor money: if the demand was not forecasted correctly it might be difficult to get extra financial support for missing doses. Donor-funded demand can be complex and therefore limits flexibility.
	Lack of demand predictability	Weak country decision-making	<ul style="list-style-type: none"> Lack of strong decision-making systems: paths leading to decisions are not always well understood and clear. Lack of strong decision-making systems may impact timely and evidence-based immunisation policy making. Lack of functional NITAGs: only one third of non-Gavi MICs have a functional NITAG (20 out of 59 countries with data in 2014).
		Poor political commitment & financing	<ul style="list-style-type: none"> Poor political commitment: in some cases, insufficient political will translates into inadequate national financing as well as inefficient use of available resources, which may affect the maintenance of immunisation services as well as new vaccine introductions. Allocation of financial resources to support immunisation: according to a root-cause analysis conducted by UNICEF in 2015 on 90 countries procuring through UNICEF SD, 39% of stockouts of vaccines were due to funding delays.
		Vaccine hesitancy	<ul style="list-style-type: none"> Vaccine hesitancy: it is becoming a growing concern across regions and income groups. It is often linked to a lack of

DEMAND			<p>confidence in vaccines and reduces demand predictability.</p> <ul style="list-style-type: none"> • <i>Example of the United States:</i> in 1999, the rationale behind the decision to minimize the use of thimerosal in some vaccines was not well communicated. As a consequence, public confidence in vaccines decreased, which led to increased vaccine hesitancy and refusal to vaccinate. The subsequent decrease in coverage may lead to outbreaks, such as the measles outbreak in the United States in 2014-15. Reactions to the outbreak, in turns, led to a rapid and unpredictable increase in demand for the measles vaccine.
		Weak procurement systems (incl. anticipation and planning, forecasting, budgeting & tendering)	<ul style="list-style-type: none"> • Weak procurement skills and lack of data: may lead to inadequate or non-existent demand forecasting. • Legal constraints on budget: in some countries, it is mandatory that budgets be done on an annual basis only, preventing the possibility to do multi-year contracts. • <i>The example of UNICEF:</i> long-term agreements and reliable long-term forecasting are both part of UNICEF vaccine procurement principles to promote healthy markets and strengthen vaccine supply security. These activities allow manufacturers to confidently make the necessary investments to ensure long term supply and be better prepared to deal with fluctuations in demand.
		Delivery issues	<ul style="list-style-type: none"> • Supply chain and stock management: for 13% of countries (6 countries) that reported district level stockout in their JRF in 2015, the cause was a breakdown of the distribution system or poor stock management at lower levels of the supply chain.
		Unaffordability	<ul style="list-style-type: none"> • Lack of access to vaccines at affordable prices: many countries, particularly MICs, have raised this issue at the World Health Assembly (e.g. resolution 68.6 on the GVAP at the 2015 WHA). This is considered a factor that limits access and may prevent demand materialization. It is also difficult to know in advance under which price ceiling a country will deem a vaccine affordable and will consider its introduction.
		Emergencies, outbreaks and surveillance	<ul style="list-style-type: none"> • Events creating unexpected demand: natural disasters and conflicts are often unpredictable and generate unexpected demand. • Using stockpiles: stockpiling is used to make sure that doses of vaccines are readily available in case of a high increase in demand, for instance during an outbreak. There are international stockpiles (e.g. the International Coordinating Group (ICG) with meningitis, cholera and yellow fever vaccines) and some countries maintain national level stockpiles (e.g. the US Paediatric Vaccine Stockpile Programme maintains a 6-month supply of routine childhood vaccines). For vaccines used both in routine immunisation and in outbreak response, stockpiling may reduce availability of vaccines for routine immunisation. • Global surveillance: surveillance systems can accelerate the response to an outbreak and therefore limit the sudden increase in vaccine demand. However, real-time surveillance is not possible in most systems and quality of currently reported data vary from country to country.
INFORMATION	Supply information	Limited global information available on current and future supply capacity and	<ul style="list-style-type: none"> • Information not easily accessible: information available is not centralised and easy to access. For instance, some manufacturers are now displaying a list of vaccines in short supply on the internet, but information is scattered across several manufacturers' websites. • No strategic planning for global supply: e.g. several countries stopped their local production of BCG because production was not sustainable and prices higher than what was available on the global market. Due to lack of intelligence on global availability of the vaccine, decision makers were probably not informed that the global production of BCG was decreasing

		vaccines at risk of a shortage.	<p>(risk assessments not well documented with global supply information).</p> <ul style="list-style-type: none"> • Limited intelligence of manufacturing capacity: limited knowledge on current and potential capacity, as well as investments on production capacity and potential to increase portfolio of vaccines produced. • Non-exhaustive information available at the global level: UNICEF has supply information from manufacturers it works with, including for non-Gavi supported vaccines and even some non-PQ products. UNICEF however does not have information on vaccines used in self-procuring countries only (e.g. aP vaccines, HepA, rabies, ...). WHO also has only partial data from prequalified manufacturers (from 23 countries).
	Demand information	Limited global information available on demand evolution, particularly for non-Gavi countries	<ul style="list-style-type: none"> • Limited demand information outside of Gavi supported countries: there is no regular collection of information on how demand is evolving or might evolve in non-Gavi countries as well as for self-financed vaccines in Gavi countries. • Impact of policy & recommendations: no information shared at the global level on new policies and schedule recommendations (e.g. adding a booster dose, new recommendations for maternal immunisation, ...) implemented in countries. These changes impact country demand patterns and may therefore disrupt the balance between supply and demand.
	Timely communication	Lack of timely communication between supply and demand, particularly for self-procuring countries	<ul style="list-style-type: none"> • Translation of policies and strategies into supply needs: lack of early translation of new policies and strategies into precise supply needs can lead to shortages because of the lead-time necessary for industry to scale up production. Lack of anticipation of vaccine calendar evolution. Lack of dialogue with industry to adapt industrial plans. • Communication not conducted in a timely manner in case of a shortage: the information often starts to circulate when the shortage is imminent or already happening, allowing little time for reactive measures to be implemented, both from the country's side and from the manufacturer's side (e.g. country stocks already very low, manufacturer unable to ramp up capacity, ...). • Lack of early warning systems: some countries use early warning systems to be informed in advance of an upcoming shortage (e.g. in Norway, legislation mandates that manufacturers notify the Norwegian Medicines Agency about impending drug shortages at least 2 months before they occur). However, many countries do not have these systems and there is no warning system at the international level covering all vaccines (UNICEF SD provides updates and warnings for the vaccines procured by the agency). When a shortage happens, countries do not necessarily know if they are the only ones impacted or if the shortage is widespread. • Allocation of doses during a shortage: lack of clarity on mechanism used by manufacturers to allocate supply in case of a shortage may lead to misunderstanding and distrust (e.g. allocations based on health priorities, contractual clauses, other arrangements, etc.)

Sources: Goldstein 2005 ; Offit 2005 ; M.S. Coleman 2005 & 2006 ; Callender 2006 ; Danzon 2005 & 2011 ; Hitchcock 2007 ; Light 2009 ; Smith 2011; Woodcock 2012 ; Gordon Douglas 2013 ; Congeni 2014 ; Yen 2015 ; Cacciatore 2016 ; BIOTEC Canada 2010 ; US CDC website; US FDA website; MesVaccins.net ; UNICEF ; V3P database ; WHO ; WHO regional and country consultations 2014-2015 ; MIC task Force ; GVAP Secretariat Report 2015 ; Press articles ; Oanda.com ; discussions with experts ; discussions with Industry representatives.

Annex 2: Actions and scope of work of the European Commission and ECDC

The European Commission, in cooperation with the World Health Organization (WHO), **the European Centre for Disease Prevention and Control (ECDC)** and the **European Medicines Agency (EMA)**, is working with the European Union (EU) Member States in the Health Security Committee (HSC) according to the Decision 1082/2013/EU on serious cross-border threats to health. The Health Security Committee coordinates health-security measures in the EU and has established a solid basis for preparedness activities by enabling EU governments to exchange information and evaluate health events, functioning as a discussion forum that advises health ministers and facilitating coordinated crisis response by EU governments.

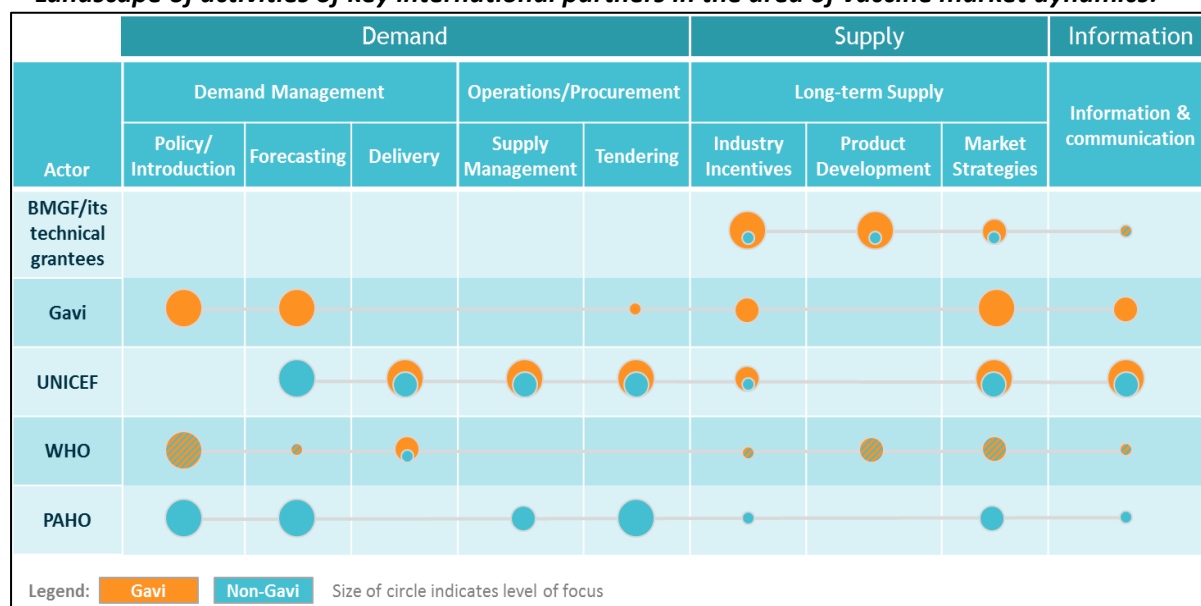
In the European Union vaccination is a competence of the Member States. Council conclusions on vaccination as an effective tool in public health, adopted in December 2014, invite the Member States and the Commission to develop joint action programmes co-financed by the Commission and the Member States to share best practices on national vaccination policies.

In respect to vaccine shortages the Commission, in cooperation with ECDC, EMA and WHO, is working with Member States to identify possible policy interventions in order to address problems related to vaccine supply. Measures proposed are *inter alia* aiming at strengthening mutual assistance of Member States in case of urgent vaccine needs or strengthening vaccine supply infrastructure in Member States, with a view to increase efficiency and reduce expenditures related to vaccine management. As vaccine shortages in the European Union are linked to the situation of the global vaccine market it is important to improve communication and exchange information, with a view to raise awareness about the interdependence of all stakeholders involved.

A shortage affecting acellular pertussis-combination vaccines has been of particular concern in the EU since 2015. This vaccine shortage is believed to be due to reduced production capacities of the acellular pertussis antigen needed for the final vaccine formulation of numerous combination vaccines, increased global demand, and vaccine lots failing to meet the necessary release criteria. This unexpected situation has forced some EU/EEA countries to adjust their vaccination programmes to address the vaccine shortage. ECDC has provided technical assistance to EU/EEA Member States proposing options for possible solutions.

Annex 3: Actions and areas of work of key partners²⁴

Landscape of activities of key international partners in the area of vaccine market dynamics:



The Bill & Melinda Gates Foundation (BMGF) focuses on product innovation and developing long-term competition in markets mainly through financial and technical support for manufacturers to help accelerate R&D and WHO prequalification of new vaccines. BMGF works closely with partners to ensure vaccine markets are healthy and serve the needs of low-income countries. BMGF also coordinates with the Gavi Secretariat to gather market intelligence and insights on the state of different markets and to develop appropriate market incentives to meet objectives identified in product roadmaps. Much of this work is achieved by funding other global health partners (CHAI, PATH, AMP, JSI, JHSPH, etc.) to leverage their specific technical expertise.

The Gavi Secretariat coordinates the participation and contribution of key Alliance members, leads in the development and implementation of the product market strategy (or ‘supply and procurement roadmap’) and monitors progress against indicators in the Alliance Supply and Procurement Strategy. The Secretariat shares available non-confidential vaccine market information. Importantly, the Secretariat produces vaccine-specific strategic demand forecasts and shares these within the Alliance, including with manufacturers. As part of product roadmap development, the Secretariat convenes consultations with technical Alliance members, additional disease/vaccine experts, and other global health organisations with relevant expertise. The Secretariat also engages with manufacturers; coordinates with UNICEF to ensure procurement decision-making aligns with roadmap objectives; and supports WHO to develop product standards and specifications. The scope of Gavi’s market shaping activities covers all countries receiving Gavi support. Gavi is committed to support governments to transition successfully towards self-financing. This includes efforts to strengthen national capacity in vaccine procurement, financing and regulation during the transition process.

The United Nations Children's Emergency Fund (UNICEF) works for a world in which every child has a fair chance in life. In 2014, UNICEF procured \$3.38 billion worth of supplies and services from all over the world (including \$1.48 billion in vaccines) in support of programmes to help children survive

²⁴ Note that this is a working document that is still under development and review.

and thrive throughout the world. Through fair and open procurement, UNICEF influences markets to ensure a diverse and reliable supplier base, a competitive landscape, and affordable and quality products in the right formulations for children. UNICEF is responsible for buying all vaccines and related items for global campaigns to eradicate polio, eliminate neonatal and maternal tetanus, and control measles. In addition, UNICEF procures vaccines for its own programmes and for Gavi. UNICEF's procurement and market influencing efforts are built on an in-depth understanding of market forces, accurate forecasting and analysis, transparency, engagement with industry, collaboration with key partners, and a drive for the best possible outcome for children.

The World Health Organization (WHO) works with partners on demand, supply and information aspects to support short term access and long term strategies aiming at strengthening healthy markets. On the supply side, WHO provides R&D support, establishes guidelines (e.g. guidelines on GMP for biological products revised in October 2015), provides technical assistance to countries (e.g. facilitating technology transfer to 14 developing countries on influenza vaccine since 2006), supports National Regulatory Authorities (NRAs) of producing countries (36 out of 44 have been assessed as functional) and manages the well-established prequalification process to ensure availability of products of assured quality (in 2015, there were more than 140 prequalified vaccines from 32 manufacturers, a 5-fold increase since 2001). Fast-tracking procedure for prequalification is also a measure to increase the supply base in a short amount of time (e.g. Green Signal BCG vaccine prequalified in February 2016). Finally, WHO explores needs and opportunities for regional vaccine production (e.g. in Africa).

On the demand side, WHO works in collaboration with partners to expand timely access to vaccines in all countries through supporting decision making processes (NITAG, cost effectiveness analyses, position papers, policies and recommendations), strengthening political commitment and financing (work with country to analyse financial needs and trends, CMYP and JRF), reducing vaccine hesitancy, collaborating with UNICEF to strengthen country procurement capabilities, strengthening NRAs and simplifying country product registration requirements (including for fast track registration). In 2015, WHO and partners developed the MIC strategy to specifically address issues that Middle Income Countries (MICs) face to raise coverage and enable new vaccine introductions. Nevertheless, it should be noted that available resources for this work are limited and unpredictable, preventing more systematic and comprehensive efforts.

The Pan American Health Organisation (PAHO) is a specialized health agency of the Inter-American System

and serves as WHO's Regional Office for the Americas. PAHO provides technical cooperation and mobilizes partnerships to improve health and quality of life in the countries of the Americas. PAHO's Revolving Fund for Vaccine Procurement has provided crucial support for the region's achievements, including its elimination of vaccine-preventable diseases and its introduction of new vaccines, such as rotavirus, pneumococcal disease, and HPV. Between June 2014 and June 2015, the fund procured more than US\$ 547 million worth of vaccines and US\$ 3.5 million worth of syringes for immunisation programmes in 41 participating countries and territories. The Revolving Fund has become an example for other international organizations and other WHO regions of an effective mechanism to ensure an uninterrupted supply of affordable, quality vaccines in the complex global vaccine market. Increasing Member States' awareness of global vaccine market dynamics and challenges, support for demand planning, and ensuring the timely availability of quality vaccines and supplies are key elements of PAHO's technical cooperation.