



# VHPB MEETING

## Hot Topics

**Prevention and control of viral hepatitis**

- 1. Vaccine Shortage**
- 2. New hepatitis B Treatment**

LISBON, PORTUGAL  
15-16 March 2018

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# Content

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This pre-meeting document contains general background information on both meeting topics and on the speakers. Furthermore a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully it will give an overview of what has been published on the topics of the meeting

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# 1. Vaccine Shortage

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## 1.1. General background

### Vaccine and shortage

#### **WHO addressing global shortages (recent actions):**

- During the last WHO's Executive board January 2018, the global shortage of, and access to medicines and vaccines was discussed
  - Report by the Director General [Document EB142/13, 2017.](#)
  - [Decision EB 142/13](#)



**EXECUTIVE BOARD  
142nd session  
Agenda item 3.6**

**EB142(3)  
24 January 2018**

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## **Addressing the global shortage of, and access to, medicines and vaccines**

The Executive Board, having considered the report on addressing the global shortage of, and access to, medicines and vaccines,<sup>1</sup> decided to recommend to the Seventy-first World Health Assembly the adoption of the following decision:

The Seventy-first World Health Assembly, having considered the report on addressing the global shortage of, and access to, medicines and vaccines, decided to request the Director-General:

- (1) to elaborate a roadmap report, in consultation with Member States, outlining the programming of WHO's work on access to medicines and vaccines, including activities, actions and deliverables for the period 2019–2023;
- (2) to submit this roadmap report to the Seventy-second World Health Assembly for its consideration in 2019, through the Executive Board at its 144th session.

(Sixth meeting, 24 January 2018)

- WHO Strategic advisory Groupe on immunization (SAGE)  
April 2016 discussed vaccine shortage  
[Presentation Preempting and responding to vaccines supply](#)  
(Claire-Ann Siegrist – Stéphanie Mariat)

Lydon P, Schreiber B, Gasca A, Dumolard L, Urfer D, Senouci K. [Vaccine stockouts around the world: Are essential vaccines always available when needed?](#) Vaccine. 2017;35(17):2121-6.

INTRODUCTION: As countries rise to the challenge of implementing the priorities of this "Decade of Vaccine" and their commitments delineated in the Global Vaccine Action Plan (GVAP), many continue to face important challenges of securing a continuous supply of essential vaccine for their national immunization programme. This study provides evidence on the incidence of vaccine stockouts in countries, their root causes and their potential impact on service delivery. METHODS: Vaccine stockout indicators collected from the WHO-UNICEF Joint Reporting Form (JRF) and UNICEF's Vaccine Forecasting Tool were analysed for the years covering the first half of the GVAP (2011 to 2015) and using 2010 as the baseline year. While the JRF collects annual information on national and subnational stockouts by vaccine, the UNICEF Vaccine Forecasting Tool has the advantage of requesting UNICEF procuring countries to report on the reasons underpinning any stockouts. RESULTS: Every year on average, one in every three WHO Member States experiences at least one stockout of at least one vaccine for at least one month. The incidence is most pronounced in Sub-Saharan Africa where 38% of countries in this area of the world report national-level stockouts. The vaccines most affected are DTP containing vaccines (often combined with HepB and Hib) and BCG. They account for respectively 43% and 31% of stockout events reported. While national level vaccine stockouts occur in countries of all income groups, middle income countries are the most affected. In 80% of cases, national level stockouts were due to reasons internal to countries. More specifically, 39% of stockouts were attributable to government funding delays, 23% were caused by delays in the procurement processes, and poor forecasting and stock management at country level accounted for an additional 18%. When a national level stockout of vaccines occurs, there is an 89% chance that a subnational stockout will occur at district level. More concerning is that if a district level stockout occurs, this will lead to an interruption of vaccination services in 96% of cases. DISCUSSION: There continues to be important challenges of ensuring a continuous availability of essential vaccines. The global community, together with countries, urgently need to design effective interventions aimed at reducing the frequency and mitigating the impact of stockouts.

# FROM SHORTAGES TO SUSTAINABLE SUPPLY

## WHAT'S BEHIND MEDICINES & VACCINES SHORTAGES

### WHAT DO WE KNOW ABOUT IT?

Shortages are global, complex and occur at multiple points in the supply chain from manufacture to procurement and distribution.

Shortages occur when the right products are not available in:

- Right quantities
- Right time
- Right place
- Right conditions

ultimately creating a stockout at the point of appropriate service delivery to people



**IMPACT:** patients and health care workers

Disruption in the supply of medicines

and vaccines can result in:

- Delays or interruption of ongoing treatments
- Use of alternative, unfamiliar or less suitable medications
- Failure to treat
- Interruption of immunization services leading to missed opportunities to protect children



Medicines in short supply include many commonly used, generic sterile injectables, antibiotics, cancer and cardiovascular medicines, and pediatric formulations.

Countries of all income groups and regions are affected, but data is lacking in low- and middle-income countries.

Reported causes of medicine stockouts in Europe include manufacturing and other supply problems, but nearly half of all medicine stockouts are due to unknown causes.

Shortages cost US hospitals US\$416 million + US\$200 million to purchase more expensive alternative medicines + US\$216 million in labor costs.



55% of vaccine stockout events (for at least one vaccine and for at least one month) occur in middle-income countries.

80%+ countries reporting district level vaccine stockouts experience interruption of vaccination services.

15 OUT OF 25 vaccines in shortage or at risk of shortage

11% of causes of national vaccine stockouts are global in nature – either resulting from a global shortage or a quality issue related to a particular vaccine.

Root cause analysis of national-level vaccine stockouts (UNICEF, 2011-12)



Manufact causes 80% incl. funding delays, poor forecasting & stock management, procurement delays

Global causes 11% incl. g. global shortage, quality issues

Other causes 9%

### WHAT ARE THE ROOT CAUSES?

SUPPLY

Complexity of manufacturing processes compounded by:

- Long lead time (up to 2 years), with up to 70% in quality control for vaccines
- Scale up production (up to 5-10 years) with significant investments and long timelines for regulatory approvals
- Divergent regulatory requirements, notably for post-approval changes
- In vivo testing and dual or multiple batch release testing performed by health authorities
- Diverse country specific product and packaging requirements

Limited number of manufacturers due to high startup investment, technical knowledge, and uncertainty in demand

Timeliness of communication between policy makers, health authorities, countries, scientific experts, and vaccine manufacturers

DEMAND

- Increased, often unpredictable, global demand
- Limited anticipation of evolution of national health programs
- Unexpected demand changes or fluctuations, incl. outbreaks
- Inflexible purchasing mechanisms and delays in payment
- Vaccine hesitancy
- Limited efficiency of supply chain systems, including coordination of stock management, delivery issues, cold chain equipment, and wastage

### WHAT CAN MANUFACTURERS DO?

Manufacturers implement a combination of approaches to pre-empt shortages and ensure reliable supply of medicines and vaccines, including:

- Establish robust quality business, and communication management practices, e.g., holistic quality management systems, market forecasting methods, and inventory management techniques
- Optimize usage of existing industrial capacity, and if sustainability can be assured, continue to invest in industrial capacity and more robust control processes to increase production
- Manage country specific product and packaging requirements and post-approval complexity
- Engage with health authorities to improve security of supply and on early notification of potential supply disruptions

### WHAT CAN OTHERS DO?

To ensure a reliable supply of medicines and vaccines, proposed additional measures include:

- Initiate early dialogue between manufacturers and public health authorities
- More timely and accurate demand forecasting to enable manufacturers to better anticipate and meet public health needs
- Introduce more appropriate and flexible procurement practices, adapted to long production cycles
- When supply is constrained, apply rational allocation and supply strategies to maximize availability to prevent or treat priority conditions or groups
- Implement consistent and harmonized regulatory approaches for the management of global post-approval changes
- Reduce duplicate testing, eliminate animal testing, and foster regulatory adaptation AND Reduce the number of special national and regional product and packaging requirements

To address this global public health issue, it is critical that there is open dialogue between all key stakeholders across the health sector. Policy makers, health authorities, countries, scientific experts, and manufacturers need to work together to overcome the many challenges from manufacture to procurement and distribution. It is a global problem that requires global, regional, and national solutions.

Further reading: Medicines shortages, WHO Drug Information Vol. 20, No.2, 2014 | Vaccine stockouts around the world Lydon et al., Vaccine 25 (2017) 2121-2126  
The Complex Journey of a vaccine – Part I (IFPMA). For more information: [www.ifpma.org](http://www.ifpma.org)



## Hepatitis Vaccines:

Source: Plotkin: Vaccines, 7th Edition

### hepatitis A

Manufacturer	Trade Name	HAV Strain	Adjuvant	Dosage	Age	Volume (mL)	Schedule (mo) <sup>b</sup>
Merck & Co., Inc.	VAQTA	CR326F	Aluminum hydroxyphosphate sulfate	25 U	12 mo–18 y	0.5	0, 6–18
				50 U	≥19 y	1.0	0, 6–18
GlaxoSmithKline Biologicals	Havrix	HM175	Aluminum hydroxide	720 EL.U.	12 mo–18 y	0.5	0, 6–12
				1,440 EL.U.	≥19 y	1.0	0, 6–12
Sanofi Pasteur, Inc. <sup>377</sup>	Avaxim	GBM	Aluminum hydroxide	80 U	12 mo–15 y	0.5	0, 6–18
				160 U	≥16 y	0.5	0, 6–18
Crucell Vaccines Inc. <sup>385</sup>	Epaxal	RG-SB	Virosomes composed of 10 µg purified influenza virus hemagglutinin and 100 µg of phospholipids (immunopotentiating reconstituted influenza virosome)	25 IU	≥12 mo	0.5	0, 6–12
Sinovac Biotech Ltd.	Healive	TZ84	Aluminum hydroxide	250 U	12 mo–15 y	0.5	0, 6
				500 U	≥16 y	1.0	0, 6

EL.U., enzyme-linked immunosorbent assay units; HAV, hepatitis A virus; IU, international units; U, units of HAV antigen.

## Hepatitis vaccine: hepatitis B

TABLE 25.3 Hepatitis B Vaccines<sup>a</sup> Prequalified<sup>b</sup> by the World Health Organization

Manufacturer	Country	Vaccine Type	Brand Name	Prequalification Date	Presentation	Administration
Sanofi Pasteur	France	DTPa-HepB-Hib	Hexacim	12/19/2014	1-dose vial	IM
Bio Farma	Indonesia	HepB	Hepatitis B	05/13/2004	1-dose Uniject	IM
Bio Farma	Indonesia	DTPw-hepB	DTP-Hep B	10/07/2004	5- & 10-dose vial	IM or SC
Bio Farma	Indonesia	DTPw-hepB-Hib	DTP-Hep B-Hib	12/19/2014	5-dose vial	IM
Center for Genetic Engineering and Biotechnology	Cuba	HepB	Heberbiovac HB	12/11/2001	1- & 10-dose vial	IM
Biological E limited	India	DTPw-HepB-Hib	DTP-HepB-Hib	11/27/2014	5- & 2-dose vial	IM
Biological E limited	India	DTPw-HepB-Hib	DTP-HepB-Hib	08/31/2011	1- & 10-dose vial (Hib lyophilized)	IM
Biological E limited	India	DTPw-HepB-Hib	DTP-HepB-Hib	05/18/2012	1- & 10-dose vial (liquid)	IM
Berna Biotech Korea Corporation, a Crucell company	Republic of Korea	Hepatitis B	Hepavax-Gene	03/23/2004	1- & 10-dose vial	IM
Berna Biotech Korea Corporation, a Crucell company	Republic of Korea	Hepatitis B	Hepavax-Gene-TF	07/31/2012	1-dose vial, thimerosal free	IM
Berna Biotech Korea Corporation, a Crucell company	Republic of Korea	DTPw-hepB-Hib	Quinvaxem	09/26/2006	1-dose vial	IM
Berna Biotech Korea Corporation, a Crucell company	Republic of Korea	DTPw-hepB-Hib	Quinvaxem in Cpad	12/24/2014	1-dose vial Cpad, compact prefilled autodisable device	IM
GlaxoSmithKline	Belgium	Hepatitis B	Engerix-B	01/01/1987	1-, 10-, & 20-dose vial	IM
GlaxoSmithKline	Belgium	DTPw-hepB	Tritanrix-HB	04/01/1998	1-, 2-, & 10-dose vial	IM
GlaxoSmithKline	Belgium	DTPw-hepB-Hib	Tritanrix-Hib	04/16/2006	1-dose vial (+ lyophilized Hib)	IM
GlaxoSmithKline	Belgium	DTPw-hepB-Hib	Tritanrix-Hib	10/29/2003	2-dose vial (+ lyophilized Hib)	IM
LG Life Science, Ltd.	Republic of Korea	Hepatitis B	Euvax B	11/22/1996	1-, 2-, 6-, & 10-dose vial	IM
LG Life Science, Ltd.	Republic of Korea	DTPw-hepB-Hib	Euforvac-Hib inj.	08/24/2012	1- & 2-dose vial +	IM

Panacea Biotec	India	DTPw-hepB-Hib	Easy Five-TT	10/02/2013	1- & 10-dose vial	IM
Serum Institute of India, Ltd.	India	HepB	Hepatitis-B vaccine (rDNA)	11/12/2004	1- & 10-dose adult; 1-dose pediatric	IM
Serum Institute of India, Ltd.	India	DTPw-hepB	Diphtheria, tetanus, pertussis, and hepatitis-B	07/21/2006	1-dose ampule & 10- & 20-dose vial	IM
Serum Institute of India, Ltd.	India	DTPw-hepB-Hib		05/26/2010	1-, 2-, 10-dose vial + lyophilized Hib	IM
Serum Institute of India, Ltd.	India	DTPw-hepB-Hib		09/22/2010	1-, 2-, 10-dose (liquid)	IM
Shantha Biotechnics Private, Ltd.	India	HepB	Shanvac-B	06/10/2002	1-, 2-pediatric dose vial and 1-, 6-, 10-, & 20-dose vial	IM
Shantha Biotechnics Private, Ltd.	India	DTPw-hepB-Hib	Shan-5	04/29/2014	1-, 10-dose vial liquid	IM

D, diphtheria; HepB: hepatitis B; Hib: *Haemophilus influenzae* type b; IM, intramuscular; P, pertussis (w, whole cell; a, acellular; subcutaneous; T, tetanus.

Merck, Sharpe and Dohme (MSD) manufactures two hepatitis B-containing vaccines: Recombivax (Recombinant Hepatitis B Comvax (Hib Conjugate [meningococcal protein conjugate] and HepB [recombinant])). Recombivax has three presentations: single dose; adult single dose; and dialysis single dose. Comvax has one pediatric dose presentation. For both vaccines, administration is intramuscular and shelf life is 36 months at 2°–8°C. These vaccines are not prequalified by the WHO.



## 1.2. Presentation related Information

### 1.2.1. Session 2: vaccine shortage current situation

Presentation related references

Definitions on vaccine shortages

*Provided by speaker: Oleg Benes*



### 1.2.2. Session 3: Manufacturing of vaccines, what can influence the vaccine supply, complexity of vaccine manufacturing

Presentation related references

Vaccine Europe

*Provided by speaker: Michel Stoffel*



<https://www.vaccineurope.eu/>

Vaccines Europe members

- Abbott Biologicals
- AstraZeneca
- CureVac
- Janssen
- GlaxoSmithKline Vaccines
- MSD
- Novavax
- Pfizer Vaccines
- Sanofi Pasteur
- Seqirus
- Takeda
- Vaxcel

Vaccines Europe (VE), is a specialised vaccines group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), the professional association of the pharmaceutical industry in Europe.

Formed in 1991, Vaccines Europe represents major innovative research-based vaccine companies as well as small and medium sized enterprises operating in Europe which account for a large share of human vaccines used worldwide. Companies represented within Vaccines Europe are involved in research and development (R&D), clinical trials, production and marketing of vaccines and are dedicated to improving public health through immunisation

### Mission

The mission of Vaccines Europe is to support improved access to immunisation, enabling better protection of the health of individuals and the wider community throughout life, with both existing vaccines and those in development.

Vaccines Europe is devoted to:

- proactively representing and voicing industry views on key issues of common interest being discussed at EU level;
- raising awareness about the value and benefit of vaccines and vaccination and the contribution of the vaccine industry in Europe and worldwide.

Vaccines Europe aims to:

- foster a favourable policy climate for the vaccine industry in Europe in order to facilitate availability and access to new and innovative vaccines worldwide;
- create a supportive environment for improved vaccine protection, innovative vaccine development and improved coverage throughout life in the interest of individuals and the community;
- support vaccine R&D through innovative vaccine applications.

### 1.2.3. Session 4: hepatitis A and B vaccine shortage (potential) Impact on public health

Presentation related references

Impact of vaccine shortage in Albania + Balkan countries

*Provided by speaker: Silvia Bino*

Presentation related references

Impact of vaccine shortage in Germany – Paul Ehrlich Institute

*Provided by speaker: Isabelle Bekeredjian-Ding*

Presentation related references

Impact of vaccine shortage in The Netherlands – RIVM

*Provided by speaker: Truus de Graaf*

### 1.2.4. Session 5: The Role of the different European stakeholders in case of vaccine shortage

List of potential European stakeholders in vaccine shortage debate (working table/ incomplete)

<b>DG Santé</b>	<p>DG Santé develops and carries out the commission's policies on food safety/public health</p> <p>Vaccination</p>	<p><a href="https://ec.europa.eu/info/departments/health-and-food-safety_en#responsibilities">https://ec.europa.eu/info/departments/health-and-food-safety_en#responsibilities</a></p> <p><a href="https://ec.europa.eu/health/vaccination/overview_en">https://ec.europa.eu/health/vaccination/overview_en</a></p>
<b>ECDC</b>	<p>The European Centre for Disease Prevention and Control (ECDC) was established in 2005. It is an EU agency aimed at strengthening Europe's defences against infectious diseases. It is located in Stockholm, Sweden.</p> <p>ECDC works in three key strategic areas: it provides evidence for effective and efficient decision-making, it strengthens public health systems, and it supports the response to public health threats</p>	<p><a href="https://ecdc.europa.eu/en/immunisation-and-vaccines">https://ecdc.europa.eu/en/immunisation-and-vaccines</a></p>

<b>European Commission</b>	See DG Santé	
<b>EMA</b>	<p>The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London. It began operating in 1995. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.</p> <p>EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by ensuring that all medicines available on the EU market are safe, effective and of high quality</p>	<a href="http://www.ema.europa.eu/ema/">http://www.ema.europa.eu/ema/</a>
<b>National - regional Minister of health/ public health</b>	See national/regional MOH + NITAG	
<b>NiTAG</b>	National Immunization Technical Advisory Groups (NITAGs) are multidisciplinary groups of national experts responsible for providing independent, evidence-informed advice to policy makers and programme managers on policy issues related to immunization and vaccines.	<a href="http://www.who.int/immunization/sage/national_advisory_committees/en/">http://www.who.int/immunization/sage/national_advisory_committees/en/</a>
<b>WHO Euro</b>	European Vaccine Action plan, 2015-2020 EVAP objective 5: Immunization programmes have sustainable access to predictable funding and high-quality supply	<a href="http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications">http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications</a>
<b>WHO HQ</b>	<p>Immunization information</p> <p>WHO Prequalified vaccines</p> <p>Executive board 142 12 jan18: addressing the global shortage of and access of medicines and vaccines</p>	<p><a href="http://www.who.int/topics/immunization/en/">http://www.who.int/topics/immunization/en/</a></p> <p><a href="http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/">http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/</a></p> <p><a href="http://apps.who.int/gb/ebwha/pdf_files/EB142/B142_13-en.pdf">http://apps.who.int/gb/ebwha/pdf_files/EB142/B142_13-en.pdf</a></p>

### 1.2.5. Session 6: initiatives taken to prevent vaccine shortages or to minimize the impact

#### Presentation related references

#### Hepatitis B: Vaccine recommendations during supply constraints

*Provided by speaker: Sema Mandal*

<https://www.gov.uk/government/publications/hepatitis-b-vaccine-recommendations-during-supply-constraints>



[Home](#) > Hepatitis B: vaccine recommendations during supply constraints

#### Guidance

### Hepatitis B: vaccine recommendations during supply constraints

Vaccine recommendations for adults and children during periods of vaccine supply constraints.

Published 21 July 2017

Last updated 26 February 2018 — [see all updates](#)

From: [Public Health England](#)

#### Documents

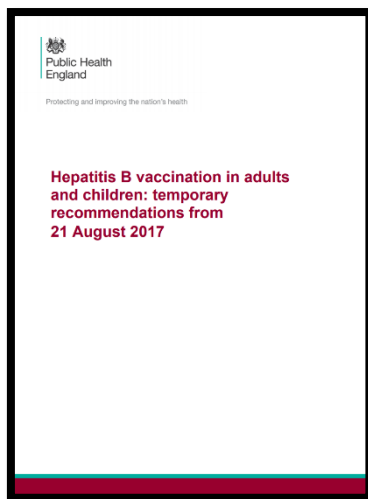


#### [Plan for phased re-introduction of hepatitis B vaccine for lower priority groups 2018](#)

Ref: Gateway number: 2017806  
PDF, 247KB, 9 pages

This file may not be suitable for users of assistive technology. [Request an accessible format.](#)

<https://www.gov.uk/government/publications/hepatitis-b-vaccine-recommendations-during-supply-constraints>



[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/639145/Hepatitis B vaccine recommendations during supply constraints .pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/639145/Hepatitis_B_vaccine_recommendations_during_supply_constraints_.pdf)

#### Summary of key principles for providers

Prioritise scarce supply for those at highest IMMEDIATE risk

- Section 1

Provide advice to individuals whose vaccination is deferred and flag them for recall

- Section 2

Advise other ways of avoiding exposure to hepatitis B

- Section 3

Use alternative vaccines where possible

- Section 4, tables 2-4

Use dose sparing schedules and defer routine boosters

- Section 5, table 5

Order and manage stock responsibly

- Section 6

<https://www.gov.uk/government/news/current-global-shortage-of-hepatitis-b-vaccine#history>

<https://www.gov.uk/government/news/current-global-shortage-of-hepatitis-b-vaccine#history>

News story

## Current global shortage of hepatitis B vaccine

There is currently a global shortage of hepatitis B vaccine which has been caused by problems in the manufacturing process.

Published 7 August 2017

Last updated 1 March 2018 — [see all updates](#)

From: [Public Health England](#)



Presentation related references

USA – Tracking Vaccine shortages and ACIP recommendations

*Provided by speaker:* John Ward – Cindy Weinbaum

[Website vaccine shortage](#)

[CDC: National Vaccine Supply Shortage](#)

Vaccine	Shortage	Temporary Change From Routine Recommendation
Diphtheria, Tetanus, & Pertussis (DTaP and Tdap)	No	
<i>Haemophilus influenzae</i> type B (Hib)	No	
Hepatitis A	See <a href="#">note<sup>1</sup></a>	
Hepatitis B	See <a href="#">note<sup>2</sup></a>	
Human Papillomavirus (HPV)	No	
Inactivated Polio (IPV)	No	
Influenza	No	See current information about <a href="#">influenza</a>
Measles, Mumps, & Rubella (MMR)	See <a href="#">note<sup>3</sup></a>	See <a href="#">Q&amp;As about monovalent M-M-R vaccines</a> Oct 2009
Meningococcal Conjugated (MCV4)	No	
Pneumococcal Conjugated (PCV)	No	
Pneumococcal Polysaccharide (PPV)	No	
Rotavirus	No	
Serogroup B Meningococcal (MenB)	No	
Td	No	
Varicella/Zoster	No	

**Note<sup>1</sup>:** In light of ongoing outbreaks of Hepatitis A among adults in several US cities, the demand for adult Hepatitis A vaccine has increased substantially over the past 6 months and vaccine supply to meet this unexpected demand in the US has become constrained. In order to address current supply constraints in the US, CDC staff are working directly with public health officials to provide guidance about how best to target vaccine distribution. In addition, US-licensed manufacturers of adult Hepatitis A vaccine are exploring options to increase domestic supply and are working collaboratively with CDC to monitor and manage public and private vaccine orders to make the best use supplies of adult Hepatitis A vaccine during this period of unexpected increased demand. Of note, the constraints described in this footnote do **not** apply to the pediatric Hepatitis A vaccine supply in the US. Updated Jan 2018

**Note<sup>2</sup>:** Merck is not currently distributing its adult Hepatitis B vaccine and does not expect to be distributing adult Hepatitis B vaccine between now and the end of 2018. Additionally, Merck anticipates that its pediatric Hepatitis B vaccine will be unavailable until April 1, 2018. Merck's supply of the dialysis formulation of Hepatitis B vaccine, however, is not affected and is expected to remain available. GSK has sufficient supplies of adult and pediatric Hepatitis B vaccines to address these anticipated gap in Merck's supply of adult and pediatric Hepatitis B vaccines during these time periods; however, preferences for a specific presentation (i.e., vial versus syringe) may not be met consistently during this time. Updated Dec 2017



## 1.3. Pubmed search Vaccine shortage

### 1.3.1. Vaccine shortage of hepatitis vaccines

Pubmed MEDLINE search on {(Hepatitis ) AND (Vaccine) AND (Shortage) } in all [Abstract/title] and filter: 'last 10 years' on was performed.  
The references were manually sorted in the different subject in an EndNote database.  
The references are listed by publication year (recent first).

Ziesenitz, V. C., Mazer-Amirshahi, M., Zocchi, M. S., Fox, E. R. and May, L. S. "**U.S. vaccine and immune globulin product shortages, 2001-15.**" *Am J Health Syst Pharm* **2017** 74(22): 1879-1886.

PURPOSE: Trends in shortages of vaccines and immune globulin products from 2001 through 2015 in the United States are described. METHODS: Drug shortage data from January 2001 through December 2015 were obtained from the University of Utah Drug Information Service. Shortage data for vaccines and immune globulins were analyzed, focusing on the type of product, reason for shortage, shortage duration, shortages requiring vaccine deferral, and whether the drug was a single-source product. Inclusion of the product into the pediatric vaccination schedule was also noted. RESULTS: Of the 2,080 reported drug shortages, 59 (2.8%) were for vaccines and immune globulin products. Of those, 2 shortages (3%) remained active at the end of the study period. The median shortage duration was 16.8 months. The most common products on shortage were viral vaccines (58%), especially hepatitis A, hepatitis B, rabies, and varicella vaccines (4 shortages each). A vaccine deferral was required for 21 shortages (36%), and single-source products were on shortage 30 times (51%). The most common reason for shortage was manufacturing problems (51%), followed by supply-and-demand issues (7%). Thirty shortages (51%) were for products on the pediatric schedule, with a median duration of 21.7 months. CONCLUSION: Drug shortages of vaccines and immune globulin products accounted for only 2.8% of reported drug shortages within a 15-year period, but about half of these shortages involved products on the pediatric vaccination schedule, which may have significant public health implications.

Matthews, P. C. and Barnes, E. "**Hepatitis B vaccine shortage: another symptom of chronic neglect?**" *BMJ* **2017** 359: j4686. Nuffield Department of Medicine, Peter Medawar Building for Pathogen Research, University of Oxford, Oxford OX1 3SY, UK.

Kmietowicz, Z. "**Doctors are told to use hepatitis B vaccine sparingly because of global shortage.**" *BMJ* **2017** 358: j3801. The BMJ.

Kendall-Raynor, P. "**Hepatitis B vaccine shortage.**" *Nurs Stand* **2017** 32(2): 15

Essential facts The hepatitis B vaccine is highly effective in preventing infection if given before exposure and is also effective post-exposure. Post-exposure vaccination should start immediately, ideally within 24 hours.

"**Advice on hep B vaccine shortage.**" *Nurs Stand* **2017** 31(51): 9

Guidance for health professionals has been issued after global shortages of the hepatitis B vaccine has severely affected UK supply.

"**National, state, and local area vaccination coverage among children aged 19-35 months--United States, 2011.**" *MMWR Morb Mortal Wkly Rep* **2012** 61: 689-696

High vaccination coverage in children by age 2 years has resulted in historically low levels of most vaccine-preventable diseases in the United States, but coverage must be maintained to reduce the burden of disease further and prevent a resurgence of these diseases, particularly in populations with lower vaccination coverage. This report describes national, state, and selected

local area vaccination coverage by age 19-35 months for children born during January 2008-May 2010, based on 2011 National Immunization Survey (NIS) results. Vaccination coverage remained above the national Healthy People 2020 target\* of 90% for  $\geq 1$  dose measles, mumps, rubella vaccine (MMR) (91.6%),  $\geq 3$  doses of hepatitis B vaccine (HepB) (91.1%),  $\geq 3$  doses of poliovirus vaccine (93.9%), and  $\geq 1$  dose of varicella vaccine (90.8%). For the birth dose of HepB, coverage increased from 64.1% in 2010 to 68.6% in 2011; for the more recently recommended  $\geq 2$  doses of hepatitis A vaccine (HepA) and rotavirus vaccines, coverage increased from 49.7% to 52.2% and from 59.2% to 67.3%, respectively; and for the full series of Haemophilus influenzae type b vaccine (Hib), coverage increased from 66.8% to 80.4%, reflecting recovery from the Hib shortage that occurred during December 2007-September 2009. The percentage of children who had not received any vaccinations remained at  $<1\%$ . Children living below the poverty level had lower coverage than children living at or above poverty for  $\geq 4$  doses of diphtheria, tetanus toxoid, and acellular pertussis vaccine (DTaP) and  $\geq 4$  doses of pneumococcal conjugate vaccine (PCV) (by 6 percentage points each); the full Hib series (by 8 percentage points); and for rotavirus vaccination (by 10 percentage points). Continued partnerships among national, state, local, private, and public entities are needed to sustain current coverage levels and ensure that coverage for the more recently recommended vaccines continues to increase for all children.

Smith, P. J. and Singleton, J. A. "**County-level trends in vaccination coverage among children aged 19-35 months - United States, 1995-2008.**" *MMWR Surveill Summ* **2011** 60(4): 1-86.

PROBLEM/CONDITION: Estimated trends in county-level vaccination coverage compared with national health objectives and associated with other variables (e.g., access to care, economic conditions, and demographic characteristics) have not been reported previously. REPORTING PERIOD: 1995-2008. DESCRIPTION OF SYSTEM: The National Immunization Survey (NIS) is an ongoing, random-digit-dialed telephone survey that gathers vaccination coverage data from households with children aged 19-35 months in 50 states and selected urban areas and territories. RESULTS: During 1995-2008, 185,336 children aged 19-35 months sampled by NIS had adequate provider data and lived in one of the 257 counties where the combined sample size for at least one of the seven biennial periods during 1995-2008 was  $\geq 35$ . Statistically significant increases in estimated vaccination coverage occurred in 27 of 233 counties (12%) with  $\geq 4$  doses of diphtheria and tetanus toxoids and acellular pertussis (DTaP); for 38 of 233 counties (16%) with  $\geq 3$  doses of polio vaccine; eight of 233 counties (3%) with  $\geq 1$  dose of measles, mumps, and rubella (MMR); nine of 233 counties (4%) with  $\geq 3$  doses of Haemophilus influenzae type B (Hib) vaccine; 193 of 233 counties (83%) with  $\geq 3$  doses of hepatitis B vaccine; 228 of 232 counties (98%) with  $\geq 1$  dose of varicella vaccine; and 187 of 192 counties (97%) with  $\geq 4$  doses of 7-valent pneumococcal conjugate vaccine (PCV7). Six of 233 (2%) counties had significant decreases in vaccination coverage for Hib. During the 2007-2008 biennial period, the percentage of 193 counties with estimated vaccine coverage that achieved the Healthy People 2010 objective of 90% vaccination coverage was 8% for DTaP/DTP vaccines, 93% for polio vaccine, 86% for MMR vaccine, 71% Hib vaccine, 94% for hepatitis B vaccine, 50% for varicella vaccine, and  $<1\%$  for PCV7. Among 104 counties, the estimated percentage of children aged 6-23 months who were administered  $\geq 1$  dose of the seasonal influenza vaccine during the 2007-2008 influenza vaccination season was 39.0% (range: 22.2%-68.8%). For most vaccines and vaccine series, higher levels of county-level vaccination coverage correlated with a higher number of pediatricians per capita, a higher number of people living in group quarters (e.g., college residence halls, residential treatment centers, skilled nursing facilities, group homes, military barracks, correctional facilities, workers' dormitories, and facilities for persons experiencing homelessness) per capita, higher per capita income, a higher number of Hispanics per capita, and having a service-dependent economy. Lower levels of county-level vaccination coverage correlated with higher number of persons in poverty per capita, a higher percentage of black children among children aged  $<5$  years, higher levels of housing stress (i.e.,  $\geq 30\%$  income for rent or mortgage and certain inadequate housing characteristics), a higher number of pediatric intensive care beds per capita, and designation as a nonmetropolitan county with an economy dependent on recreation activities. INTERPRETATION: During 1995-2008, significant increases in vaccination coverage for individual vaccines occurred in many counties for the newly recommended vaccines, varicella

and PCV7. PUBLIC HEALTH ACTIONS: In counties that did not meet the Healthy People 2010 vaccination coverage objectives, states should evaluate strategies to achieve these objectives. The Guide to Community Preventive Services provides a summary of interventions that increase community vaccination coverage, including provider reminder-recall systems that remind parents to return to clinics to administer missed doses to children and assessment and feedback on the performance of vaccination providers. In counties where significant decreases in Hib vaccination coverage occurred, additional research is warranted to determine whether the recent shortage in the Hib vaccine was the sole cause of these decreases. In counties with a high proportion of children living in poverty, interventions to increase vaccination coverage among these children are needed. Additional research is required to understand potential barriers to increased coverage with these vaccines, the role of vaccination providers and their resource constraints, and factors associated with access to health care among children.

### 1.3.2. Impact of vaccine shortages on public health

McCarthy NL, Irving S, Donahue JG, Weintraub E, Gee J, Belongia E, Baggs J. **Vaccination coverage levels among children enrolled in the Vaccine Safety Datalink.** *Vaccine.* 2013;31(49):5822-6. INTRODUCTION: The Vaccine Safety Datalink (VSD) is a collaborative project whose infrastructure provides comprehensive medical and immunization histories for more than 9 million adults and children annually, a predominantly insured population. This study provides the coverage rates of recommended vaccines among children 19-35 months in the VSD from 2005 through 2010. We examine the consistency in vaccine coverage levels, detect possible trends, and evaluate any effect of vaccine shortages on coverage in the VSD. METHODS: We included data from all 10 VSD sites, and examined each year independently. Coverage rates were defined as the percentage of children in the VSD aged 19, 24, or 35 months in a given study year who had received the specified Advisory Committee on Immunization Practices (ACIP) recommended vaccine(s). RESULTS: We assessed coverage on 658,154 children. The overall coverage rate for children receiving all of the specified ACIP recommended vaccines was 73%, 80%, and 78% at ages 19, 24, and 35 months respectively. The range of coverage across all ages and years was 95-97% for polio vaccine, 91-97%, for MMR vaccine, 94-97% for HepB vaccine, 81-95% for DTaP vaccine, 90-95% for varicella vaccine, 66-91% for PCV, and 93-98% for Hib vaccine. Coverage rates of 4 or more doses of PCV were relatively low in 2005 possibly due to a vaccine shortage, and increased sharply in 2007. Hib vaccine coverage was relatively stable among all ages until 2009 when rates declined among children aged 19 and 24 months also during a vaccine shortage. CONCLUSIONS: Vaccine coverage in the VSD is high, but there is a decline from 2005 to 2010. The results of this study provide benchmark data for future studies, and describe how vaccine supply shortages and resulting changes in ACIP recommendations may have affected vaccine coverage rates in the VSD.

Jackson ML, Rose CE, Cohn A, Coronado F, Clark TA, Wenger JD, . . . Hennessy TW. **Modeling insights into Haemophilus influenzae type b disease, transmission, and vaccine programs.** *Emerging infectious diseases.* 2012;18(1):13-20. In response to the 2007-2009 Haemophilus influenzae type b (Hib) vaccine shortage in the United States, we developed a flexible model of Hib transmission and disease for optimizing Hib vaccine programs in diverse populations and situations. The model classifies population members by age, colonization/disease status, and antibody levels, with movement across categories defined by differential equations. We implemented the model for the United States as a whole, England and Wales, and the Alaska Native population. This model accurately simulated Hib incidence in all 3 populations, including the increased incidence in England/Wales beginning in 1999 and the change in Hib incidence in Alaska Natives after switching Hib vaccines in 1996. The model suggests that a vaccine shortage requiring deferral of the booster dose could last 3 years in the United States before loss of herd immunity would result in increasing rates of invasive Hib disease in children <5 years of age.

White KE, Pabst LJ, Cullen KA. **Up-to-date Haemophilus influenzae type b vaccination coverage during a vaccine shortage.** *Pediatrics.* 2011;127(3):e707-12. OBJECTIVES: We sought to assess Haemophilus influenzae type b (Hib) vaccination coverage in

diverse areas of the United States during the 2008-2009 Hib vaccine shortage. Interim recommendations for Hib vaccination during the shortage called for deferral of the booster dose only among children not at high risk for disease; the primary series given during the first year of life continued to be recommended for all children. METHODS: Vaccination data on approximately 123,000 children were collected from 8 Immunization Information System (IIS) sentinel sites. Completion of the primary Hib series (with 2 or 3 doses depending on vaccine type) by 9 months old during the vaccine shortage was compared with coverage of 2 vaccines given at similar ages (7-valent pneumococcal conjugate vaccine and diphtheria, tetanus acellular pertussis vaccine) in children born between November 1, 2007, and March 31, 2008. RESULTS: During the shortage period, Hib vaccination coverage for the primary series was 7.8 to 10.3 percentage points lower than diphtheria, tetanus acellular pertussis vaccine and 7-valent pneumococcal conjugate vaccine coverage for children by the age of 9 months in 7 of 8 sentinel sites. CONCLUSIONS: A significant decrease in Hib vaccination coverage for the primary series was observed and was consistent across several US localities. Close collaboration between the public health community and vaccine providers is essential during vaccine shortages to ensure that interim vaccination recommendations are clear, widely disseminated, and closely followed, and that access to available vaccine supplies is maintained.

Horowitz IN, Baorto E, Davis J, Barisciano L. **Haemophilus influenzae type B meningitis in a previously healthy child.** Pediatric emergency care. 2010;26(10):759-62.

Vaccines have proven successful in virtually eradicating certain infectious diseases that typically attack the pediatric population. Since 1988, when the conjugate vaccine was introduced, the incidence of invasive Haemophilus influenzae type B disease was reduced dramatically. However, immunization rates have decreased in certain parts of the country because of a combination of vaccine shortage and widespread parental perception that vaccines are harmful. We present the case of a previous healthy child, who ultimately succumbed to H. influenzae type B meningitis where multiple factors were likely responsible for his acquisition of the disease.

### 1.3.3. Lessons learnt from other vaccines shortages

Zipursky S, Patel M, Farrell M, Gonzalez AR, Kachra T, Folly Y, . . . Hampton LM. **Lessons Learned From Managing the Planning and Implementation of Inactivated Polio Vaccine Introduction in Support of the Polio Endgame.** The Journal of infectious diseases. 2017;216(suppl\_1):S15-S23. The Immunization Systems Management Group (IMG) was established as a time-limited entity, responsible for the management and coordination of Objective 2 of the Polio Eradication and Endgame Strategic Plan. This objective called for the introduction of at least 1 dose of inactivated polio vaccine (IPV) into the routine immunization programs of all countries using oral polio vaccine (OPV) only. Despite global vaccine shortages, which limited countries' abilities to access IPV in a timely manner, 105 of 126 countries using OPV only introduced IPV within a 2.5-year period, making it the fastest rollout of a new vaccine in history. This achievement can be attributed to several factors, including the coordination work of the IMG; high-level engagement and advocacy across partners; the strong foundations of the Expanded Programme on Immunization at all levels; Gavi, the Vaccine Alliance's vaccine introduction experiences and mechanisms; innovative approaches; and proactive communications. In many ways, the IMG's work on IPV introduction can serve as a model for other vaccine introductions, especially in an accelerated context.

Parker LA, Rumunu J, Jamet C, Kenyi Y, Lino RL, Wamala JF, . . . Cabrol JC. **Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan.** The Lancet Infectious diseases. 2017;17(4):e123-e7.

Shortages of vaccines for epidemic diseases, such as cholera, meningitis, and yellow fever, have become common over the past decade, hampering efforts to control outbreaks through mass reactive vaccination campaigns. Additionally, various epidemiological, political, and logistical challenges, which are poorly documented in the literature, often lead to delays in reactive

campaigns, ultimately reducing the effect of vaccination. In June 2015, a cholera outbreak occurred in Juba, South Sudan, and because of the global shortage of oral cholera vaccine, authorities were unable to secure sufficient doses to vaccinate the entire at-risk population—approximately 1 million people. In this Personal View, we document the first public health use of a reduced, single-dose regimen of oral cholera vaccine, and show the details of the decision-making process and timeline. We also make recommendations to help improve reactive vaccination campaigns against cholera, and discuss the importance of new and flexible context-specific dose regimens and vaccination strategies.

Huang WT, Lin HC, Yang CH. **Undervaccination with diphtheria, tetanus, and pertussis vaccine:**

**National trends and association with pertussis risk in young children.** *Human vaccines & immunotherapeutics*. 2017;13(4):757-61.

**BACKGROUND:** The high coverage for  $\geq 3$  pertussis vaccine doses among Taiwanese children might not imply timely vaccination. Recently, resurgence of pertussis and challenges with availability of DTaP-IPV-Hib prompted this study. **METHODS:** In the 1996-2012 national birth cohort, we calculated the prevalence and days of undervaccination against pertussis by age 36 months. We also compared the odds of undervaccination in each laboratory-confirmed pertussis patient at ages 3-35 months with sex-, residence-, and age-matched controls from the general population, using conditional logistic regression. **RESULTS:** The prevalence of undervaccination was 60.6% (median 16 days) and decreasing ( $p < 0.0001$ ). Among 145 cases and 2,900 controls, 58 (40.0%) and 721 (24.9%) were undervaccinated (OR 2.28, 95% CI 1.57-3.31). The attributable risk percent was 22.5% (95% CI 14.5-27.9). **CONCLUSIONS:** Undervaccination was decreasing. Approximately up to one-fifth pertussis cases in children aged 3-35 months could have been prevented with on-time vaccination.

Gershman MD, Angelo KM, Ritchey J, Greenberg DP, Muhammad RD, Brunette G, . . . Sotir MJ.

**Addressing a Yellow Fever Vaccine Shortage - United States, 2016-2017.** *MMWR Morbidity and mortality weekly report*. 2017;66(17):457-9.

Recent manufacturing problems resulted in a shortage of the only U.S.-licensed yellow fever vaccine. This shortage is expected to lead to a complete depletion of yellow fever vaccine available for the immunization of U.S. travelers by mid-2017. CDC, the Food and Drug Administration (FDA), and Sanofi Pasteur are collaborating to ensure a continuous yellow fever vaccine supply in the United States. As part of this collaboration, Sanofi Pasteur submitted an expanded access investigational new drug (eIND) application to FDA in September 2016 to allow for the importation and use of an alternative yellow fever vaccine manufactured by Sanofi Pasteur France, with safety and efficacy comparable to the U.S.-licensed vaccine; the eIND was accepted by FDA in October 2016. The implementation of this eIND protocol included developing a systematic process for selecting a limited number of clinic sites to provide the vaccine. CDC and Sanofi Pasteur will continue to communicate with the public and other stakeholders, and CDC will provide a list of locations that will be administering the replacement vaccine at a later date.

Wahid R, Holt R, Hjorth R, Berlanda Scorza F. **Chemistry, manufacturing and control (CMC) and clinical trial technical support for influenza vaccine manufacturers.** *Vaccine*.

2016;34(45):5430-5.

With the support of the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services, PATH has contributed to the World Health Organization's (WHO's) Global Action Plan for Influenza Vaccines (GAP) by providing technical and clinical assistance to several developing country vaccine manufacturers (DCVMs). GAP builds regionally based independent and sustainable influenza vaccine production capacity to mitigate the overall global shortage of influenza vaccines. The program also ensures adequate influenza vaccine manufacturing capacity in the event of an influenza pandemic. Since 2009, PATH has worked closely with two DCVMs in Vietnam: the Institute of Vaccines and Medical Biologicals (IVAC) and VABIOTECH. Beginning in 2013, PATH also began working with Torlak Institute in Serbia; Instituto Butantan in Brazil; Serum Institute of India Private Ltd. in India; and Changchun BCBT Biotechnology Co. (BCBT) in China. The DCVMs supported under the GAP program all had existing influenza vaccine manufacturing capability and required technical

support from PATH to improve vaccine yield, process efficiency, and product formulation. PATH has provided customized technical support for the manufacturing process to each DCVM based on their respective requirements. Additionally, PATH, working with BARDA and WHO, supported several DCVMs in the clinical development of influenza vaccine candidates progressing toward national licensure or WHO prequalification. As a result of the activities outlined in this review, several companies were able to make excellent progress in developing state-of-the-art manufacturing processes and completing early phase clinical trials. Licensure trials are currently ongoing or planned for several DCVMs.

Palkonyay L, Fatima H. **A decade of adaptation: Regulatory contributions of the World Health Organization to the Global Action Plan for Influenza Vaccines (2006-2016).** Vaccine. 2016;34(45):5414-9.

The Global Action Plan (GAP) for Influenza Vaccines is a decade-long initiative that brings together a diverse range of stakeholders to work towards reducing anticipated global shortage of influenza vaccines and ensuring more equitable access to vaccines during the next influenza pandemic. Since its inception in 2006, significant progress has been made towards all the main objectives of GAP, namely: (1) an increase in seasonal vaccine use, (2) an increase in vaccine production, and (3) progress in research and development of more effective vaccines. The Technology Transfer Initiative (TTI), conceived and managed by WHO under the GAP, contributed to increasing regional influenza vaccine production capacity. This was achieved by facilitating technology transfer in 14 low- and middle-income countries, through grants to manufacturers to establish or strengthen influenza vaccine production capacity and support to their national regulatory authorities. Five of the countries subsequently licensed locally produced influenza vaccines; two pandemic and three seasonal vaccines received WHO prequalification. The success of GAP can be largely attributed to the regulatory support provided by WHO to both manufacturers and regulators. This support had two components: (1) direct regulatory support to GAP/TTI, and (2) support to GAP-related WHO programmes, such as the Pandemic Influenza Vaccine Deployment Initiative in 2010 and the Pandemic Influenza Preparedness Framework since 2013, especially in non-vaccine-producing countries. Temporary adaptation of the assessment process for influenza vaccines in the WHO Vaccine Prequalification Programme to the A(H1N1) pandemic situation in 2009 was instrumental to the success of the WHO Pandemic Influenza Vaccine Deployment Initiative in its attempt to meet the demand for pandemic vaccines in countries that received donated vaccines.

McLean KA, Goldin S, Nannei C, Sparrow E, Torelli G. **The 2015 global production capacity of seasonal and pandemic influenza vaccine.** Vaccine. 2016;34(45):5410-3.

A global shortage and inequitable access to influenza vaccines has been cause for concern for developing countries who face dire consequences in the event of a pandemic. The Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 to increase global capacity for influenza vaccine production to address these concerns. It is widely recognized that well-developed infrastructure to produce seasonal influenza vaccines leads to increased capacity to produce pandemic influenza vaccines. This article summarizes the results of a survey administered to 44 manufacturers to assess their production capacity for seasonal influenza and pandemic influenza vaccine production. When the GAP was launched in 2006, global production capacity for seasonal and pandemic vaccines was estimated to be 500million and 1.5billion doses respectively. Since 2006 there has been a significant increase in capacity, with the 2013 survey estimating global capacity at 1.5billion seasonal and 6.2billion pandemic doses. Results of the current survey showed that global seasonal influenza vaccine production capacity has decreased since 2013 from 1.504billion doses to 1.467billion doses. However, notwithstanding the overall global decrease in seasonal vaccine capacity there were notable positive changes in the distribution of production capacity with increases noted in South East Asia (SEAR) and the Western Pacific (WPR) regions, albeit on a small scale. Despite a decrease in seasonal capacity, there has been a global increase of pandemic influenza vaccine production capacity from 6.2 billion doses in 2013 to 6.4 billion doses in 2015. This growth can be attributed to a shift towards more quadrivalent vaccine production and also to increased use of adjuvants. Pandemic influenza vaccine production capacity is at its highest recorded levels however challenges remain in maintaining this capacity and in ensuring access in the event of a

pandemic to underserved regions.

Hendry AJ, Dey A, Beard FH, Khandaker G, Hill R, Macartney KK. **Adverse events following immunisation with bacille Calmette-Guerin vaccination: baseline data to inform monitoring in Australia following introduction of new unregistered BCG vaccine.**

Communicable diseases intelligence quarterly report. 2016;40(4):E470-E4.

In recent years there has been a global shortage of bacille Calmette-Guerin (BCG) vaccine and, from September 2012, unregistered vaccines have needed to be used in Australia (a Danish product initially until the end of 2015, and a Polish product used in some jurisdictions from early 2016). We examined rates and types of adverse events following immunisation (AEFI) with BCG vaccine reported to the Therapeutic Goods Administration between 2009 and 2014 in children aged less than 7 years. Reporting rates of AEFI with BCG vaccine increased from 87 per 100,000 doses (registered Sanofi Pasteur product) in 2009 to 201 per 100,000 doses (unregistered Danish Statens Serum Institute product) in 2014, with Victoria having the highest rate each year. Substantial variation between jurisdictions exists, suggesting differential reporting of BCG vaccine doses administered and/or BCG vaccine-related AEFI. The most commonly reported reactions were abscess (31%), injection site reaction (27%) and lymphadenopathy/lymphadenitis (17%). This study provides baseline data on BCG vaccine safety to inform surveillance. Given the current use of unregistered vaccines in the context of vaccine supply issues, improved recording of both administered BCG vaccine doses and the reporting of BCG vaccine-related AEFI are required to facilitate close monitoring of vaccine safety.

Nedeljkovic J, Kovacevic-Jovanovic V, Milosevic V, Seguljev Z, Petrovic V, Muller CP, Hubschen JM. **A Mumps Outbreak in Vojvodina, Serbia, in 2012 Underlines the Need for Additional Vaccination Opportunities for Young Adults.** PloS one. 2015;10(10):e0139815.

In 2012, mumps was introduced from Bosnia and Herzegovina to Vojvodina, causing an outbreak with 335 reported cases. The present manuscript analyses the epidemiological and laboratory characteristics of this outbreak, identifies its main causes and suggests potential future preventive measures. Sera of 133 patients were tested for mumps-specific antibodies by ELISA and 15 nose/throat swabs were investigated for mumps virus RNA by RT-PCR. IgG antibodies were found in 127 patients (95.5%). Mumps infection was laboratory-confirmed in 53 patients, including 44 IgM and 9 PCR positive cases. All other 282 cases were classified as epidemiologically-confirmed. More than half of the patients ( $n = 181$ , 54%) were 20-29 years old, followed by the 15-19 age bracket ( $n = 95$ , 28.4%). Twice as many males as females were affected (67% versus 33%). Disease complications were reported in 13 cases (3.9%), including 9 patients with orchitis and 4 with pancreatitis. According to medical records or anamnestic data, 190 patients (56.7%) were immunized with two doses and 35 (10.4%) with one dose of mumps-containing vaccine. The Serbian sequences corresponded to a minor genotype G variant detected during the 2011/2012 mumps outbreak in Bosnia and Herzegovina. Vaccine failures, the initial one-dose immunization policy and a vaccine shortage between 1999 and 2002 contributed to the outbreak. Additional vaccination opportunities should be offered to young adults during transition periods in their life trajectories.

Azman AS, Lessler J. **Reactive vaccination in the presence of disease hotspots.** Proceedings Biological sciences. 2015;282(1798):20141341.

Reactive vaccination has recently been adopted as an outbreak response tool for cholera and other infectious diseases. Owing to the global shortage of oral cholera vaccine, health officials must quickly decide who and where to distribute limited vaccine. Targeted vaccination in transmission hotspots (i.e. areas with high transmission efficiency) may be a potential approach to efficiently allocate vaccine, however its effectiveness will likely be context-dependent. We compared strategies for allocating vaccine across multiple areas with heterogeneous transmission efficiency. We constructed metapopulation models of a cholera-like disease and compared simulated epidemics where: vaccine is targeted at areas of high or low transmission efficiency, where vaccine is distributed across the population, and where no vaccine is used. We find that connectivity between populations, transmission efficiency, vaccination timing and the amount of vaccine available all shape the performance of different allocation strategies. In

highly connected settings (e.g. cities) when vaccinating early in the epidemic, targeting limited vaccine at transmission hotspots is often optimal. Once vaccination is delayed, targeting the hotspot is rarely optimal, and strategies that either spread vaccine between areas or those targeted at non-hotspots will avert more cases. Although hotspots may be an intuitive outbreak control target, we show that, in many situations, the hotspot-epidemic proceeds so fast that hotspot-targeted reactive vaccination will prevent relatively few cases, and vaccination shared across areas where transmission can be sustained is often best.

Matrajt L, Halloran ME, Longini IM, Jr. **Optimal vaccine allocation for the early mitigation of pandemic influenza.** PLoS computational biology. 2013;9(3):e1002964.

With new cases of avian influenza H5N1 (H5N1AV) arising frequently, the threat of a new influenza pandemic remains a challenge for public health. Several vaccines have been developed specifically targeting H5N1AV, but their production is limited and only a few million doses are readily available. Because there is an important time lag between the emergence of new pandemic strain and the development and distribution of a vaccine, shortage of vaccine is very likely at the beginning of a pandemic. We coupled a mathematical model with a genetic algorithm to optimally and dynamically distribute vaccine in a network of cities, connected by the airline transportation network. By minimizing the illness attack rate (i.e., the percentage of people in the population who become infected and ill), we focus on optimizing vaccine allocation in a network of 16 cities in Southeast Asia when only a few million doses are available. In our base case, we assume the vaccine is well-matched and vaccination occurs 5 to 10 days after the beginning of the epidemic. The effectiveness of all the vaccination strategies drops off as the timing is delayed or the vaccine is less well-matched. Under the best assumptions, optimal vaccination strategies substantially reduced the illness attack rate, with a maximal reduction in the attack rate of 85%. Furthermore, our results suggest that cooperative strategies where the resources are optimally distributed among the cities perform much better than the strategies where the vaccine is equally distributed among the network, yielding an illness attack rate 17% lower. We show that it is possible to significantly mitigate a more global epidemic with limited quantities of vaccine, provided that the vaccination campaign is extremely fast and it occurs within the first weeks of transmission.

Fairbrother G, Donauer S, Staat MA, Broder K, Salisbury S, Morrow AL, . . . Schwartz B. **Cincinnati pediatricians' measured and reported immunizing behavior for children during the national shortages of pneumococcal conjugate vaccine.** Vaccine. 2013;31(17):2177-83.

BACKGROUND: The United States has experienced two shortages of heptavalent pneumococcal conjugate vaccine (PCV7). National guidelines called for deferring the third and fourth PCV7 doses from healthy children during these shortages. However, recommendations were not the same during the first and second shortages, and recommendations changed over time during each of the shortages as shortages worsened. OBJECTIVES: To measure PCV7 immunizing behavior for healthy children during shortage and non-shortage periods and assess the accuracy of the physicians' reported immunizing behavior when compared to their actual immunizing behavior. METHODS: We reviewed medical records in 14 randomly selected practices to measure actual immunizing behavior during shortage and non-shortage periods. We surveyed pediatricians in the Greater Cincinnati area to ascertain reported immunizing behavior. Actual and reported immunizing behaviors were compared. RESULTS: 2888 medical records were reviewed; surveys were obtained from 51 pediatricians (65% response rate). During periods of non-shortage, 74% of healthy children received their first two doses of PCV7 on time, whereas during periods of shortage, only 66% of healthy children received their first two doses of PCV7 on time. Compared with measured immunizing behavior from chart reviews, 54-76% of the pediatricians overestimated their compliance with guidelines to defer the fourth PCV7 dose while only 5-20% underestimated their compliance. CONCLUSIONS: Physicians often overestimated the percentage of children whose vaccine doses they deferred during vaccine shortages. Despite these findings, physicians were able to maintain high coverage with the first two PCV7 doses among healthy children.



### 1.3.4. Public health recommendation in case vaccine shortage

Kontturi A, Santiago B, Tebruegge M, von Both U, Salo E, Ritz N. **The impact of Bacille Calmette-Guerin shortage on immunisation practice and policies in Europe - A Paediatric Tuberculosis Network European Trials Group (ptbnet) survey.** *Tuberculosis* (Edinburgh, Scotland). 2016;101:125-9.

BACKGROUND: Recent reports indicate an ongoing BCG shortage that may influence immunisation practice. This study aimed to determine current availability of BCG vaccine across Europe, and implications on immunisation practices and policies in Europe. METHODS: Web-based survey among Paediatric Tuberculosis Network European Trials Group (ptbnet) members, between May and October 2015. RESULTS: Twenty individuals from 13 European countries participated. Ongoing shortages were reported in eight countries routinely using BCG (8/11, 73%). As a consequence of the shortage, BCG was not given as completely unavailable in some countries (2/8, 25%), was given only whenever available (1/8, 13%), or only in certain regions of the country (1/8, 13%). Strategies reported to reduce loss of immunisation were administration to selected high-risk individuals (2/8, 25%), or cohorting vaccinees on specific days to maximise the use of multi-dose vials (3/8, 38%). Authorities in two countries each were considering a change of manufacturer/supplier (2/8, 25%). CONCLUSIONS: The BCG shortage in Europe leads to significant changes in immunisation policies including changes of BCG vaccine strain and manufacturer. In addition, infants and children eligible for immunisation are at risk of not receiving BCG. To ensure necessary BCG immunisations, collaboration between national health agencies and vaccine manufacturers is crucial.

Huang AS, Chen WC, Huang WT, Huang ST, Lo YC, Wei SH, . . . Chang FY. **Public Health Responses to Reemergence of Animal Rabies, Taiwan, July 16-December 28, 2013.** *PloS one*. 2015;10(7):e0132160.

Taiwan had been free of indigenous human and animal rabies case since canine rabies was eliminated in 1961. In July 2013, rabies was confirmed among three wild ferret-badgers, prompting public health response to prevent human rabies cases. This descriptive study reports the immediate response to the reemergence of rabies in Taiwan. Response included enhanced surveillance for human rabies cases by testing stored cerebrospinal fluids (CSF) from patients with encephalitides of unknown cause by RT-PCR, prioritizing vaccine use for postexposure prophylaxis (PEP) during periods of vaccine shortage and subsequent expansion of PEP, surveillance of animal bites using information obtained from vaccine application, roll out of preexposure prophylaxis (PrEP) with vaccine stock restoration, surveillance for adverse events following immunization (AEFI), and ensuring surge capacity to respond to general public inquiries by phone and training for healthcare professionals. Enhanced surveillance for human rabies found no cases after testing 205 stored CSF specimens collected during January 2010-July 2013. During July 16 to December 28, 2013, we received 8,241 rabies PEP application; 6,634 (80.5%) were consistent with recommendations. Among the 6,501 persons who received at least one dose of rabies vaccine postexposure, 4,953 (76.2%) persons who were bitten by dogs; only 59 (0.9%) persons were bitten by ferret-badgers. During the study period, 6,247 persons received preexposure prophylaxis. There were 23 reports of AEFI; but no anaphylaxis, Guillain-Barre syndrome, or acute disseminated encephalomyelitis were found. During the study period, there were 40,312 calls to the Taiwan Centers for Disease Control hotline, of which, 8,692 (22%) were related to rabies. Recent identification of rabies among ferret-badgers in a previously rabies-free country prompted rapid response. To date, no human rabies has been identified. Continued multifaceted surveillance and interministerial collaboration are crucial to achieve the goal of rabies-free status in Taiwan.

Tanaka S, Sugita S, Marui E. **[A study on the 1946 smallpox epidemic in Japan and measures taken against it].** *Nihon ishigaku zasshi [Journal of Japanese history of medicine]*. 2014;60(3):247-59. In early 1946, immediately after World War II, there was a smallpox epidemic in Japan. In this paper we investigated trends in the occurrence of smallpox by week and region using official

documents of the General Headquarters, Supreme Commander for the Allied Powers (GHQ/SCAP), which are stored in the National Diet Library Modern Japanese Political History Materials Room, and summarized the measures taken against this epidemic. The following two points were clarified: 1) The 1946 smallpox epidemic peaked in Week 13 (March 24-30; 1,405 new patients), and the highest morbidity during this epidemic was seen in Hyogo Prefecture, followed by Osaka Prefecture, Aichi Prefecture, Tokyo Prefecture, and Hokkaido Prefecture. 2) Measures taken against this epidemic were classified into the following three stages: 1. "Vaccine shortage/Manufacture acceleration stage," 2. "Vaccine sufficiency/Smallpox vaccination program implementation stage," and 3. "Detection of defects in vaccination technique/Reimplementation of the smallpox vaccination program stage".

Moriarty LF, Omer SB, Seib K, Chamberlain A, Wells K, Whitney E, . . . Bednarczyk RA. **Changes in immunization program managers' perceptions of programs' functional capabilities during and after vaccine shortages and pH1N1.** Public health reports (Washington, DC : 1974). 2014;129 Suppl 4:42-8.

**OBJECTIVES:** We surveyed U.S. immunization program managers (IPMs) as part of a project to improve public health preparedness against future emergencies by leveraging the immunization system. We examined immunization program policy and Immunization Information System (IIS) functionality changes as a result of the Haemophilus influenzae type B (Hib) vaccine shortage and pandemic influenza A(H1N1) (pH1N1). Evaluating changes in immunization program functionalities and policies following emergency response situations will assist in planning for future vaccine-related emergencies. **METHODS:** We administered three consecutive surveys to IPMs from 64 state, city, and territorial jurisdictions in 2009, 2010, and 2012. We compared IPMs' responses across either two or three years (e.g., changes in response or consistent responses across years) using McNemar's test. **RESULTS:** Immunization programs maintained increases in functionality related to communication systems with health-care providers during this period. Immunization programs often did not maintain changes to IIS functionalities made from 2009 to 2010 (e.g., identifying high-risk and priority populations, tracking adverse events, and mapping disease risk) in the post-pandemic period (2010-2012). About half of IPMs reporting additional IIS functionality in identifying high-risk populations from 2009 to 2010 reported no longer having this function in 2012. There was an 18% decline in respondents reporting geographic information systems risk-mapping capability in IIS from 2010 to 2012. **CONCLUSIONS:** Because of the Hib vaccine shortage and pH1N1, immunization program needs and efforts changed to address evolving situations. The lack of sustained increases in resources or system functions after the pandemic highlights the need for comprehensive, sustainable public health emergency preparedness systems and related resources.

### [Some Examples of Website with recommendations in case of hepatitis vaccine shortage](#)



The screenshot shows the Travel Health Pro website header with navigation links: COUNTRY INFORMATION, LATEST NEWS, OUTBREAK SURVEILLANCE, and DISINFECTION. Below the header, a breadcrumb trail reads: Home / Latest News / Hepatitis A vaccine shortage: implications and adv... The article title is "HEPATITIS A VACCINE SHORTAGE: IMPLICATIONS AND ADVICE FOR CLINICAL PRACTICE" dated 23 Jun 2017. The sub-headline states: "Public Health England and NaTHNaC offer guidance for health professionals during the current hepatitis A vaccine shortage".

<https://travelhealthpro.org.uk/news/225/hepatitis-a-vaccine-shortage-implications>

## Global Shortage of Hepatitis A Vaccine and Dose Sparing Recommendations

16 JUNE 2017

[Home](#) > [News](#) > News Record Page

The current global shortage of hepatitis A vaccine is ongoing and continues to affect the supply of hepatitis A containing vaccines in the United Kingdom. Consequently it has become necessary to consider options for hepatitis A dose sparing as some products may be unavailable or may need to be prioritised for special risk groups.

<http://www.travax.nhs.uk/news/news-record-page?newsid=22188>



### Hepatitis B vaccine shortage: Public Health Unit Advice

There is a shortage of hepatitis B vaccines in the private market that is expected to last until late 2018. Funded hepatitis B vaccines provided for the National Immunisation Program by Queensland Health (including for high risk groups; refer to the Australian Immunisation Handbook for details) are not affected by the shortage. The private market shortage will mainly affect:

- Healthcare workers and healthcare students requiring vaccination
- Travellers seeking hepatitis B vaccination

While monovalent hepatitis B vaccines are the ideal for providing hepatitis B protection, when a complete course is unavailable due to the shortages it is acceptable to substitute for all or part of a course with:

- Another brand if available
- A multivalent hepatitis B-containing vaccine such as Twinrix (refer to Table 4.4.1 in the Australian Immunisation Handbook for the various Twinrix and Twinrix Junior schedules)
- Give two paediatric vaccines (e.g. H-B-VAXII Paediatric) instead of one adult dose. As the vaccines are pre-loaded they should be given in different limbs or at least 2.5cm apart in the same limb). To get on to AIR as a valid dose for a person aged  $\geq 20$  years, the two paediatric doses must be recorded as one adult dose.

If the person is  $<20$  years of age: 3 doses of hepatitis B (paediatric vaccine) is equivalent to a full course

GSK is expecting shortages of Twinrix by the end of July. If only a single Twinrix dose is needed and used (e.g. to finish an incomplete previous course of hepatitis B vaccine), there will only be short term hepatitis A protection, and additional doses of Hepatitis A vaccine (e.g. monovalent) may be required for full protection.

The manufacturer Seqirus has said H-B-VAXII (adult) is not available. There is limited private availability of H-B-VAXII (paediatric) because of the high demand.

This advice for hepatitis B vaccine interchangeability is consistent with a review of hepatitis B vaccines published by WHO on 7 July 2017

<http://apps.who.int/iris/bitstream/10665/255841/1/WER9227.pdf>

Sunshine Coast Public Health Unit

Central Queensland Public Health Unit

<https://www.ourphn.org.au/wp-content/uploads/Hepatitis-B-vaccine-shortageJuly17.pdf>

## Hepatitis B

Vaccination for  
Hep B

About Hep B

Transmission

Disease Course  
of Hep B

Testing for Hep B

Symptoms of  
Hep B

Treatment for  
Hep B

## Vaccination for Hep B

August 28, 2017

### Global Shortage of Hepatitis B Vaccine

There is currently a global shortage of preventative vaccine for hepatitis B. The Australian Government Department of Health has advised it is currently working closely with hepatitis B vaccine suppliers as well as state and territory governments to better understand the extent and impact of the shortage and to consider options to address it. People eligible for publicly funded hepatitis B vaccine under the **National Immunisation Program** or state & territory government programs should have no difficulty but those who fall outside these programs may experience difficulty or delays in obtaining the vaccine.

If you are experiencing any difficulties please call 1800 437 222 for more information regarding hepatitis B vaccinations in your state or territory.

The latest information for clinical providers is [located here >>](#)

<https://www.hepatitisaustralia.com/hepatitis-b-facts/vaccination-for-hep-b>

## 1.4. Speakers information – Vaccine shortage

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.



**OLEG BENES,**

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**MICHEL STOFFEL**

**SILVIA BINO** *Epidemiology and Control of Infectious Diseases, Institute of Public Health, Albania*

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#### **ISABELLE BEKEREDJIAN-DING** *Microbiology Paul-Ehrlich Instituut, Germany*

From PubMed search [Name]:

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#### **TRUUS DE GRAAF, RIVM, THE NETHERLANDS**

Dr. Truus de Graaf is Head Programmes and Vaccine Supply of the Department of Vaccine Supply and Prevention Programmes at the National Institute for Public Health and the Environment (RIVM). She received her PhD in Biochemistry at the Free University of



Amsterdam and was Post doctoral fellow at the Institute of Molecular and Cell Biology in Singapore. Since 1999 she has held different positions in the public health sector at the RIVM and the former Netherlands Vaccine Institute, and from 2011 onwards she has her current position. With her team she is responsible for the procurement and supply of vaccines and other pharmaceutical products for all Dutch public prevention programmes. She has experience with and knowledge of vaccine R&D and production, coordination of prevention programmes, procurement (European Tenders) and logistics. Also involved in the EU Joint Procurement Initiative.



## TARIK DERROUGH

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## **SEMA MANDAL** *Immunisation, Hepatitis and Blood Safety, Public Health England, UK*

Dr Sema Mandal (MBBS, MRCP, MSc FFPH) has been a medical consultant epidemiologist in Public Health England (PHE) since 2013, where she is the lead for viral hepatitis in the Immunisation, Hepatitis and Blood Safety Department, in the National Infection Service. Sema is the PHE clinical lead for the introduction of universal hepatitis B immunisation into the routine childhood programme in 2017 and is responsible for establishing a PHE led, cross-agency, National Strategic Group for Viral Hepatitis. Sema is a co-applicant and PI on several hepatitis research projects and holds an honorary senior clinical lecturer position at University of Bristol. She was also seconded to WHO during the recent Ebola epidemic to work on the Guinea vaccine trial. Before joining PHE, Sema spent 4 years at the US Centers for Disease Control (CDC) in Atlanta as an Epidemic Intelligence Service (EIS) Fellow and then staff epidemiologist in the Meningitis and Vaccine Preventable Diseases Branch (NCIRD). Prior to specialising in public health medicine, Sema worked in internal medicine, GUM and A&E in London, UK and Sydney, Australia. She previously worked for Médecins sans Frontières as a field medical doctor in South Sudan.

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## **JOHN WARD** *CDC, Atlanta, USA*

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#### **DAVID FITZSIMONS, rapporteur**

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## 2. New hepatitis B treatment

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### 2.1 Presentation related Information

#### 2.1.1 Session 9: Overview new treatment/treatment strategies for hepatitis B in the pipeline

##### Presentation related references

**New treatment - Review based on: Novel targets for hepatitis B virus therapy.**

*Provided by speaker: Barbara Testoni*

Testoni B, Durantel D, Zoulim F. **Novel targets for hepatitis B virus therapy.** Liver international : official journal of the International Association for the Study of the Liver. 2017;37 Suppl 1:33-9.

Treatment with either pegylated interferon-alpha (pegIFN-alpha) or last generation nucleos(t)ide analogues (NAs) successfully leads to serum viral load suppression in most chronically infected hepatitis B (CHB) patients, but HBsAg loss is only achieved in 10% of the cases after a 5-year follow-up. Thus, therapy must be administered long-term and it will not completely eliminate infection because of the persistent hepatitis B virus (HBV) minichromosome in infected cells, and cannot completely abolish the risk of developing severe sequelae such as cirrhosis and hepatocellular carcinoma. Recent progress in the development of in vitro and in vivo models of HBV infection have helped renew interest in the investigation of the viral life cycle, as well as specific virus-host cell interactions to identify new targets for the development of new antiviral drugs. This includes either direct inhibition of viral replication by targeting fundamental steps such as entry, cccDNA formation/stability, viral transcripts, capsid assembly and secretion or the manipulation of the host immune system for better defence against infection. Multiple strategies are currently under investigation, including boosting endogenous innate responses and/or restoring adaptive immunity via engineering of HBV-specific T cells or via the use of inhibitors of negative regulators, as well as therapeutic vaccines. It is increasingly clear that multiple therapeutic strategies must be combined to reach a cure of HBV and that the definition of clinical, virological and immunological correlates for the management of treatment are urgently needed.

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#### Presentation related references

##### Treatment guidelines (EASL)

*Provided by speaker: Pietro Lampertico*

#### **EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of hepatology. 2017;67(2):370-98.**

Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to several factors including vaccination policies and migration. This Clinical Practice Guideline presents updated recommendations for the optimal management of HBV infection. Chronic HBV infection can be classified into five phases: (I) HBeAg-positive chronic infection, (II) HBeAg-positive chronic hepatitis, (III) HBeAg-negative chronic infection, (IV) HBeAg-negative chronic hepatitis and (V) HBsAg-negative phase. All patients with chronic HBV infection are at increased risk of progression to cirrhosis and hepatocellular carcinoma (HCC), depending on host and viral factors. The main goal of therapy is to improve survival and quality of life by preventing disease progression, and consequently HCC development. The induction of long-term suppression of HBV replication represents the main endpoint of current treatment strategies, while HBsAg loss is an optimal endpoint. The typical indication for treatment requires HBV DNA >2,000IU/ml, elevated ALT and/or at least moderate histological lesions, while all cirrhotic patients with detectable HBV DNA should be treated. Additional indications include the prevention of mother to child transmission in pregnant women with high viremia and prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy. The long-term administration of a potent nucleos(t)ide analogue with high barrier to resistance, i.e., entecavir, tenofovir disoproxil or tenofovir alafenamide, represents the treatment of choice. Pegylated interferon-alfa treatment can also be considered in mild to moderate chronic hepatitis B patients. Combination therapies are not generally recommended. All patients should be monitored for risk of disease progression and HCC. Treated patients should be monitored for therapy response and adherence. HCC remains the major concern for treated chronic hepatitis B patients. Several subgroups of patients with HBV infection require specific focus. Future treatment strategies to achieve 'cure' of disease and new biomarkers are discussed.

#### Presentation related references

##### What is new on HBsAg and other diagnostic markers in HBV infection?

*Provided by speaker: Christoph Höner zu Siederdisen*

#### **Honer Zu Siederdisen C, Maasoumy B, Cornberg M. What is new on HBsAg and other diagnostic markers in HBV infection? Best practice & research Clinical gastroenterology. 2017;31(3):281-9.**

Challenges in the management of chronic hepatitis B virus (HBV) infection involve the prediction of the natural course to identify patients who require antiviral therapy and the prediction of functional cure as ultimate goal of antiviral therapy. HBV DNA as marker for viral replication is important but not sufficient for an adequate management of patients with chronic HBV infection. Data on the quantification of additional HBV marker such as hepatitis B surface antigen (HBsAg), hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA (HBV RNA) have accumulated in recent years. Here we review the current evidence how to use these markers and discuss open issues that require additional research.

## 2.1.2 Session 10: Impact on Public Health of new treatments and how can policy makers be prepared

### Presentation related references

#### Elimination of Hepatitis B: Is It a Mission Possible

*Provided by speaker: Tai-Chung Tseng*

Tseng TC, Kao JH. Elimination of Hepatitis B: Is It a Mission Possible? BMC medicine. 2017;15(1):53.

Chronic hepatitis B virus (HBV) infection is a global public health issue. Although the disease cannot be cured effectively, disease management has been improved over the past decade. The introduction of potent nucleos(t)ide analogues (NAs) to suppress viral replication represented a giant leap in the control of this disease. It has been shown that tenofovir treatment, a potent NA, complements current immunoprophylaxis to diminish mother-to-infant transmission in pregnant women with a high viral load. For patients with chronic HBV infection, quantitative hepatitis B surface antigen is a useful tool to define inactive carriers and to guide antiviral therapy. Quantification of HBV mutants is also useful in predicting long-term outcomes more precisely than ever. The next challenge is how to achieve an HBV cure; although immunotherapy is a promising strategy, the current results from two clinical trials using therapeutic vaccines to induce HBV-specific immune response in patients with chronic HBV infection are disappointing. In the coming years, we are expecting to see a combination of therapeutic agents with various modes of action to complete the mission of HBV elimination.

1. Tseng TC, Liu CJ, Su TH, et al. [Fibrosis-4 Index Helps Identify HBV Carriers With the Lowest Risk of Hepatocellular Carcinoma](#). Am J Gastroenterol 2017;112:1564-1574.
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### Presentation related references

#### The cost-effectiveness of hepatitis B case-finding interventions in the UK

*Provided by speaker: Jack Williams*

### Related literature

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#### Presentation related references

#### **Challenges in warranting access to prophylaxis and therapy for hepatitis B virus infection**

*Provided by speaker:* Christoph Höner zu Siederdisen

Debarry J, Cornberg M, Manns MP. **Challenges in warranting access to prophylaxis and therapy for hepatitis B virus infection**. Liver international : official journal of the International Association for the Study of the Liver. 2017;37 Suppl 1:67-72.

Despite an available vaccine and efficient treatment for hepatitis B virus (HBV) infection, chronic HBV infection still remains a major global threat, and one of the top 20 causes of human mortality worldwide. One of the major challenges in controlling HBV infection is the high number of undiagnosed chronic carriers and the lack of access to prophylaxis and treatment in several parts of the world. We discuss relevant barriers that need to be overcome to achieve global control of HBV infection and make eradication possible. Most important, vaccination must be scaled-up to lower the risk of vertical transmission and decrease the number of new infections, and comprehensive screening programs must be linked to care to obtain a better rate of diagnosis and treatment. This can probably only be achieved if sustainable funding is available. We therefore emphasize the importance of making the management of viral hepatitis a global health priority.

## 2.2 Pubmed search New hepatitis B treatment public health impact

Pubmed MEDLINE search on {((Therapy OR Treatment) AND (Hepatitis B ) AND (new) AND (Public Health)) } in all [Abstract/title] and filter: 'last 10 years' 'Review' on was performed. The references were manually sorted in the different subject in an EndNote database. The references are listed by publication year (recent first).

### New treatment

Arends, J. E., Lieveld, F. I., Ahmad, S. and Ustianowski, A. "**New Viral and Immunological Targets for Hepatitis B Treatment and Cure: A Review.**" *Infect Dis Ther* **2017** 6(4): 461-476.

Although current therapies can be successful at suppressing hepatitis B viral load, long-term viral cure is not within reach. Subsequent strategies combining pegylated interferon alfa with nucleoside/nucleotide analogues have not resulted in any major paradigm shift. An improved understanding of the hepatitis B virus (HBV) life cycle and virus-induced immune dysregulation has, however, revealed many potential therapeutic targets, and there are hopes that treatment of hepatitis B could soon be revolutionized. This review summarizes the current developments in HBV therapeutics-both virus directed and host directed.

Testoni, B., Durantel, D. and Zoulim, F. "**Novel targets for hepatitis B virus therapy.**" *Liver Int* **2017** 37 Suppl 1: 33-39.INSERM, U1052,

Treatment with either pegylated interferon-alpha (pegIFN-alpha) or last generation nucleos(t)ide analogues (NAs) successfully leads to serum viral load suppression in most chronically infected hepatitis B (CHB) patients, but HBsAg loss is only achieved in 10% of the cases after a 5-year follow-up. Thus, therapy must be administered long-term and it will not completely eliminate infection because of the persistent hepatitis B virus (HBV) minichromosome in infected cells, and cannot completely abolish the risk of developing severe sequelae such as cirrhosis and hepatocellular carcinoma. Recent progress in the development of in vitro and in vivo models of HBV infection have helped renew interest in the investigation of the viral life cycle, as well as specific virus-host cell interactions to identify new targets for the development of new antiviral drugs. This includes either direct inhibition of viral replication by targeting fundamental steps such as entry, cccDNA formation/stability, viral transcripts, capsid assembly and secretion or the manipulation of the host immune system for better defence against infection. Multiple strategies are currently under investigation, including boosting endogenous innate responses and/or restoring adaptive immunity via engineering of HBV-specific T cells or via the use of inhibitors of negative regulators, as well as therapeutic vaccines. It is increasingly clear that multiple therapeutic strategies must be combined to reach a cure of HBV and that the definition of clinical, virological and immunological correlates for the management of treatment are urgently needed.

Lok, A. S., Zoulim, F., Dusheiko, G. and Ghany, M. G. "**Hepatitis B cure: From discovery to regulatory approval.**" *Hepatology* **2017** 66(4): 1296-1313.

The majority of persons currently treated for chronic hepatitis B require long-term or lifelong therapy. New inhibitors of hepatitis B virus entry, replication, assembly, or secretion and immune modulatory therapies are in development. The introduction of these novel compounds for chronic hepatitis B necessitates a standardized appraisal of the efficacy and safety of these treatments and definitions of new or additional endpoints to inform clinical trials. To move the field forward and to expedite the pathway from discovery to regulatory approval, a workshop with key stakeholders was held in September 2016 to develop a consensus on treatment endpoints to guide the design of clinical trials aimed at hepatitis B cure. The consensus reached



was that a complete sterilizing cure, i.e., viral eradication from the host, is unlikely to be feasible. Instead, a functional cure characterized by sustained loss of hepatitis B surface antigen with or without hepatitis B surface antibody seroconversion, which is associated with improved clinical outcomes, in a higher proportion of patients than is currently achieved with existing treatments is a feasible goal. Development of standardized assays for novel biomarkers toward better defining hepatitis B virus cure should occur in parallel with development of novel antiviral and immune modulatory therapies such that approval of new treatments can be linked to the approval of new diagnostic assays used to measure efficacy or to predict response. Combination of antiviral and immune modulatory therapies will likely be needed to achieve functional hepatitis B virus cure. Limited proof-of-concept monotherapy studies to evaluate safety and antiviral activity should be conducted prior to proceeding to combination therapies. The safety of any new curative therapies will be paramount given the excellent safety of currently approved nucleos(t)ide analogues. (Hepatology 2017).

Su, T. H. and Kao, J. H. "**Unmet Needs in Clinical and Basic Hepatitis B Virus Research.**" *J Infect Dis* **2017** 216(suppl\_8): S750-S756

Chronic hepatitis B (CHB) has become a treatable and controllable disease. The current nucleos(t)ide analogue (NUC) and pegylated interferon therapies effectively help slow disease progression and reduce the risk of cirrhosis, hepatocellular carcinoma (HCC), and CHB-associated mortality. Long-term viral suppression is easily achievable by NUC therapy, with limited adverse reactions. However, several unmet requirements still exist, including safety and risk-stratified HCC surveillance among patients who received long-term NUC therapy. Criteria for determining which patients should receive finite-duration NUC therapy and which should receive combination therapy with both NUC and pegylated interferon remain unsettled. The management of hepatitis B virus (HBV) e antigen-positive viremic patients with normal liver function and the incorporation of new biomarkers to help manage CHB require further exploration. To achieve functional cure (ie, HBV surface antigen seroclearance) and complete cure (ie, eradication of covalently closed circular DNA) of CHB, several challenges in basic research must be addressed, including the development of an efficient cell culture system and animal models for HBV investigation, development of treatment to eradicate covalently closed circular HBV DNA, and development of immunotherapy for CHB. This brief review focuses on unmet needs in both clinical and basic HBV research.

Block, T. M., Locarnini, S., McMahon, B. J., Rehermann, B. and Peters, M. G. "**Use of Current and New Endpoints in the Evaluation of Experimental Hepatitis B Therapeutics.**" *Clin Infect Dis* **2017** 64(9): 1283-1288.

New hepatitis B virus (HBV) therapies are expected to have breakthrough benefit for patients. HBV functional cure is sustained hepatitis B surface antigen loss and anti-HBs gain, with normalization of serum aminotransferases off therapy. Virologic or complete cure additionally includes loss of HBV covalently closed circular DNA. Currently available endpoints of therapy are inadequate to evaluate the efficacy of many of the new therapeutics. Therefore, either new ways of using the existing virologic endpoints and laboratory values or entirely new biomarkers are needed. In this review, we discuss the currently used endpoints, potential new endpoints, as well as what new markers are needed to assess the ability of HBV therapeutics to achieve functional and virologic cure in various phases of HBV infection. In addition, we discuss how patient selection from differing phases of HBV impacts the choice of HBV drug(s) needed to achieve cure.

Gehring, A. J. "**New treatments to reach functional cure: Rationale and challenges for emerging immune-based therapies.**" *Best Pract Res Clin Gastroenterol* **2017** 31(3): 337-

The landscape for chronic HBV therapy is rapidly evolving. The latest generation of antiviral drugs provide robust virus suppression with a high barrier to resistance that facilitates long-term treatment. However, low rates of HBsAg loss demonstrate that additional strategies are needed to consistently achieve a functional cure. The immune system can clear HBV and establish long-term control over the virus. Sufficiently boosting HBV immunity in chronic patients has been very difficult due to immune exhaustion, immune dysregulation, and inhibitory pathways suppressing the immune response. Therapeutic vaccines employing new technology, vectors and new immunomodulatory drugs that can elicit direct antiviral effects and cancel inhibitory mechanism

may be able to overcome exhaustion. This review will discuss the justification for immunotherapy, lessons from previous trials and new vaccines/drugs in early stage clinical trials. The challenges of correlating immune responses induced by these drugs to clinical efficacy will also be addressed.

Durantel, D. **"New treatments to reach functional cure: Virological approaches."** Best Pract Res Clin Gastroenterol **2017** 31(3): 329-336.

Current therapies of chronic hepatitis B (CHB) remain limited to pegylated-interferon-alpha (pegIFN-alpha) or any of the five approved nucleos(t)ide analogues (NA). If viral suppression can be achieved in the majority of patients with the high-barrier-to-resistance new-generation of NA, i.e. entecavir and tenofovir, HBsAg loss is achieved by PEG-IFN-alpha and/or NA in only 10% of patients, after a 5-year follow-up. Attempts to improve the response by administering two different NA or a combination of NA and PEG-IFN-alpha have not provided a dramatic increase in the rate of "functional cure". Because of this and the need of long-term NA administration, there is a renewed interest regarding the understanding of various steps of the HBV replication cycle, as well as specific virus-host cell interactions, in order to define new targets and develop novel drugs. This includes the direct inhibition of several HBV life cycle steps by either entry inhibitors, drugs targeting cccDNA, siRNA targeting viral transcripts, capsid assembly modulators, and approaches targeting the secretion of viral envelope proteins. The addition of one or several new drugs to current therapies should offer the prospect of a markedly improved response to treatments and an increased rate of functional cure. This should lead to a reduced risk of antiviral drug resistance, and to a decreased incidence of cirrhosis and hepatocellular carcinoma (HCC). In this chapter, we review investigational and early clinical efforts regarding the identification and characterization of antiviral targets that are being evaluated for the development of innovative DAA concepts for chronic HBV infections.

Soriano, V., Barreiro, P., Benitez, L., Pena, J. M. and de Mendoza, C. **"New antivirals for the treatment of chronic hepatitis B."** Expert Opin Investig Drugs **2017** 26(7): 843-851.

INTRODUCTION: Current treatment with oral nucleos(t)ides entecavir or tenofovir provide sustained suppression of HBV replication and clinical benefit in most chronic hepatitis B virus (HBV) infected persons. However, HBV rebound generally occurs upon drug discontinuation due to persistence of genomic HBV reservoirs as episomic cccDNA and chromosomic integrated HBV-DNA. There is renewed enthusiasm on HBV drug discovery following recent successes with antivirals for hepatitis C and immunotherapies for some cancers. Areas covered: New drugs that target distinct steps of the HBV life cycle have been developed, including inhibitors of viral entry, new polymerase inhibitors, capsid and assembly inhibitors, virus release blockers, and disruptors of cccDNA formation and transcription. Alongside these antivirals, agents that enhance anti-HBV specific immune responses are being tested, including TLR agonists, checkpoint inhibitors and therapeutic vaccines. Expert opinion: The achievement of a 'functional cure' for chronic HBV infection, with sustained HBsAg clearance and undetectable viremia once medications are stopped, represents the next step in the pace towards HBV elimination. Hopefully, the combination of new drugs that eliminate or functionally inactivate the genomic HBV reservoirs (cccDNA and integrated HBV-DNA) along with agents that enhance or activate immune responses against HBV will lead to a 'definitive cure' for chronic HBV infection.

Testoni, B., Durantel, D. and Zoulim, F. **"Novel targets for hepatitis B virus therapy."** Liver Int **2017** 37 Suppl 1: 33-39.

Treatment with either pegylated interferon-alpha (pegIFN-alpha) or last generation nucleos(t)ide analogues (NAs) successfully leads to serum viral load suppression in most chronically infected hepatitis B (CHB) patients, but HBsAg loss is only achieved in 10% of the cases after a 5-year follow-up. Thus, therapy must be administered long-term and it will not completely eliminate infection because of the persistent hepatitis B virus (HBV) minichromosome in infected cells, and cannot completely abolish the risk of developing severe sequelae such as cirrhosis and hepatocellular carcinoma. Recent progress in the development of in vitro and in vivo models of HBV infection have helped renew interest in the investigation of the viral life cycle, as well as specific virus-host cell interactions to identify new targets for the development of new antiviral drugs. This includes either direct inhibition of viral replication by targeting fundamental

steps such as entry, cccDNA formation/stability, viral transcripts, capsid assembly and secretion or the manipulation of the host immune system for better defence against infection. Multiple strategies are currently under investigation, including boosting endogenous innate responses and/or restoring adaptive immunity via engineering of HBV-specific T cells or via the use of inhibitors of negative regulators, as well as therapeutic vaccines. It is increasingly clear that multiple therapeutic strategies must be combined to reach a cure of HBV and that the definition of clinical, virological and immunological correlates for the management of treatment are urgently needed.

Kao, J. H., Asselah, T., Dou, X. G. and Hamed, K. **"Telbivudine therapy for chronic hepatitis B: A journey to identify super-responders and to optimize treatment using the roadmap model."** *J Gastroenterol Hepatol* **2017** 32(1): 73-81.

Hepatitis B virus (HBV) infection is one of the most serious health problems worldwide with a high risk for cirrhosis and liver cancer. Several antiviral agents have been approved for the treatment of chronic hepatitis B, leading to a rapid reduction in HBV DNA and normalization of serum alanine aminotransferase levels. Telbivudine, a potent inhibitor of HBV replication, has been shown to be well tolerated. Because of the emergence of drug resistance, optimization strategies for telbivudine therapy have been shown to improve patient responses. Optimal baseline characteristics in so-called super-responders have been used to predict the virological response. Baseline HBV DNA levels  $< 9 \log_{10}$  copies/mL ( $2 \times 10^8$  IU/mL) or alanine aminotransferase levels of more than or equal to twofold the upper limit of normal in HBeAg-positive patients and HBV DNA  $< 7 \log_{10}$  copies/mL ( $2 \times 10^6$  IU/mL) in HBeAg-negative patients were strong predictors for virological response. In addition, the roadmap model, based on early virological response at week 24 of therapy, is considered as a powerful tool to identify patients at risk of treatment failure (HBV DNA  $\geq 300$  copies/mL, i.e. 60 IU/mL) and to reduce the risk of antiviral resistance. When considering pre-treatment characteristics and on-treatment responses, telbivudine may provide physicians with a wide choice of options to effectively treat patients with chronic hepatitis B, especially those with or at risk of renal impairment, or women of childbearing age.

Chen, G. F., Wang, C. and Lau, G. **"Treatment of chronic hepatitis B infection-2017."** *Liver Int* **2017** 37 Suppl 1: 59-66

Since the registration of the first effective nucleoside analogue against the hepatitis B virus almost two decades ago, major progress has been made in the management of chronic hepatitis B infection. However, hepatitis B-related morbidity and mortality remain a major global health threat. This is partly due to the escalating costs and the decrease in compliance related to the need for prolonged therapy for most patients who cannot be "cured". New biomarkers such as quantitative hepatitis B surface antigen might help to determine if hepatitis B e antigen negative patients can be taken off nucleos(t)ide analogues. On the other hand, novel compounds that target the viral life cycle or modulate host immune response are in the pipeline. In the next few years, one should expect breakthrough advancement to be made leading to a "cure" for patients with chronic hepatitis B infection by inducing hepatitis surface antigen loss with or without the development of the hepatitis B surface antibody. In addition, attention and necessary actions should also be taken in patients with hepatitis B infection who are being treated with immunosuppressive therapy and direct anti-viral (DAAs) agents for hepatitis C infection to prevent hepatitis from hepatitis B reactivation.

Hong, X., Kim, E. S. and Guo, H. **"Epigenetic regulation of hepatitis B virus covalently closed circular DNA: Implications for epigenetic therapy against chronic hepatitis B."** *Hepatology* **2017** 66(6): 2066-2077.

Hepatitis B virus (HBV) infection represents a significant public health burden worldwide. Although current therapeutics manage to control the disease progression, lifelong treatment and surveillance are required because drug resistance develops during treatment and reactivations frequently occur following medication cessation. Thus, the occurrence of hepatocellular carcinoma is decreased, but not eliminated. One major reason for failure of HBV treatment is the inability to eradicate or inactivate the viral covalently closed circular DNA (cccDNA), which is a stable episomal form of the viral genome decorated with host histones and nonhistone proteins.

Accumulating evidence suggests that epigenetic modifications of cccDNA contribute to viral replication and the outcome of chronic HBV infection. Here, we summarize current progress on HBV epigenetics research and the therapeutic implications for chronic HBV infection by learning from the epigenetic therapies for cancer and other viral diseases, which may open a new venue to cure chronic hepatitis B. (Hepatology 2017;66:2066-2077).

Arends, J. E., Lieveld, F. I., Ahmad, S. and Ustianowski, A. **"New Viral and Immunological Targets for Hepatitis B Treatment and Cure: A Review."** *Infect Dis Ther* **2017** 6(4): 461-476.

Although current therapies can be successful at suppressing hepatitis B viral load, long-term viral cure is not within reach. Subsequent strategies combining pegylated interferon alfa with nucleoside/nucleotide analogues have not resulted in any major paradigm shift. An improved understanding of the hepatitis B virus (HBV) life cycle and virus-induced immune dysregulation has, however, revealed many potential therapeutic targets, and there are hopes that treatment of hepatitis B could soon be revolutionized. This review summarizes the current developments in HBV therapeutics-both virus directed and host directed.

Majewska, A., Mlynarczyk-Bonikowska, B., Malejczyk, M., Majewski, S. and Mlynarczyk, G. **"Antiviral Medication in Sexually Transmitted Diseases. Part III: Hepatitis B, Hepatitis C."** *Mini Rev Med Chem* **2017** 17(4): 328-337.

In the previous parts of the series the antiviral agents used in genital herpes, genital HPV infection and therapeutic options in HIV infections were presented. The sexual contact is one of the major routes in the transmission of HBV and also possible modes of transmission of HCV. In this review we present the clinical indications, mechanisms of action, and side effects of presently available medication for the management of HBV and HCV infections. Currently a revolution is happening in the therapy of chronic hepatitis, especially caused by HCV. Direct-acting antivirals promise to open a new era in treating of chronic HCV infection. Efficacious, simplified and well tolerated interferon-free, and in some cases ribavirin-free regimens are available already and several other inhibitors currently are in the clinical trials.

Yang, N. and Bertoletti, A. **"Advances in therapeutics for chronic hepatitis B."** *Hepatol Int* **2016** 10(2): 277-285. Viral Hepatitis

Chronic hepatitis B infection remains a major disease burden globally, and leads to high risk of hepatocellular carcinoma development. Current therapies of nucleot(s)ide analogues and interferon alpha treatment remain limited in their efficacy. Several key findings in the hepatitis B virus (HBV) life cycle have led to the development of novel antiviral drugs to inhibit viral replication and persistence. In addition, recent studies on HBV-specific innate and adaptive immune responses have advanced development of immunotherapy to restore immune mediated virus control in chronic hepatitis B patients. In this review, we discuss potential new therapeutic strategies targeting HBV or the host immune system that might lead to a sustained cure for chronic hepatitis B.

## Treatment strategy

Emery, J. S. and Feld, J. J. **"Treatment of hepatitis B virus with combination therapy now and in the future."** *Best Pract Res Clin Gastroenterol* **2017** 31(3): 347-355.

Chronic Hepatitis B continues as a significant public health problem despite the availability of safe and effective antivirals and a highly effective protective vaccine. Current therapy, however rarely leads to cure and lifelong therapy is often required, contributing to poor uptake and ongoing morbidity. New insights into the hepatitis B viral life cycle and the host immune response have expanded the potential targets for drug therapies with interesting antiviral candidates and novel immunotherapeutic approaches in early stage development. Yet, HBV persistence is multifactorial - due to an intrahepatic reservoir and ongoing HBV-mediated immune dysregulation, making "cure" unlikely to be realized through even the most efficacious monotherapy. Building on the success seen in the treatment of hepatitis C (HCV) and human immunodeficiency virus (HIV), combination therapy may be an essential strategy to improve

efficacy and decrease viral breakthrough. Combinations acting on immune and viral targets are particularly attractive. However, creating synergy while balancing efficacy and safety remains a clear challenge. Various approaches to combination therapy are reviewed, highlighting strengths and challenges of each potential strategy. Overall, combination therapies are attractive as the next step towards cure and are a key strategy for achieving treatment with finite durations and durable endpoints.

Gane, E. J. "**Future anti-HBV strategies.**" *Liver Int* **2017** 37 Suppl 1: 40-44.

Although current oral antivirals can maintain viral suppression and reduce the risk of liver-related complications, lifelong therapy is associated with high cost, risk of breakthrough and potential toxicity. There is a need to develop a finite course of treatment which can provide sustained off-treatment virological and clinical response. The likely marker of such a clinical HBV CURE would be HBsAg clearance, but in addition cccDNA elimination would be required to prevent future reactivation (ie complete HBV cure). Chronic HBV infection is characterised by high viral and antigen burden and inadequate host immune responses, both of which will need to be overcome to achieve HBV CURE. Innovative approaches to restore innate and adaptive immune responses against HBV currently in clinical development include therapeutic vaccines, TLR-7 and TLR-8 agonists. In future, strategies to reverse T-cell exhaustion such as checkpoint inhibitors may be feasible. Currently, the only antivirals in clinical use are the HBV polymerase inhibitors. However, many other steps of HBV virion life cycle can be targeted by small molecules, including inhibitors of HBV entry, nucleocapsid formation and virion assembly and release. siRNAs could inhibit many different steps by blocking multiple HBV transcripts. But, the ultimate goal will be to successfully eradicate or silence cccDNA. It is likely that successful HBV cure will require combination of immunomodulatory, antiviral and cccDNA silencing strategies. Efficacy, safety, route of administration and cost will ultimately determine the impact of these new regimens on the burden of HBV.

### Monitoring program – improved screening?

Easterbrook, P. J., Roberts, T., Sands, A. and Peeling, R. "**Diagnosis of viral hepatitis.**" *Curr Opin HIV AIDS* **2017** 12(3): 302-314.

**PURPOSE OF REVIEW:** Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and HIV-HBV and HCV coinfection are major causes of chronic liver disease worldwide. Testing and diagnosis is the gateway for access to both treatment and prevention services, but there remains a large burden of undiagnosed infection globally. We review the global epidemiology, key challenges in the current hepatitis testing response, new tools to support the hepatitis global response (2016-2020 Global Hepatitis Health Sector strategy, and 2017 WHO guidelines on hepatitis testing) and future directions and innovations in hepatitis diagnostics. **RECENT FINDINGS:** Key challenges in the current hepatitis testing response include lack of quality-assured serological and low-cost virological in-vitro diagnostics, limited facilities for testing, inadequate data to guide country-specific hepatitis testing approaches, stigmatization of those with or at risk of viral hepatitis and lack of guidelines on hepatitis testing for resource-limited settings. The new Global Hepatitis Health Sector strategy sets out goals for elimination of viral hepatitis as a public health threat by 2030 and gives outcome targets for reductions in new infections and mortality, as well as service delivery targets that include testing, diagnosis and treatment. The 2017 WHO hepatitis testing guidelines for adults, adolescents and children in low-income and middle-income countries outline the public health approach to strengthen and expand current testing practices for viral hepatitis and addresses who to test (testing approaches), which serological and virological assays to use (testing strategies) as well as interventions to promote linkage to prevention and care. **SUMMARY:** Future directions and innovations in hepatitis testing include strategies to improve access such as through use of existing facility and community-based testing opportunities for hepatitis testing, near-patient or point-of-care assays for virological markers (nucleic acid testing and HCV core antigen), dried blood spot specimens used with different serological and nucleic acid test assays, multiplex and multi-disease platforms to enable testing for multiple analytes/pathogens and potential self-testing for viral hepatitis

Honer Zu Siederdisen, C., Maasoumy, B. and Cornberg, M. "**What is new on HBsAg and other diagnostic markers in HBV infection?**" Best Pract Res Clin Gastroenterol **2017** 31(3): 281-289. Challenges in the management of chronic hepatitis B virus (HBV) infection involve the prediction of the natural course to identify patients who require antiviral therapy and the prediction of functional cure as ultimate goal of antiviral therapy. HBV DNA as marker for viral replication is important but not sufficient for an adequate management of patients with chronic HBV infection. Data on the quantification of additional HBV marker such as hepatitis B surface antigen (HBsAg), hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA (HBV RNA) have accumulated in recent years. Here we review the current evidence how to use these markers and discuss open issues that require additional research.

## Public health

Subic M, Zoulim F. **How to improve access to therapy in hepatitis B patients.** *Liver international : official journal of the International Association for the Study of the Liver.* 2018;38 Suppl 1:115-21.

Despite the availability of a preventive vaccine and active antiviral treatments that stop disease progression and reduce the risk of hepatocellular carcinoma, hepatitis B is still a major public health problem. Only an estimated 10% of the 257 million people living with HBV have been diagnosed and as few as 1% are being adequately treated. Barriers to diagnosis and treatment include: (i) limited awareness and lack of knowledge about HBV infection and HBV-related diseases; (ii) under-diagnosis with insufficient screening and referral to care; (iii) limited treatment due to drug availability, costs, reimbursement policies and the need for long-term or life-long therapy. These barriers and the actions needed to improve access to treatment are strongly influenced by the prevalence of infection and affect middle-high vs low-middle income countries differently, where most HBV carriers are found. In high-prevalence regions and low-to middle-income countries, the main challenges are availability and cost while in low-prevalence regions and middle-to high-income countries low screening rates, public awareness, social stigma and discrimination play an important role. Overcoming these challenges on a global scale is a complex clinical and public health challenge and multilateral commitment from pharmaceutical companies, governments, funders and the research community is lacking. The new WHO 2016 Global Health Sector Strategy on viral hepatitis targets testing and treatment, suggesting that important but strong actions are needed from advocacy groups, scientific societies and funding agencies to foster awareness and access to cure.

## 2.3 Speakers information – New hepatitis B treatment

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.

**BARBARA TESTONI**, Cancer Research Center of Lyon, INSERM, France  
Dr Barbara Testoni, PhD obtained her PhD in Genetics and Molecular Biology at the University of Milan, working on eukaryotic transcriptional regulation in the setting of skin development. Then, she moved to the University of Rome "La Sapienza" and, at

present, she works as a Principal Investigator at the Cancer Research Center of Lyon (CRCL), in the “Viral Hepatitis” team. Her research interests mainly include the investigation of the epigenetic mechanisms at the basis of host and viral gene regulation during HCV and HBV infections, with particular focus on the transcriptional regulation of the HBV minichromosome.

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1. Vionnet J, Pascual M, Testoni B, Combet C, Godat S, Vijgen S, Aubert V, Rubbia-Brandt L, Zoulim F, Moradpour D. **Late hepatitis B reactivation following DAA-based treatment of recurrent hepatitis C in an anti-HBc-positive liver transplant recipient.** Hepatology. 2017 Sep 16
2. Testoni B, Levrero M, Zoulim F. **Challenges to a Cure for HBV Infection.** Semin Liver Dis. 2017 Aug;37(3):231-242.
3. Lucifora J, Salvetti A, Marniquet X, Mailly L, Testoni B, Fusil F, Inchauspé A, Michelet M, Michel ML, Levrero M, Cortez P, Baumert TF, Cosset FL, Challier C, Zoulim F, Durantel D. **Detection of the hepatitis B virus (HBV) covalently-closed-circular DNA (cccDNA) in mice transduced with a recombinant AAV-HBV vector.** Antiviral Res. 2017 Jul 11;145:14-19. E-pub ahead of print
4. Guerrieri F, Belloni L, D'Andrea D, Pediconi N, Le Pera L, Testoni B, Scisciani C, Floriot O, Zoulim F, Tramontano A, Levrero M. **Genome-wide identification of direct HBx genomic targets.** BMC Genomics. 2017 Feb 17;18(1):184. doi: 10.1186/s12864-017-3561-5.
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6. Lebossé F\*, Testoni B\*, Fresquet J, Facchetti F, Galmozzi E, Fournier M, Hervieu V, Berthillon P, Berby F, Bordes I, Durantel D, Levrero M, Lampertico P, Zoulim F. **Intrahepatic innate immune response pathways are downregulated in untreated chronic hepatitis B patients.** J Hepatol. 2016 Dec 30. (\*equal contribution)
7. Kumar R, Testoni B, Fresquet J, Lim TK, Hao Y, Tan HH, Chow WC, Zoulim F. **Development of hepatocellular carcinoma in chronic hepatitis B patients with advanced fibrosis is independent of viral genotype.** J Med Virol. 2017 May;89(5):845-848

**PIETRO LAMPERTICO**, *Gastroenterology and Hepatology Division, University of Milan, Italy*

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2. D'Ambrosio R, Aghemo A, Rumi MG, Degasperis E, Sangiovanni A, Maggioni M, . . . Lampertico P. **Persistence of hepatocellular carcinoma risk in hepatitis c patients with a response to ifn and cirrhosis regression.** Liver international : official journal of the International Association for the Study of the Liver. 2018.
3. Boni C, Vecchi A, Rossi M, Laccabue D, Giuberti T, Alfieri A, . . . Ferrari C. **TLR7 Agonist Increases Responses Of HBV-Specific T Cells And Natural Killer Cells In Patients With Chronic Hepatitis B Treated With Nucleos(T)Ide Analogues.** Gastroenterology. 2018.
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**CHRISTOPH HÖNER ZU SIEDERDISSEN**, *Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical school, Germany*

**Biography :** Christoph Höner zu Siederdisen, MD, studied Medicine in Hannover and Toronto. He researched the regulation of t-cell development by chemokines for his doctoral thesis 2006–2009. In 2010, he received his medical degree from Hannover Medical School. He has finished his residency in internal medicine and is currently a fellow for gastroenterology in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School (Director Prof. Dr. M.P. Manns). His fields of interest include gastrointestinal and liver diseases, HCV, HBV, liver transplantation and gastrointestinal oncology. His clinical research focuses on viral hepatitis. Specifically he investigates options to stop nucleos(t)ide analogue treatment in HBsAg negative hepatitis B and searches for predictors of HbsAg loss. He also researches the real-world impact of the new HCV treatment options. He is involved in several phase II und phase III studies in the field of viral hepatitis and gastrointestinal oncology

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3. Honer Zu Siederdisen C, Maasoumy B, Cornberg M. **What is new on HBsAg and other diagnostic markers in HBV infection?** Best practice & research Clinical gastroenterology. 2017;31(3):281-9.
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5. Honer Zu Siederdisen C, Maasoumy B, Marra F, Deterding K, Port K, Manns MP, . . . Wedemeyer H. **Drug-Drug Interactions With Novel All Oral Interferon-Free Antiviral Agents in a Large Real-World Cohort.** Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;62(5):561-7.



6. Honer Zu Siederdisen C, Cornberg M. **Management of HBV and HBV/HDV-Associated Liver Cirrhosis**. Visceral medicine. 2016;32(2):86-94.

**TAI-CHUNG TSENG** *Department of Internal Medicine, National Taiwan University Hospital, Taiwan*

Dr. Tai-Chung Tseng is now an attending physician at National Taiwan University Hospital in Taipei, Taiwan. He completed his doctoral research in Prof Jia-Horng Kao's lab and received his Ph.D. degree in 2013. His works focus on the how the viral and host factors affect the long-term prognosis of the HBV carriers. The most important work is to identify the role of HBsAg quantification in predicting the different outcomes, such as HBsAg clearance and HCC development, in a large cohort of HBV carriers. These important findings are not only published in the leading GI journals, such as Gastroenterology and Hepatology but are also validated in other independent research groups. He recently shifted his research interests toward HBV immunology and hope to achieve functional HBV cure via safe and effective immunotherapy in the future.

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5. Tseng TC, Liu CJ, Yang HC, et al. **Higher proportion of viral basal core promoter mutant increases the risk of liver cirrhosis in hepatitis B carriers**. Gut 2015;64:292-302
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**JACK WILLIAMS**, *London School of Hygiene and Tropical Medicine (LHSTM), London, UK*

Biography: Jack is a Research Fellow in Health Economics at the London School of Hygiene & Tropical Medicine, working for the department of Health Services Research and Policy. Jack's research focuses on the cost-effectiveness of public health interventions aimed to improve both the diagnosis and the engagement in care of individuals with hepatitis B and C living in the UK.

**DAVID FITZSIMONS**, *rapporteur*

1. Larson HJ, Van Damme P, FitzSimons D **A hepatitis-free future: strategy first, then pricing.** *Lancet Infect Dis.* 2016 Apr;16(4):399-400
2. FitzSimons D, Hendrickx G, Lernout T, Badur S, Vorsters A, Van Damme P. **Incentives and barriers regarding immunization against influenza and hepatitis of health care workers.** *Vaccine* 2014;32:4849-4854.
3. FitzSimons D, McMahon B, Hendrickx G, Vorsters A, Van Damme P. **Burden and prevention of viral hepatitis in the Arctic region, Copenhagen, Denmark, 22-23 March 2012.** *Int J Circumpolar Health.* 2013 Jul 17;72
4. FitzSimons DW. **World Health Organization.** *Acta Med Port.* 2013 May-Jun;26(3):186-7.
5. FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. **Identification and management of persons with chronic viral hepatitis in Europe.** *European Gastroenterology & Hepatology* 2012;8(1).
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9. FitzSimons D, François G, De Carli G, Shouval D, Prüss-Ustün A, Puro V, Williams I, Lavanchy D, De Schryver A, Kopka A, Ncube F, Ippolito G, Van Damme P. **Hepatitis B virus, hepatitis C virus and other blood-borne infections in healthcare workers: guidelines for prevention and management in industrialized countries.** *Occup Environ Med.* 2008 Jul;65(7):446-51.
10. FitzSimons D, Vorsters A, Hoppenbrouwers K, Van Damme P; **Viral Hepatitis Prevention Board (VHPB); European Union for School and University Health and Medicine (EUSUHM).** **Prevention and control of viral hepatitis through adolescent health programmes in Europe.** *Vaccine.* 2007 Dec 17;25(52):8651-9. Epub 2007 Oct 23.