



Viral Hepatitis Prevention Board (VHPB)

Introduction



VHPB



**More than 35 years active in the control and prevention of
viral hepatitis in Europe**

VIRAL HEPATITIS PREVENTION BOARD

The **Viral Hepatitis Prevention Board (VHPB)** is an international board of experts in viral hepatitis, continuously active since 1992. Board members meet twice a year to discuss technical and country specific issues, with a focus on Europe. These meetings provide a forum for experts to exchange ideas and to develop consensus guidelines on issues related to viral hepatitis prevention and control, all in line with WHO's viral hepatitis elimination goals and focusing on the public health impact. Focus audiences are, in first instance, opinion leaders, policymakers, and health care professionals.



VHPB mission

■ Mission statement

The objective of VHPB is to contribute to the **control** and **prevention** of **viral hepatitides**:

- by drawing the attention to this important public health problem
- by issuing prevention and control guidance and catalyse the development of recommendations,
- by encouraging actions to improve control, prevention and elimination.

All activities are in line with **viral hepatitis elimination goals** defined by **WHO** Global Health strategy

Focus audiences are, in first instance, opinion leaders, policymakers, public health and health care professionals



Way of Working

International Organisations



Ivana Dragojevic
ELPA



Funmi Lesi
WHO HQ



Stela Bivol
WHO Euro



Erika Duffell
ECDC



Rania Tohme
CDC



Shira Zelber-Sagi
EASL



John Ward
Task Force



Public Health



Sandra Dudareva
Germany



Sema Mandal
UK



Silvia Bino
Albania



Mira Kojouharova
Bulgaria

Academia



Thomas Berg
Germany



Stephane Chevaliez
France



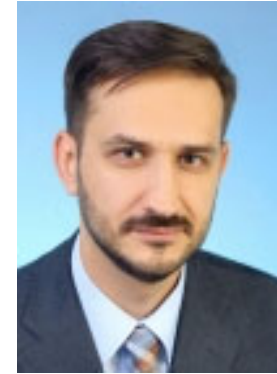
Sharon Hutchinson
Scotland



Paolo Bonanni
Italy



Rui Tato Marinho
Portugal



Vladimir Chulanov
Russia



Pierre Van Damme
Belgium
VHPB Executive Secretary



Thomas Vanwolleghem
Belgium



Vana Papaevangelou
Greece



Angela Dominguez
Spain



Mojca Maticic
Slovenia



Maria Buti
Spain

VHPB Honorary Advisors

- Prof. Dr. Selim Badur
- Dr. Hans Blystad
- Dr. Claire Cameron
- Prof. Dr. Pietro Crovari
- Dr. Nedret Emiroglu
- Prof. Dr. Alain Goudeau
- Prof. Dr. Peter Grob †
- Dr. Nicole Guérin
- Priv.Doiz. Dr. Med. Habil. Johannes F. Hallauer †
- Prof. Dr. Med. Wolfgang Jilg
- Dr. Mark Kane
- Dr. Daniel Lavanchy †
- Dr. Harold Margolis †
- Dr. Antons Mozalevskis
- Dr. Eric Mast
- Dr. Elisabeth McCloy
- Prof. Dr. André Meheus †
- Prof Helène Norder
- MSc. Tatjana Reic
- Prof. Dr. Lars Rombo
- Dr. Françoise Roudot-Thoraval
- Dr. Colette Roure
- Dr. Craig Shapiro
- Prof. Dr Daniel Shouval
- Dr. Steven Wiersma
- Dr. Alessandro Zanetti

These honorary members are elected for a lifelong term and are invited to VHPB meetings on an ad hoc basis.



VHPB secretariat

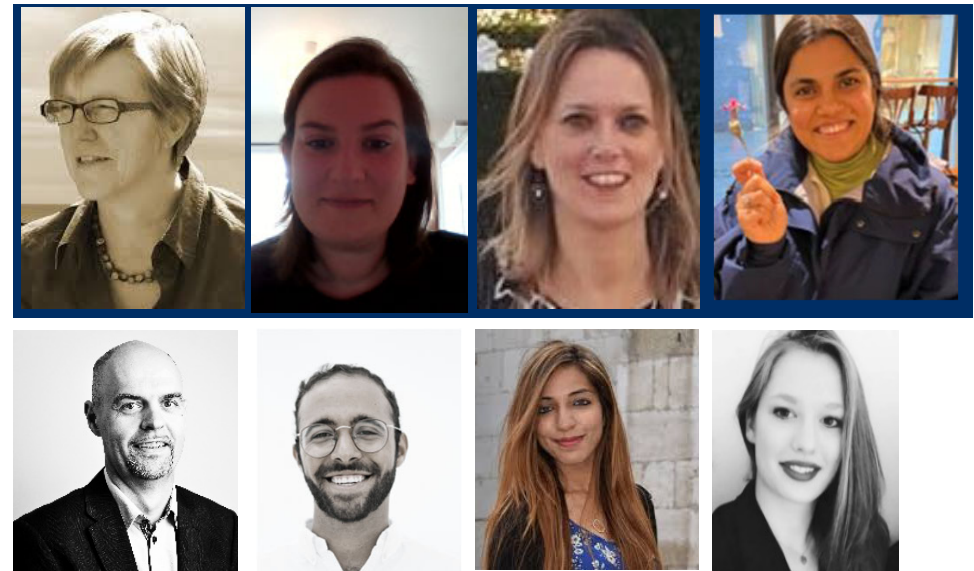


Executive secretary

- Pierre Van Damme

Personnel involved

- Greet Hendrickx
- Sara Valckx
- Brenda Janssens
- Xenia Mikulla
- Sakshi Jindal
- Ricardo Burdier
- Dur-e-Nayab Waheed
- Alex Vorsters



All secretariat members have additional tasks in the VAXINFECTIO department of the University of Antwerp

Located within the facilities of the Centre for the Evaluation of Vaccination (CEV), University of Antwerp



HPV prevention and control board and Adult Immunization board are embedded in the same facilities.

Funding

- VHPB is supported by *unrestricted grants* from the vaccine industry (GlaxoSmithKline Biologicals, Gilead, Merck, Sanofi) and several universities in Europe and other institutions
- VHPB is not a legal entity, all grants are collected by the **University of Antwerp**
- The VHPB does accept **unrestricted grants** from companies to support their activities including web development but maintains all editorial control over the content of the site. Editorial control of the site rests entirely with the secretariat of the VHPB
- All participants at the meetings as well as Board members are never payed for their activities and input in the VHPB. Only their participation costs are reimbursed in line with the rules of the University of Antwerp.

VHPB modus operandi



WAY OF WORKING

The VHPB provides evidence-based expertise to support the control and prevention of all types of viral hepatitis. Its mission includes:

- Highlighting the significance of viral hepatitis as a public health issue.
- Developing prevention strategies and facilitating the creation of recommendations.
- Promoting initiatives to enhance control and prevention efforts.

The VHPB organises at least two international meetings per year, offering a platform for dissemination and discussions. Meetings usually cover a specific topical issue in viral hepatitis prevention and control, or have the intention to discuss viral hepatitis management in a specific country or region. The meetings are set up to promote sharing, learning, inspiring and foster collaboration, with the ultimate goal to contribute to the fight against viral hepatitis.

Visit: <https://www.vhpb.org/meetings/>

Two meetings per year

1. Technical meeting

- Discuss, review and issue guidelines or recommendations for critical issues in viral hepatitis focusing on public health impact

2. Country meeting

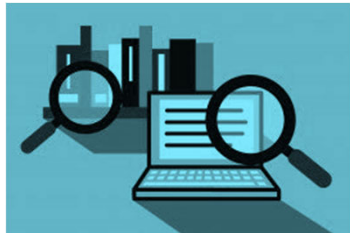
- Understand strategies and programs to control viral hepatitis in the country
- Monitor progress of countries in control of viral hepatitis, verify the WHO elimination goals
- Create a platform where people of the country involved in viral hepatitis can discuss and can start future initiatives
- Initiate or accelerate the development of a National viral hepatitis plan
- Draft guidelines to support countries based on lessons learned from other countries

Meetings - Way of working



Meeting topics- countries
Objectives – meeting outcome

Literature –web review



Draft agenda

Potential speakers

Potential participants





VHPB TECHNICAL MEETING
 Online

The impact of COVID-19 on the
(1) prevention of viral hepatitis
(2) 2030 WHO elimination goals

18 & 25 March 2021 – 16h30 until 20h00
[Draft MEETING agenda](#)

MEETING OBJECTIVES

The impact of COVID-19 on the prevention of viral hepatitis

- Evaluate the impact of the COVID-19 pandemic on National/regional vaccination and prevention programs for viral hepatitis
- Discuss how increasing vaccine hesitancy due to the pandemic may endanger the high coverage rates of hepatitis B vaccination
- Evaluate lessons learned from existing catch up programmes
- Discuss the scale up of the public health needs to improve prevention and immunization of viral hepatitis which were negatively influenced by the pandemic

The impact of COVID-19 on the viral hepatitis elimination goals

- Evaluate the impact of the COVID-19 pandemic on viral hepatitis, screening, control & treatment in Europe
- What is the influence of the COVID-19 pandemic on the elimination goals, regionally and on country level
- Review the possible implementation of control measures, new prevention strategies and monitoring systems during and after a pandemic, lessons learnt
- Assess the (extra) needs to achieve the goal of eliminating viral hepatitis as a major public health threat in Europe by 2030 as defined by WHO's Regional office for Europe. Discuss successes, issues and the new challenges

Part 1: The impact of COVID-19 on the prevention and vaccination of viral hepatitis

Thursday 18 March 2021

Introduction of the participants

Chair: **Geert Hendrickx**

16:30-17:00

- Welcome and opening of the meeting
- Introduction of the participants

Session 1.1: COVID-19 impact on hepatitis prevention in risk groups

Chair: **Marko Kerecikas**

17:00-17:40

How is the pandemic affecting harm reduction services working on HIV, hepatitis and STIs

Pre-recorded

[Discussion in HIV, Hepatitis and STI services due to Covid](#)

Watch [Saxena](#) (WHO)

EMCDDA

Impact of COVID-19 on harm reduction services

Live

Jane Mountney (head of public health EMCDDA)

Correlation Network

How harm reduction must go on – focusing on hepatitis

Pre-recorded

Eberhard Schutz (C-CHRN)

This is a draft version of the VHPB meeting agenda, not all proposed speakers confirmed yet

Countries covered

- Italy (2002)
- Germany and the Nordic Countries (2003)
- France (2004)
- UK (2005)
- Spain (2006)
- Greece (2007)
- The Netherlands (2008)
- Turkey (2009)
- Portugal (2010)
- Bulgaria (2011)
- Arctic Region (2012)
- Israel (2013)
- Brazil (2014)
- Baltic states (2015)
- Albania (2016)
- Belgium – Luxembourg (2017)
- The Russian Federation (2018)
- Hungary (2019)
- Balkan Meeting (2022)



Special meeting Romania 2018

Broad range of topics covered in 30 years

- Hepatitis B vaccination
 - Universal Immunisation programs
(transition from risk group strategy to universal immunization)
 - Adolescent and new-born programmes
 - Safety issues
 - long term efficacy Surveillance best practice
 - Vaccine shortage
 - Non-responders
 - Occult hepatitis
 - Long term (+25y) HBV vaccination and treatment (2022)
- Hepatitis B and C asymptomatic infection and chronic carriage
 - Surveillance activities
 - Identification and management
 - Treatment of hepatitis C a public health challenge
 - Impact of treatment non-responders on public health
 - Perinatal transmission
- Treatment as Prevention (2020)
 - Of HCV in risk groups
 - Of HBV to prevent MTCT & progression of liver disease
- Injection safety and safe blood supply
 - Realization that ~50% injections unsafe in developing world
- HBV mutants and variants
 - Prediction “Escape mutants” would negate gains of immunization.
- Prevention and control of hepatitis in migrants and refugees
 - Increasingly important issue
- How to reach risk groups
- Hepatitis A and E
 - Hepatitis A: one dose (2020)
- Hepatitis D (2021)
- Economical analysis
 - A viral hepatitis free future: how to make it affordable
- The impact of COVID-19 on the prevention and control of viral hepatitis (2021)



The Role of VHPB in the Elimination debate

- Create awareness for viral hepatitis as a public health problem
- Bring together all stakeholders in a Country/Europe to share knowledge and enthusiasm for the elimination goals
- Together with other organisations in Europe fight for attention for the elimination of viral hepatitis in the region
- Looking and disseminate all evidence-based material to support the elimination debate
- Create a platform where academics, scientists, public health representative and health care providers can meet and share information
- Catalyse the creation of guidelines and recommendation for the prevention and control of viral hepatitis



Viral Hepatitis Prevention Board

VHPB technical meeting

Addressing Hepatitis A in Europe in 2026 –
Challenges, Strategies, and Opportunities

13-14 October 2026

Antwerp, Belgium

Meeting Objectives

- **Review the current HAV epidemiological landscape, burden of disease and immunity gaps in the WHO-Euro region.** Analyse trends in incidence, outbreaks, and immunity gaps, highlighting key risk groups and regional disparities.
- **Discuss transmission risks and diagnosis.** Assess the role of travel, migration, and foodborne exposure in shaping HAV risk, and discuss interventions such as risk-based screening, pre-travel vaccination and increasing public awareness.
- **Compare and evaluate national HAV prevention strategies and outcomes.** Examine the impact of universal and targeted vaccination (e.g. food handlers, MSM, teachers, travellers...), with lessons learned from country/regional case studies to identify good practices and implementation gaps.
- **Assess long-term protection.** Review current evidence on the durability of immunity following vaccination.
- **Promote evidence-based, cost-effective policymaking for HAV prevention.** Highlight health economic and scientific evidence that can inform national policies, strengthen surveillance, and support alignment with WHO viral hepatitis elimination goals.



Intended impact

- **Strategic guidelines for effective HAV prevention and vaccination policies**, including identification of immunity gaps
- **Strengthened collaboration between policymakers, public health specialists, healthcare professionals, and academic researchers**, fostering integration of HAV strategies within broader hepatitis elimination frameworks



Viral Hepatitis Prevention Board

VHPB TECHNICAL MEETING · SESSION 1

Addressing Hepatitis A in Europe in 2026

Why the VHPB,

Why now,

Why these objectives



Why the VHPB?

Almost three decades of work on hepatitis A as a vaccine-preventable disease



Hepatitis A has been on the VHPB agenda since 2007

2007

Miami, USA

First global hepatitis A meeting: 200+ experts from 46 countries asked “Has the time come to control hepatitis A globally?” – and recommended stepwise introduction of universal childhood vaccination.



2009

Antwerp, Belgium

Hepatitis A and E: update on prevention and epidemiology. Growing importance of HAV in intermediate-endemicity regions; need for global control (FitzSimons, Hendrickx, Vorsters, Van Damme, Vaccine 2010).

“Hepatitis A and E: update on prevention and epidemiology”

Viral Hepatitis Prevention Board Meeting
Antwerp, Belgium, 12-13 March 2009.

2020

Virtual meeting

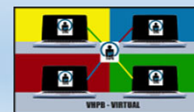
Hepatitis A vaccination: one dose – reviewing the evidence for single-dose schedules.

VHPB TECHNICAL MEETING

Hepatitis A vaccination: One dose

Background document

11 June 2020 – 17h tot 20h



2026

Antwerp, Belgium

Addressing hepatitis A in Europe in 2026 – challenges, strategies and opportunities.



Addressing Hepatitis A in Europe in 2026 · Antwerp, 13–14 October 2026

2009 → 2026: what we said then, where we stand now

Theme	2009 Antwerp meeting (Vaccine 2010)	2026
Epidemiology	Growing importance of HAV as countries move to intermediate endemicity; rise in cases in the Czech Republic (2008) and an outbreak in Latvia	Resurgence again in Czechia, Slovakia, Austria and Hungary; shift to MSM and marginalised adults
Vaccines	Long-term immunity after vaccination being documented	20–25 years of follow-up; durability of a single dose still the open question
Surveillance	Call for harmonised HAV typing and outbreak alerts (EVENT network)	HAVNet, the EU Reference Laboratory and wastewater monitoring – but data completeness varies
Policy	WHO position paper under review; need for control at global level	WHO position paper updated (2022); national policies in Europe still a patchwork



Sources: FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Vaccine 2010;28(3):583-8; VHPB meeting programme, March 2009; background document

Why the VHPB is well placed to convene this discussion

VHPV is independent, multidisciplinary forum

Policymakers, public health specialists, healthcare providers, civil society and academics around one table.

From evidence to recommendations

A track record of meeting discussions into published conclusions and policy-relevant outputs for more than 32 years

A whole-hepatitis perspective

Positioned to bring hepatitis A into the broader viral hepatitis elimination agenda.

Create awareness for hepatitis A on Public health level

A European network complemented with Global experts

Country experiences across the WHO European Region and beyond, to learn what works and why.

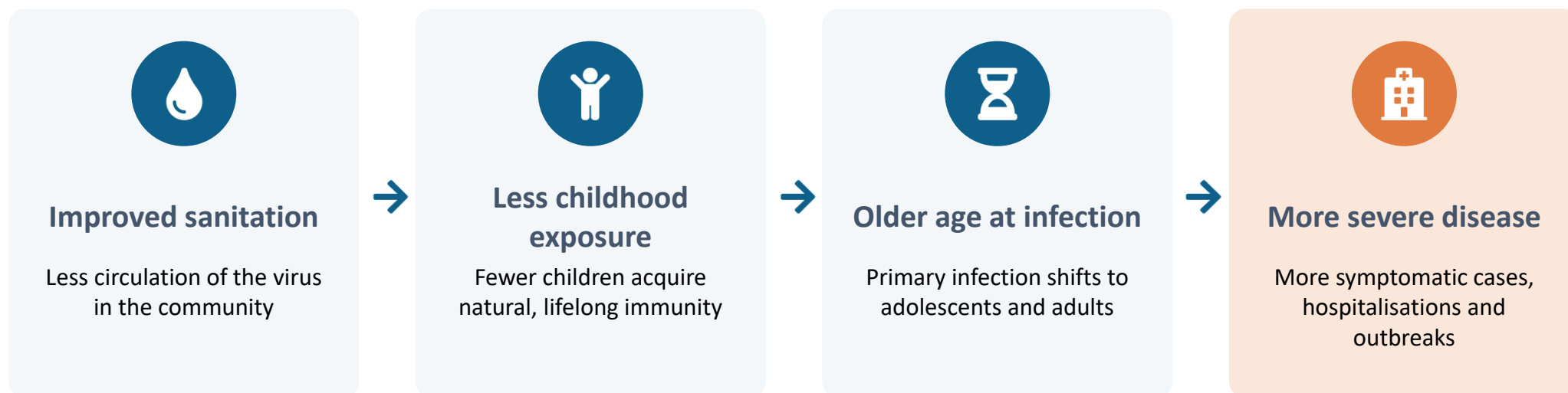


Why now?

A significant, yet often overlooked, public health concern in Europe



The paradox: better hygiene has created susceptible adults



Not a new warning. The 2009 VHPB meeting in Antwerp already highlighted the growing public health importance of hepatitis A in countries moving towards intermediate endemicity, and the need for control at global level (FitzSimons, Hendrickx, Vorsters, Van Damme, Vaccine 2010).

Europe: low incidence, high susceptibility

139,793

notified hepatitis A cases in
29 EU/EEA countries,
2010–2019

3.2

cases per 100,000
population per year – a low
baseline

>47,000

hospitalisations reported
over the same decade

>60%

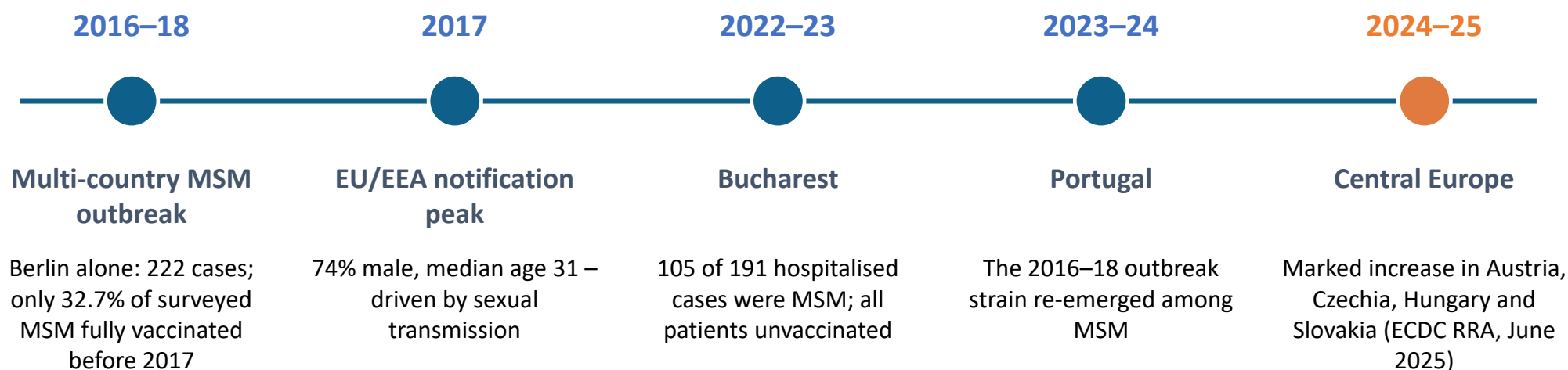
of all cases reported by six
eastern EU countries

Susceptible to recurrent, large cross-border outbreaks. Notifications peaked in 2014 and 2017, and surveillance data on travel, hospitalisation, death and transmission route remain suboptimal.

Source: Severi et al., Euro Surveill 2023 (TESSy notifications 2010–2019)



The warning signals keep coming



Sources: Zimmermann et al., 2021; Severi et al., 2023; Paun et al., 2026; Rosendal et al., 2024; ECDC, 2025; Hofmeister et al., 2026

VHPB technical meeting · Addressing Hepatitis A in Europe in 2026 · Antwerp, 13–14 October 2026

Why now: four reasons converge



A growing susceptible adult population

Declining natural immunity means more symptomatic, severe disease when infection occurs.



Resurgent outbreaks in vulnerable groups

MSM, people experiencing homelessness, people who use drugs and Roma communities – groups that are hard to reach.



Uneven policies across Europe

Large differences in schedules, indications, reimbursement and coverage.



Left out of the elimination agenda

The WHO 2030 goal focuses on hepatitis B and C – yet hepatitis A is vaccine-preventable and entirely controllable.



The evidence and the tools have moved on



WHO position paper (2022)

A single dose of inactivated vaccine is considered equivalent to two doses in children; targeted vaccination of risk groups in low-endemicity settings.



One dose works at population level

Brazil (one dose since 2014): incidence fell from 3.19 to 0.87 per 100,000, preventing an estimated 14,468 cases in 2015–2018.



Long-term protection

Alaska: 81% still protected 25 years after childhood vaccination. Durability of a single dose remains the open question.



New surveillance tools

Wastewater monitoring, molecular typing via HAVNet, and the EU Reference Laboratory (EURL-PH-FWDV, designated 2024).

Why these objectives?



Each objective answers a gap

Objective	The gap it addresses	Sessions
1 Review epidemiology, burden and immunity gaps	Low incidence masks high susceptibility; regional disparities; immunity gaps from lack of vaccination and waning immunity	2, 3
2 Discuss transmission risks and diagnosis	Travel, migration, food and sexual transmission; limited integrated HAV testing	2, 3
3 Compare national prevention strategies	Universal vs targeted vaccination (food handlers, MSM, teachers, travellers); lessons from country case studies	5, 6
4 Assess long-term protection	Durability of a single dose beyond 25 years; adults over 40 and immunocompromised people	3, 4, 5
5 Promote evidence-based, cost-effective policy	need to strengthen surveillance and align with WHO elimination goals	5, 6



Sources: background document, Part 1 and Sessions 2–6; Cabezas et al., 2026; Plans-Rubió et al., 2024; Valcarcel-Nazco et al., 2023

Two days: from evidence to recommendations



Expected outcomes



Analysis of effective HAV prevention and vaccination policies, including identification of immunity gaps



Policy recommendations-relevant evidence and analyses for sustainable, data-driven decisions at national and regional level



Stronger collaboration, integrating HAV strategies into broader hepatitis elimination frameworks

Outcome

- Website – vhpb.org
- Report
 - Website
 - Scientific paper



Practical meeting info

- Please keep the time that is foreseen in the agenda
- This is an **interactive meeting**, but make sure that when you have a question or comment use the mic
- Online Participants
 - Please switch on your video while introducing yourself and every
 - Keep yourself on mute when not speaking
 - Please make use of the chat function to ask any burning question or raise your (virtual) hand



Thank you

- For your presence
- For your input in this meeting
- For all the efforts

Wish you all a fruitful meeting



NEWS FROM THE VIRAL HEPATITIS PREVENTION BOARD



VIRAL HEPATITIS

ACTION ON HEPATITIS A AS A COMMUNITY HEALTH RISK

HEPATITIS A: TAKE STEPS TO CONTROL SPREAD OF INFECTION

VHPB calls for research into occupational risks	2
Report on the hepatitis A meeting in Marlow	3
Hepatitis A is top travel illness	15
National pictures of hepatitis A infection	16



By the way ...

VIRAL HEPATITIS

PUBLISHED BY THE VIRAL HEPATITIS PREVENTION BOARD

October 1997
Volume 6 - Number 1

CONTENTS

EDITORIAL 1

MEETING NEWS 2-4
..... 14-16

■ Vaccine news

- Paediatric combined vaccines: clinical trials in Italy and Greece 2
- Combined hepatitis vaccines equal monovalent

EDITORIAL

This issue of *Viral Hepatitis* takes a close look at the issues surrounding the development of combined vaccines, in particular, their introduction into immunization programmes, and their role in preventing HBV and HAV infection in at-risk groups. We also revisit the subject of hepatitis A, and have included an update of the report on the epidemiology, transmission routes, and means of preventing hepatitis A infection presented previously in *Viral Hepatitis* (1995: Vol 3, No 1).

Combined vaccines are the future for childhood immunization - not only for hepatitis B but for other antigens as well. They are a necessity, not a luxury, and once in widespread use will bring with them a host of benefits: fewer injections and a simplified immunization schedule; cost reductions; and better acceptance by parents and physicians. These improvements should pave the way for the introduction of new antigens and, in the case of hepatitis B, should spur countries that have not yet made HB vaccine part of their routine immunization programmes to do so. Persons at increased risk of hepatitis A and hepatitis B - such as travellers and military personnel - will also benefit from the introduction of combined vaccines. Hepatitis A and hepatitis B are the two most common vaccine-preventable diseases in travellers from low to high endemicity areas. A combined HA-HB vaccine is already available in some

UPDATE ON HEPATITIS A

Based on the *Viral Hepatitis Report on the Hepatitis A meeting in Marlow, UK (Viral Hepatitis, 1995; 3: 3-14)* and on information presented by Dr Beth Bell of the Centers for Disease Control and Prevention, Atlanta, GA, USA. Prepared by Dr Pierre Van Damme, Dr Mark Kane and Margaret Van der Elst.

Modes of HAV transmission

- Faeco-oral route (95%)
 - ==> person-to-person contact
 - ==> contaminated food or water
 - ==> salads and fruits washed in contaminated water
 - ==> contaminated shellfish
- Infected plasma (<5%)
- Sexual route (<5%)

1.

HEPATITIS A: DISEASE AND EPIDEMIOLOGY

1.1. Introduction

Hepatitis A is an inflammatory disease of the liver caused by the hepatitis A virus (HAV), and spread by faeco-oral transmission¹⁻³. HAV has a worldwide distribution which relates to the level of economic development, and transmission often occurs in epidemics.

In many developed and developing countries, disease incidence and prevalence decline as hygiene, sanitation and living standards improve. As HAV endemicity decreases, the average age of exposure and subsequent infection shifts to older age groups. As severity of clinical disease is age-related, this shift increases the number of clinical infections, morbidity and mortality³.

1.3. Disease

HAV is a single-stranded RNA virus which chooses the hepatocyte as the primary target cell. HAV has no cytolitic activity on liver cells. It seems more likely that liver cell damage is caused by activation of the T-cell mediated immune response as a result of the presence and replication of the virus. Infection with HAV is usually self-limiting.

The incubation of a HAV infection varies between 15 and 50 days, with a mean duration of approximately one month^{14,15}. Prodromal symptoms such as malaise, fatigue and loss of appetite are not obviously related to liver disease. Patients are infectious during the period in which HAV is secreted in the bile and present in the stool, usually



PERSISTENT OUTBREAK OF HEPATITIS A SEEN IN PUGLIA, ITALY

During the first 11 months of 1996 (with peak incidence in August), an outbreak of hepatitis A occurred in Puglia, Italy, a region in the southeast of the country. This was the largest and most persistent epidemic of hepatitis A reported from Puglia since the infection became notifiable in 1989. The outbreak began in the city of Bari and subsequently spread throughout the region.

By the end of 1996, 5,620 cases had been notified, for a cumulative incidence rate of 137.3/100,000. This compares with previous rates per 100,000 of: 22 in 1990; 18 in 1991; 68 in 1992; 22 in 1993; 33 in 1994; and four in 1995. The outbreak was highest in Bari City (381.3/

100,000), and overall, people aged five to 34 accounted for 96% of all cases of notified hepatitis A.

Outbreak investigation showed a strong association between illness and the consumption of raw seafood and the storage of seafood in sea water at the place of sale. Recommendations on the handling and consumption of seafood had little impact on the epidemic which did not subside until week⁴².

As presented by Prof Paolo Bonanni, University of Florence, Italy.

Reference: Lopalco PL, Malfait P, Salmaso S, Germinario C, Quarto M, Barbuti S, A Persisting Outbreak of Hepatitis A in Puglia, Italy, 1996: Epidemiological Follow-up. Eurosurveillance, 1997; 2: 31-32.



Single Dose Inactivated Hepatitis A Vaccine: Rationale and Clinical Assessment of the Safety and Immunogenicity

P. Van Damme, C. Mathei, S. Thoelen, A. Meheus, A. Safary, and F.E. André
Department of Epidemiology, University of Antwerp (P.V.D., C.M., S.T., A.M.), Antwerp, and SmithKline Beecham Biologicals (A.S., F.E.A.), Rixensart, Belgium

In comparison with the classical immunisation schedules (0-1-6 or 0-1-12 months) for hepatitis A, a 0- and 12- or a 0- and 6-month schedule would have important advantages by reducing the number of injections and discomfort and increasing scheduling convenience and patient compliance. It would be convenient if a single dose with enough antigen could protect both rapidly and for at least 12 months, when the booster dose would be given. Several clinical trials have been carried out with an inactivated hepatitis A vaccine containing 1,440 EL.U. (1 ml), according to a 0-12 and a 0-6 vaccination schedule.

This hepatitis A vaccine is safe and well tolerated. It offers a rapid seroresponse: 14 days after a single dose the seroconversion is 88% (95% C.I.: 84.6-90.9). The 0-12 schedule study showed good persistence of hepatitis A virus (HAV) antibodies with a seroconversion rate of almost 95% at month 12. Booster doses given at 6 or 12 months result in a substantial rise in antibody levels. According to these antibody titres, the 1,440 EL.U. vaccine can be expected to confer comparable duration of protection as the 720 EL.U. vaccine, i.e., 10-20 years. Preliminary data show that timing of the booster may not be critical for the antibody response.

In conclusion, the 1,440 EL.U. hepatitis A vaccine is safe, offers rapid seroconversion, and is highly immunogenic. The persistence of HAV antibodies until month 12 allows a certain flexibility in the administration of the booster: month 6 or 12, and a 0-12 or 0-6 schedule can increase the vaccination compliance. © 1994 Wiley-Liss, Inc.

KEY WORDS: vaccine trials, immunogenic, review

INTRODUCTION

Hepatitis A virus (HAV) is enterically transmitted and causes an acute inflammation of the liver. Hepatitis A affects large numbers of people worldwide; its epidemiology is closely related to socioeconomic factors,

overcrowding, poor hygiene, and inadequate sanitation [Hadler, 1991; Gust, 1992; Shapiro et al., 1992]. Due to better general hygiene in many developed and developing countries, disease incidence has decreased in the younger age groups; the age of acquisition of infection has shifted to older age groups, leaving a large proportion of adolescents and young adults susceptible to infection with HAV [Papaevangelou, 1992]. From epidemiological studies, several groups at higher risk for HAV have been recognised: travellers to endemic regions [Steffen, 1993], some categories of health care workers [Klein et al., 1984], personnel in day care centres [Hadler et al., 1980] and institutions for the mentally handicapped [Tassopoulos et al., 1987], sewage workers [Poole and Shakespeare, 1993], and military personnel [Baneroff and Lemon, 1984].

In 1979, Provost and Hilleman demonstrated that HAV can replicate in primate cells in culture. The attenuated vaccine candidates, developed through this early research, elicited only a weak antibody response. Another approach for the development of a hepatitis A vaccine was similar to that used by Dr. Jonas Salk for the formalin-inactivated poliovirus vaccine [Provost and Hilleman, 1978]. These early candidate vaccines, prepared from infected marmoset livers, were shown to induce neutralising antibodies. More recently, commercial manufacturers have started to produce cell culture-derived purified vaccines [Lemon, 1992].

An inactivated hepatitis A vaccine (Havrix™, SmithKline Beecham Biologicals, Rixensart, Belgium) was licensed for the first time in Switzerland in late December 1991 and is available in an increasing number of countries. At present more than 50,000 healthy subjects have been enrolled in clinical trials [André et al., 1992] and over 1 million vaccine doses are distributed per year worldwide. This vaccine contains 720 ELISA units (EL.U.) of killed hepatitis A antigen, and is manufactured with the HM175 virus strain [Peetermans, 1992]. The primary vaccination course consists of two injections at 0 and 1 month or 0 and 14 days, followed

Accepted for publication July 13, 1994.

Address reprint requests to Dr. Pierre Van Damme, Department of Epidemiology, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium.

Inactivated Hepatitis A Vaccine: Reactogenicity, Immunogenicity, and Long-Term Antibody Persistence

P. Van Damme, S. Thoelen, M. Cramm, K. De Groote, A. Safary, and A. Meheus
Department of Epidemiology and Community Medicine, University of Antwerp, Antwerp (P.V.D., S.T., M.C., K.D.G., A.M.), and SmithKline Beecham Biologicals, Rixensart (A.S.), Belgium

This trial evaluated the reactogenicity, kinetics of antibody induction, and long-term immunogenicity of a 720 enzyme-linked immunosorbent assay units (EL.U.) antigen dose of an inactivated hepatitis A vaccine (Havrix™, SmithKline Beecham Biologicals, Rixensart, Belgium). One hundred six healthy adult volunteers were enrolled to receive vaccine intramuscularly according to a 0, 1, and 6-month schedule. The vaccine was well tolerated. The most frequently reported local symptom was soreness, observed following 37.1% of all doses. Headache was the most frequently reported general symptom observed following 12.9% of documented vaccine doses. The administration of one vaccine dose induced seropositivity (anti-hepatitis A virus [HAV] $\geq$ 20 mIU/ml) in 91% of all vaccinees 1 month later. The second vaccine dose resulted in seropositivity of the remaining vaccinees at month 2. All subjects remained seropositive for HAV antibodies at month 6, at which time the booster vaccine dose was given. At month 7, all vaccinees had anti-HAV titres $>$ 200 mIU/ml.

Serological results obtained at months 12, 18, 24, and 36 showed that antibodies against HAV induced by the vaccine booster dose persist for at least 30 months following its administration. All 49 subjects followed up until month 36 had antibody titres $\geq$ 20 mIU/ml. The geometric mean titre (GMT) decreased by 60% from month 1 to month 12; between month 12 and 36, the GMT decreased by approximately 14% per period of 12 months. According to the vaccine-induced antibody kinetics and the magnitude of antibody level decrease over time, the predicted duration of antibody persistence is estimated to be at least 20 years. © 1994 Wiley-Liss, Inc.

KEY WORDS: antibody kinetics, side effects, booster

INTRODUCTION

Hepatitis A virus (HAV) causes an acute inflammation of the liver; HAV is a food- and water-borne infection spread by faecal-oral transmission [Hadler, 1991]. The epidemiology of HAV is closely related to poor hygiene, inadequate sanitation, and overcrowding. HAV has a worldwide distribution. Improvement in standards of hygiene has led to a decline in incidence of HAV infections in childhood, the prevalence of antibodies against HAV has shifted to older age groups, leaving a large proportion of adolescents and adults susceptible to infection with HAV [Hadler, 1991; Tilzey and Banatvala, 1991].

An inactivated hepatitis A vaccine (Havrix™), developed by SmithKline Beecham Biologicals, is now available in an increasing number of countries worldwide [André et al., 1990; André, 1991]. This vaccine contains 720 enzyme-linked immunosorbent assay (ELISA) units (EL.U.) of hepatitis A antigen, and is administered following a primary course of two injections, the second dose given 2-4 weeks after the first one, with a booster dose 6 or 12 months later [André et al., 1990, 1992; André, 1991; Anonymous, 1992; Just and Berger, 1992]. This vaccine has been proven to be highly immunogenic and safe [André et al., 1990; André, 1991; Anonymous, 1992; Just and Berger, 1992], and a protective efficacy of 94% has been shown in a large field trial [Innis et al., 1994].

As for hepatitis B vaccines, attention has now turned to the evaluation of the persistence of hepatitis A vaccine-induced antibodies, the duration of protection offered by these antibodies, and the need for vaccine booster doses. Because this inactivated hepatitis A vaccine was developed recently, only few data are published on the persistence of antibodies and immunogenicity for a medium to long period [Wiedermann et al., 1992; Just and Berger, 1992]. Persistence of antibodies after immunisation can be determined only by continued observation in time. This paper analyses the immunogenicity of the vaccine until 36 months after the first dose.

Accepted for publication July 13, 1994.

Address reprint requests to Dr. Pierre Van Damme, Department of Epidemiology, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium.

Cost-Effectiveness Analysis of Vaccination Against Hepatitis A in Travellers

E. Van Doorslaer, G. Tormans, and P. Van Damme

*Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands (E.V.D.);
Department of Epidemiology and Community Medicine, University of Antwerp, Antwerp, Belgium (G.T., P.V.D.)*

Hepatitis A virus (HAV) infection is a substantial risk for travellers from low endemic countries to high endemic destinations. Costs and effects of alternative options for prevention were compared using formal decision analysis. General indications for the optimal prevention of hepatitis A were derived from a cost-effectiveness analysis. Various possible strategies for prevention of hepatitis A in travellers were compared to doing nothing: active immunisation using either the existing vaccine (HAVRIX 720) or the new vaccine (HAVRIX™ 1440); first screening for the presence of HAV antibodies and then vaccinating only susceptibles; and passive immunisation with immunoglobulin. Using a number of assumptions as baseline and for an average duration and frequency of travel from low to high endemic countries, threshold values were obtained for the choice between passive and active immunisation. Passive immunisation remains the most cost-effective prevention strategy for those expected to travel not more frequently than twice over the next 10 years and for short stays (£7,000–9,000 per infection prevented). For travellers expected to travel three or more times in 10 years or for trips exceeding a period of 6 months, active immunisation before the first trip is the most cost-effective option (£7,500 or less per infection prevented). When travel frequency increases to once a year in the next 10 years, costs per infection prevented decrease to about £3,500. Screening for the presence of antibodies before vaccination is only justified for older travellers or those leaving from countries with moderate endemicity, i.e., with an average HAV prevalence of at least 30%. © 1994 Wiley-Liss, Inc.

KEY WORDS: HAV, immunisation, economic evaluation

INTRODUCTION

One of the risks faced by travellers from low endemic countries to high endemic destinations is the risk of infection with the hepatitis A virus (HAV). Possible

preventive strategies, together with advice on hygiene and dietary precautions, include passive and active immunisation. Prophylaxis with immunoglobulin provides relatively cheap but short-term protection while the vaccine (HAVRIX 720) offers longer term protection but at greater cost. Furthermore, a screening test with high predictive value is available if one wants to assess the presence of natural immunity before engaging in preventive measures.

Tormans et al. [1992b] compared the cost-effectiveness of these prevention alternatives for Belgian travellers and concluded that active immunisation was more cost-effective than passive immunisation for frequent travellers. With the development of the inactivated hepatitis A vaccine with a one-dose primary course, it seems worthwhile to re-examine the relative cost-effectiveness of the alternative strategies. The cost-effectiveness of the new "one-step" vaccination approach is compared with the already existing alternatives and some recommendations for rational prevention policy will be derived in relation to the origin, destination, and type of travel. This will be done by calculating the expected cost per HAV infection prevented for the various strategies and for different travel characteristics.

MATERIALS AND METHODS

The basic decision tree depicted in Figure 1 summarises the six alternatives that have been considered in the simulation model used to calculate expected costs and expected effects of each intervention strategy. Five possible strategies for prevention of HAV infection in travellers are compared to doing nothing: active immunisation with the existing inactivated hepatitis A vaccine (HAVRIX 720) consisting of two doses and a booster dose [André et al., 1992] or with the new formulation consisting of a single dose and a booster [Van Damme et al., 1994]; first screening for the presence of HAV antibodies in the blood and then vaccinating only susceptibles with one of the two vaccines; and passive

Accepted for publication July 13, 1994.

Address reprint requests to Eddy Van Doorslaer, Ph.D., Institute for Medical Technology Assessment, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.