Vaccines save lives and protect against disability. The success of the organized immunization programmes is indisputable. Significant efforts are now being made by many stakeholders worldwide to roll out old and new vaccines to all children and adolescents.

It is therefore most unfortunate that more and more countries report stock-outs. Earlier this year the World Health Organization reported worldwide significant shortage of BCG vaccines and provided guidance on how to prioritize globally constrained BCG vaccine supply (1) as well as shortage of inactivated polio vaccines important for countries meeting the targets of the Polio Eradication and Endgame Strategic Plan (2).

To continue p 2

Kari Johansen
MD, PhD, European Centre for Disease Prevention and Control, Stockholm, Sweden
Further, the European Centre for Disease Prevention and Control, in a rapid risk assessment reported shortage of acellular pertussis-containing pediatric combination vaccines (tetravalent, pentavalent and hexavalent) in the EU/EEA (3).

The reported shortages have been documented to have an impact on vaccine coverage with the affected vaccines and put children worldwide at risk for developing infectious diseases that are vaccine-preventable if vaccines are available.

- The reasons for stock-outs seem to be multifactorial and all reasons are likely not known. In this issue of the ADVAC newsletter we cover the acellular pertussis-containing combination vaccines only. In 2015, the two large vaccine producers GSK and SanofiPasteur have been unable to deliver enough acellular pertussis-containing tetra-, penta- and hexavalent pediatric combination vaccines. A summary of a presentation made by industry representatives at the recent ADVAC alumni meeting held during the SAGE meeting in Geneva, Switzerland in this issue explain why there is a shortage and suggest options they wish to explore with Public Health Authorities, Regulatory Agencies and Scientific Societies to decrease complexity, reduce cycle times and increase efficiency.

- One of the options they propose is to identify possible correlates of protection for pertussis and the industry wish to see increased scientific efforts in this area. Very timely, a call for public-private partnership under the EC Joint Undertaking Innovative Medicine Initiative (IMI) on this topic was published in March 2015 (4). The overall objectives foreseen of this project are ‘to pursue the identification and validation of biomarkers of protective immunity to pertussis and the establishment of models of pertussis infection that will enable the refinement of current vaccination schedules and expedite the development and testing of novel or improved vaccine formulations’.

- Another option they propose is adaptation of vaccination schedules in the crisis situation. Should that be done temporarily it is essential to document vaccination events in manual or electronic immunization registries (5) to ensure that all children and adolescents receive all recommended vaccine doses needed for protection. Immunization registries could also support improved vaccination coverage overall with the recommended vaccines.

All efforts by involved stakeholders should now focus on identifying possible options for changing the current shortage situation to reduce the risk of children acquiring vaccine-preventable diseases.

References
1. Guidance on how to prioritize globally constrained BCG vaccine supply to countries produced by WHO Dept. of Immunizations, Vaccines and Biologicals, the WHO Global Tuberculosis Programme and UNICEF Supply and Programme Divisions 22 July 2015
2. Countries using and planning to introduce IPV and the global status of bOPV registration
3. Shortage of acellular pertussis-containing vaccines and impact on immunisation programmes in the EU/EEA 8 October 2015
4. IMI call text Pertussis vaccination research launched March 2015
5. K Johansen, P L Lopalco, J Giesecke Immunisation registers – important for vaccinated individuals, vaccinators and public health Eurosurveillance, Volume 17, Issue 16, 19 April 2012

Kari Johansen
Expert Influenza and other Vaccine Preventable Diseases Surveillance and Response Support Unit European Center for Disease Prevention and Control, Stockholm
September
- 24 - Philadelphia, USA: Scientific Committee

October
- 8 - San Diego, USA: Debate on "Are measles outbreaks enough reason for vaccine mandate enforcement?" with Edwin Asturias, Saad Omer & Stanley Plotkin.
- 20 - Geneva, Switzerland, during SAGE Meeting: Debate on "Dealing with vaccine shortage" with Okwo Bele & François Meurice.

November
- 20 - Rio de Janeiro, Brazil, during WSPID: Debate on "The Use of Dengue vaccines" with Hal Margolis and Edwin Asturias.

January
- 22 - Paris, France: Scientific Committee Meeting

May
- 10 - 14 - Brighton, UK: ESPID meeting & alumni get together meeting

June
- 23 May - 6 June - Veyrier du Lac, France: 17th ADVAC, selected participants will be known in the next newsletter

Next ESPID Meeting

One of ADVAC historical partners is ESPID.
Every year ESPID supports one or two members if those are selected participants for the 2016 ADVAC course selection.
For the 17th ADVAC, ESPID would again help people to benefit from the 2016 course, free of charge.
The ADVAC Alumni Get together meeting took place during ID Week 2015 in San Diego, California.

It was hosted at the enchanting Horton Grand Hotel in historic San Diego in California.

The subject of the ADVAC debate was to deliberate if measles outbreaks are enough reason for vaccine mandate enforcement.

Attended by 28 alumni from different corners of the world, and moderated by our forefather Dr. Stanley Plotkin, the debate provided a lively discussion on immunization mandates in the US.

Dr. Saad Omer (ADVAC 2006) eloquently provided justifications for this regulatory strategy and its “escape valves” while Dr. Edwin Asturias (ADVAC 2001) took the counterargument of the need for more education and openness to regain the population trust in vaccination programs.

A post-debate discussion by the alumni in the audience reached the conclusion that mandates while effective, are not enough as a strategy to maintain community protection, and education. Building public trust ensure long term confidence in immunizations.

Edwin J.Asturias, Associate Director, Center for Global Health, University of Colorado, Denver
The 10th ADVAC Alumni get-together was held October 21st, 2015 during the WHO SAGE meeting in Geneva, Switzerland. The topic of this meeting was ‘Shortage of pediatric vaccines’.

Public health perspective

Dr Jean-Marie Okwo-Bele from WHO HQ presented the global picture of stock-outs over time from 2010 to 2014. In this time-period the number of countries that reported stock-outs varied between 50 and 67 countries of the in total 194 WHO Member States during the different years (See table 1).

The average number of stock-out events in these countries was between 2.06 and 2.28 and the average duration of any stock-out was between 32 and 53 days.

Information on the actual impact of stock-out events on achieved vaccination coverage available for 17 countries was also presented. As expected a significant impact was reported: for BCG vaccines an estimated average 4% reduction was reported, for DTP 7%, polio 5% and measles 5% (See table 2).

Six countries experienced stock-outs for all four vaccines assessed namely BCG, DTP combination vaccine, polio and measles vaccine: Côte d’Ivoire, Haiti, Indonesia, Iraq, Papua New Guinea and the Philippines. Important for the polio eradication goal is that three of these countries reported estimated reduction in polio vaccination coverage in 2014 due to stock-outs greater than...

Table 1. Number of WHO Member States reporting vaccine stock-outs from 2010 to 2014

<table>
<thead>
<tr>
<th>WHO Member States (194)</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td># countries with stock-outs</td>
<td>67</td>
<td>66</td>
<td>57</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>% countries with stock-outs</td>
<td>35%</td>
<td>34%</td>
<td>29%</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>In countries with stock-outs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # stock-out events</td>
<td>151</td>
<td>148</td>
<td>119</td>
<td>111</td>
<td>110</td>
</tr>
<tr>
<td>Average # stock-out events</td>
<td>2.25</td>
<td>2.24</td>
<td>2.09</td>
<td>2.06</td>
<td>2.28</td>
</tr>
<tr>
<td>Max # stock-out events</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Average duration of stock-out (days)</td>
<td>44.5</td>
<td>34.6</td>
<td>33.5</td>
<td>31.5</td>
<td>52.7</td>
</tr>
</tbody>
</table>
In 2015 many of the European countries, that in the 2010-2014 period did not report any difficulties with stock-outs, started to report stock-outs for vaccines included in the routine immunization programmes such as BCG and the acellular pertussis-containing pediatric combination vaccines providing protection against diphtheria, invasive disease caused by Haemophilus influenza type b, hepatitis B, pertussis, polio and tetanus. The vaccine producers cannot deliver when countries are trying to procure.

**Industry perspective**

The industry was represented by François Meurice from GSK and Corinne Bardone from Sanofi Pasteur. Their presentation focused on the acellular pertussis-containing pediatric combination vaccines. No presentation at this meeting dealt with the BCG shortage.

The vaccine industry representatives reported that they are currently experiencing supply constraints affecting the acellular pertussis-containing pediatric combination vaccines. This shortage affects the acellular pertussis-containing hexavalent, pentavalent and tetravalent combination vaccines and the constraints are affecting many countries in the world. It was stressed that vaccine manufacturing operations are long and complex processes lasting between 18 to 24 months. It is estimated that 70% of this time is devoted to quality control testing. The regulatory environment is changing somewhat with new emerging markets procuring the vaccines, e.g. new countries want to re-test batches and visit the two manufacturers in Europe that produce these vaccines. Batch release was mentioned often being the main bottleneck. Industry is dependent upon Official Medicines Control Laboratories (OMCL) in national regulatory authorities for batch release. Dual testing conducted by the manufacturer’s laboratory and by the OMCL is the current praxis in the EU/EEA. With increased demand worldwide the OMCL testing capacity has not necessarily increased.

Further, the industry representatives reported an increasing demand for vaccines due to population growth in the EU/EEA, increased global demand for these vaccines, changed epidemiology leading to increased demands (e.g. pertussis outbreaks in young infants leading to introduction of maternal vaccination programmes), and an increased influx of refugees to the EU/EEA from areas with suboptimal vaccination coverage and therefore in need of vaccination. In addition, the manufacturing processes are expected to become more «lean» and therefore allow for fewer surpluses being produced resulting in reduced flexibility.

Particular issues raised by the industry representatives were the lack of correlates of protection for pertussis and that the current in vivo test used for potency assessment can represent an important source of variability in obtained results. This has had an impact on batch release of the acellular pertussis-containing vaccines since a number of the batches produced have been «out of specs» and therefore not released. The industry is currently seeking ways to change/improve the in vivo test in collaboration with regulatory authorities. It is unknown how long this will take.
Meanwhile the industry wishes to see an open dialogue between Public Health Authorities, Scientific Societies and Vaccine Manufacturers to decrease complexity, reduce cycle times and increase efficiency. Options they wish to explore are e.g:

- Adaptation of vaccination schedules in the crisis situation
- Adoption of standard packaging, e-packaging in the future
- Aligning (standardizing?) the type (presentation? packaging?) of pertussis-containing combination products across countries
- Timely anticipation of vaccine quantities needed (improving country demand forecasting and procurement)
- Refining regulatory specifications to reduce complexity for vaccine manufacturing for
  - post-approval changes
  - batch release

The meeting ended with a short question & answer session. Since this problem is complex and likely not solved in the near future it was decided to establish a possibility for ADVAC alumni to communicate on the issue. Invitations will come.

Kari Johansen, MD, PhD
European Centre for Disease Prevention and Control

Table 2. Estimated reduction in coverage due to stock-outs in 17 countries from which further information was available

<table>
<thead>
<tr>
<th>Estimated reduction in coverage due to stockouts</th>
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<tbody>
<tr>
<td>For 17 countries</td>
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<tr>
<td>Average (w)</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Max</td>
</tr>
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## New scientific committee

*List of new members who joined in October 2015*

<table>
<thead>
<tr>
<th>Dr Michael Makanga</th>
<th>Director of South-South Cooperation and Head of the Africa Office. Coming with a rich background, experience and knowledge of South-South partnerships in clinical trials and vaccines development.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr H. Keipp Talbot</td>
<td>Keipp Talbot coming with research interests including the molecular epidemiology of human coronaviruses and the evaluation of new influenza vaccines.</td>
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<td>Vanderbilt University</td>
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<tr>
<td>Dr Orin Levine</td>
<td>Bill &amp; Melinda Gates Foundation: Dr. Orin Levine leads the foundation's efforts to accelerate the introduction of new vaccines and related technologies and to improve routine immunization systems.</td>
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<td>Bill &amp; Melinda Gates Foun-</td>
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<td>Dr Rana Hajjah, CDC</td>
<td>Rana Hajjah, Director, Division of Bacterial diseases NCIRD at Centers for Disease Control and Prevention</td>
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<td>CDC</td>
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