Challenges for registration of vaccines in receiving countries

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Outline of the presentation

- Some definitions
- Main causes behind vaccine shortages
- Market segmentation and use of aP vs wP containing vaccines
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- Countries role in addressing aP vaccine shortages
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- Options for flexibilities
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Vaccine Security

- ✓ Vaccine Security, defined as the “sustained, uninterrupted supply of affordable vaccines of assured quality”, is recognised as a key component of successful national immunisation programmes.
- ✓ Over the past couple of years, many countries, across regions and income groups, have reported shortages of vaccines
- ✓ Shortages sometimes cause critical disruptions in timely immunisation services.

Shortage vs Stock outs

- ✓ 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.

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 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).

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Main causes behind vaccine shortages

- ✓ 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. 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.
- ✓ 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.

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Main causes behind vaccine shortages

Category	Factors	Description
Supply	Production issues	• Batch failures due to complexity of production of Biological Products • Long and complex production process and QC testing • Capacity of NRAs, workload
	Limited supplier base	• Investment for production of Biologics is high, and therefore highly related to market attractiveness • Preference for more profitable markets. Ex. BCG • Cannibalisation between vaccines: penta vs. DTwP and DTaP based penta vs. hexa • Limited number of manufacturers (mergers) and less producing countries (60 to 14) • Local production (less flexibility to market fluctuations, public sector more risky, etc)
Demand	Little demand flexibility	• Safety concerns • Inefficient and unharmonized registration procedures may deter manufacturers to pursue registration • Limited info on interchangeability of products limits availability • Single award tenders or restriction to specific product categories (aP rather than wP) • Low elasticity of demand resources
	Lack of demand predictability	• Weak country decision making mechanisms including lack of NITAGs • Poor political commitment and financing • Vaccine hesitancy (result of antivaccination lobbying) • Weak procuring systems including for planning, forecasting, budgeting and tendering) • Weak supply chain and stock management • Unaffordability (particularly in MICs) • Emergency outbreaks and surveillance (Stockpiling may reduce vaccine availability for routine immunization • Good surveillance can accelerate response to an outbreak and thus limit the increase in demand

Main causes behind vaccine shortages

Category	Factors	Description
Information	Supply information	• Limited global information availability on current and future supply capacity and therefore vaccines at risk of shortage
	Demand information	• Limited global information on demand evolution particularly for non-GAVI countries • Lack or limited information on new policies and changes in schedule recommendations 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 • Lack of warning systems at global level in case of shortage • Lack of clarity on mechanism used by manufacturers to allocate supply in case of a shortage may lead to misunderstanding and distrust

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Market segmentation

Segmentation of the vaccine market between HIC, MIC, LMIC and LIC affects a number of vaccine categories. Some examples include.

- Until recently IPV was used in HIC and some MICs and OPV used in the rest of the world. This segmentation is no longer applicable in view of the changes in schedules targeted at eradication of polio diseases
- aP based combinations used mostly in HIC (and few MICs) and wP based combinations used in the rest of the world
- Future potential for market segmentation with regards to Gardasil 9-valent and Gardasil 4-valent (Merck)

Market segmentation is a mechanism applied by manufacturers in order to increase revenues and cost-recovery from vaccine development in those markets that can afford it.

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Impact of market segmentation for aP

- ✓ Common knowledge about pertussis vaccines indicates that aP containing vaccines are usually less reactogenic and equally effective to wP containing vaccines
- ✓ This leads sometimes to the impression that countries using wP containing vaccines are treated "as second class countries"
- ✓ However a closer look at the issue may allow to have a clearer perspective of the situation:

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WHO position paper on pertussis vaccines

Whole cell pertussis containing vaccines

- The wP vaccines are produced from cultures of selected *B. pertussis* strains that are subsequently killed, usually by heating or treatment with formalin.
- The methods used for production vary among manufacturers and therefore wP vaccines are relatively heterogeneous.
- The impact of the varying amounts of biologically active PT, lipopolysaccharide, TCT or ACT on vaccine effectiveness is unclear.
- All wP vaccines are combined with diphtheria toxoid and tetanus toxoid (DTwP). Some wP vaccines are also combined with *Haemophilus influenzae* type b (Hib), and hepatitis B (HepB). Combinations including inactivated poliovirus (IPV) are in development.
- All wP vaccines contain aluminium salts as adjuvant, and some have thiomersal or phenoxyethanol added as preservatives in multidose vials.

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WHO position paper on pertussis vaccines (2)

Whole cell pertussis containing vaccines

- The immune response to wP vaccines is directed against an array of bacterial antigens.
- Significant differences in the immune responses to various antigens have been observed with different wP vaccines.
- Immunogenicity data are difficult to interpret and compare for wP vaccines and data from clinical trials showed that highly efficacious wP vaccines did not necessarily induce the highest measurable antibody titres.
- There is no established immunological correlate of protection against pertussis disease, although the presence of antibody to PT is believed to play a role in protection against severe disease in infants.
- Different wP vaccines may have different antigenic content and methods of production and control, leading to variations in post-vaccination immune responses.

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WHO position paper on pertussis vaccines (3)

Whole cell pertussis containing vaccines

- ✓ An updated systematic review of immunogenicity indicates that 3-dose schedules and 2 + 1 schedules (at ages 3, 5 and 10–13 months) of wP given in infancy are effective against pertussis disease in the first 5 years of life.
- ✓ Data on effectiveness are only available for schedules initiated at around 2–3 months of age.
- ✓ Little is known about the effectiveness of wP vaccines in older age groups because, the reactogenicity of wP vaccine was considered too high for routine use in older children, adolescents and adults.

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WHO position paper on pertussis vaccines (4)

Acellular pertussis containing vaccines

- ✓ These vaccines contain one or more of the following purified antigens: PT, FHA, PRN, and FIM types 2 and 3.
- ✓ Vaccines differ in the number of components
  - ✓ 1component PT only
  - ✓ 2 components PT and FHA
  - ✓ 3 components PT, FHA, and PRN
  - ✓ 5 components PT, FHA, PRN, and FIM types 2 and 3
- ✓ They differ also in concentration of the antigen components, the bacterial clone used in production, methods of purification and detoxification (glutaraldehyde, formaldehyde, H2O2 or genetic), adjuvants, and the use of preservatives, such as thiomersal and phenoxyethanol.
- ✓ The exact contribution of the individual aP antigens to protection is not clear.

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WHO position paper on pertussis vaccines (5)

Immunogenicity, efficacy and effectiveness of pertussis containing vaccines

- ✓ A randomized controlled trial comparing 3-component and 5-component aP-containing vaccines with a wP vaccine concluded that the efficacies of the wP vaccine and the aP vaccines were similar against culture-confirmed pertussis with at least 21 days of paroxysmal cough
- ✓ In a study in Germany, a 4-component aP vaccine had an efficacy of 83% (95%, CI: 76%–88%) against typical pertussis.
- ✓ In a study in Italy, efficacies of 84% (95%, CI: 76%–89%) and 84% (95%, CI: 76%–90%) against typical pertussis were reported for 2 different 3-component aP vaccines compared with a poorly efficacious wP vaccine
- ✓ In a randomized double-blind trial in Senegal, a 2-component DTaP vaccine was compared with a DTwP vaccine. Absolute efficacy estimates derived from this study showed that the aP vaccine provided less protection than the wP vaccine: 74% (95%, CI: 51%–86%) versus 92% (95%, CI: 81%–97%) using the WHO case definition, although the difference was not statistically significant.

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WHO position paper on pertussis vaccines (6)

Efficacy and effectiveness of acellular pertussis containing vaccines

- ✓ A systematic review of 3 large, double-blind randomized controlled trials of aP vaccines concluded that multicomponent aP vaccines have higher protective efficacy than 1-component and 2-component aP vaccines against both typical whooping cough and mild pertussis disease.
- ✓ A systematic review that included 49 randomized controlled trials and 3 cohort studies concluded that 1-component and 2-component aP vaccines had lower absolute efficacies than vaccines with ≥3 components: (67%–70% efficacy versus 80%–84%).
- ✓ However, in observational studies of vaccine effectiveness conducted after long-term large-scale use of licensed 2-component aP-containing vaccines and of 1-component aP vaccine in the Danish national immunization programme, all of these aP-containing vaccines demonstrated high effectiveness in preventing pertussis irrespective of specific antigen content.

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Hence, the higher efficacy numbers for multi-component vaccines compared to the 1-component and 2-component vaccines in the randomized clinical trials should be interpreted with caution.

WHO position paper on pertussis vaccines (7)

Comparison of the effectiveness of wP-containing and aP-containing vaccines

- ✓ Experience in the UK suggests that the lower immunogenicity of the Hib antigen in the DTaP–Hib combination may be clinically relevant compared with the DTwP–Hib combination vaccine when schedules do not include a booster dose in the second year of life.
- ✓ Recent mathematical modelling studies from Australia, England and Wales, and the USA, as well as data from a baboon model of pertussis that closely resembles the human disease, support the hypothesis that transition from wP to aP vaccines may be associated with disease resurgence.
  - In the baboon model, the aP vaccines studied protected against disease but had limited impact on infection or transmission of pertussis to other animals, whereas DTwP vaccines were effective in preventing infection and transmission.
  - It is plausible that in humans, as in nonhuman primates, asymptomatic or mildly symptomatic infections in DTaP-immunized persons may result in transmission of *B. pertussis* to others and may drive pertussis outbreaks.

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WHO position paper on pertussis vaccines (8)

Comparison of the effectiveness of wP-containing and aP-containing vaccines (continued)

- The baboon study suggests a significant role of Th1 and Th17 cells in the immune response to natural infection and to DTwP vaccine. The model suggests that both Th1 and Th17 memory responses are needed to produce sterilizing mucosal immunity. In baboons the aP vaccines induce higher Th2, but lower Th1 and Th17 responses, and are less effective in clearing the pertussis organisms and preventing transmission. Corresponding studies in humans are needed.

✓ Although the reasons for the resurgence of pertussis were found to be complex and varied by country, the shorter duration of protection and probable lower impact of aP vaccines on infection and transmission are likely to play critical roles.

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WHO position paper on pertussis vaccines (9)

Duration of protection and need for booster doses

- ✓ There is limited evidence on the duration of clinical protection conferred by wP vaccines. Available data suggest that duration of immunity acquired after a 3-dose series of wP vaccine is estimated to range from 4 to 12 years.
- ✓ For the vaccines currently in use, a 2014 systematic review indicates a maximum annual loss of protection of 13% and a minimum loss of 2% following a primary vaccination series with wP containing vaccines.
- ✓ In Sweden, a 2-dose primary aP immunization series with a booster at age 12 months provided protection against pertussis for approximately 5 years
- ✓ There is increasing evidence that protection following booster doses of aP vaccines wanes faster in individuals primed with aP rather than with wP vaccines
- ✓ Ongoing passive surveillance in the USA has demonstrated an increase in the incidence of pertussis among children aged 7–10 years who had been vaccinated with 5 doses of aP vaccine.
- ✓ Data also suggest a faster waning of protection following repeated booster doses. In contrast, wP vaccine used for at least the 1st dose followed by aP vaccines provides longer-lasting protection irrespective of the subsequent doses.

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Example of aP containing vaccines: Countries role in addressing aP vaccine shortage

Category	Factors	Countries role
Supply	Production issues	No role
	Limited supplier base	No role
Demand	Little demand flexibility	**Increase demand flexibility**
	Lack of demand predictability	**Review status of demand forecasting and planning**
Information	Supply information	No role
	Demand information	**Timely communication to procuring agency about demand, change in schedules, vaccines newly introduced in the NIP**
	Timely communication	No additional role

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Increased demand flexibility. The EMA example of aP vaccine shortage

Background:

- Early in 2015, there was a shortage of acellular pertussis-containing combination vaccines for use in EU immunisation programmes
- The shortage, currently affecting some of the EU/EEA Member States had direct consequences for the delivery of national vaccination programmes, with some countries having to revise their childhood vaccination policy.
- Discontinuing or delaying primary vaccination schemes would have dramatic consequences, in particular for the prevention of pertussis and invasive disease due to Haemophilus influenzae type b in infants and young children.

- As much as possible, the infant and young children immunisation schedule should be preserved in order to ensure the early and adequate protection of newborns. Preference should be given to the use of combined vaccines with the highest number of antigens.
  - Priority should be given to preserving the infant primary immunisation schedule (first year of life) over the first toddler booster dose (second year of life).
  - If applicable, the first toddler booster dose should be prioritised over the school-entry booster dose.

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Options for flexibilities due to vaccine shortage

- Possible adjustments to the primary immunisation series (0–2 years)
  - Priority should be given to preserving the infant primary immunisation schedule (first year of life) over the first toddler booster dose (second year of life).
  - If applicable, the first toddler booster dose should be prioritised over the school-entry booster dose.
- Options for vaccine substitution in the immunisation schedule
- Building stockpiles to ensure immunisation programmes are maintained during future shortages.

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Thank you
谢谢
Merci
Спасибо
شكراً
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