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Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology

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SUMMARY. For the first time a global meeting on hepatitis A virus (HAV) infection as vaccine preventable disease was organized at the end of 2007. More than 200 experts from 46 countries gathered to investigate the changing global HAV epidemiology reflecting the increasing numbers of persons at risk for severe clinical disease and mortality from HAV infection. The benefits of childhood and adult hepatitis A (HepA) vaccination strategies and the data needed by individual countries and international health organizations to assess current HepA prevention strategies were discussed. New approaches in preventing HAV infection including universal HepA vaccination were considered. This introductory paper summarizes the major findings of the meeting and describes the changing epidemiology of HAV infections and the impact of HepA vaccination strategies in various countries. Implementation of HepA vaccination strategies should take into account the level of endemicity, the level of the socio-economic development and sanitation, and the risk of outbreaks. A stepwise strategy for introduction of HepA universal immunisation of children was recommended. This strategy should be based on accurate surveillance of cases and qualitative documentation of outbreaks and their control, secure political support on the basis of high-quality results, and comprehensive cost-effectiveness studies. The recognition of the need for increased global attention towards HepA prevention is an important outcome of this meeting.

Keywords: Global hepatitis A meeting, hepatitis A, hepatitis A vaccination, infectious disease control, public health, surveillance.

MEETING OBJECTIVES AND TARGETED OUTCOME

On 30 November and 1 December 2007, the first global meeting on hepatitis A virus (HAV) infection as a vaccine-preventable disease was held in Miami, Florida, USA: a joint initiative of the United States Centers for Disease Control and Prevention (CDC), the Centre for the Evaluation of Vaccination – a World Health Organization (WHO) Collaborating Centre for Prevention and Control of Viral Hepatitis – at the University of Antwerp, the WHO and the Pan American Health Organization (PAHO). This international gathering offered a unique opportunity for public health representatives and officers, epidemiologists, virologists, hepatologists, viral hepatitis and infectious disease specialists, as well as travel medicine doctors to review diagnostic tools, surveillance, outbreak control and cost-effectiveness of hepatitis A (HepA) vaccination. Taken together, the presentations and discussions provide policy makers with evidence regarding the large and possibly increasing burden of disease associated with HAV and the need to consider broader implementation of HepA vaccination for individual countries particularly those with growing populations of persons susceptible to HAV infection.

The meeting brought together more than 200 experts from 46 countries to discuss the changing global HAV epidemiology reflecting the increasing numbers of persons at risk for severe clinical disease and mortality from HepA, the benefits of childhood and adult HepA vaccination strategies in preventing HAV infection and the data needed by

Abbreviations: ALF, Acute liver failure; CDC, Centers for Disease Control and Prevention; CLD, chronic liver disease; GAVI, Global Alliance for Vaccines and Immunization; HAV, hepatitis A virus; HepA, hepatitis A; HepB, hepatitis B; IDU, intravenous drug user; IG, immune globulin; LAC, Latin American and Caribbean nations; MoH, Ministry of Health; MSM, men having sex with men; NIP, national immunization plan; PAHO, Pan American Health Organization; WHO, World Health Organization.

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international health organizations and individual countries to assess current HepA prevention strategies, and consider new approaches including universal HepA vaccination.

This introduction provides a summary of the major findings and conclusions of the meeting and introduces 12 papers describing the changing epidemiology of HAV infections and the impact of HepA vaccination strategies in Argentina, Brazil, Italy, China, Russia, Ukraine, Spain, Belarus, Israel and Turkey. This issue contains detailed epidemiological and burden of disease information in the country papers and in the summary table of this introduction. However, there are indeed many elements of the meeting that are not covered in this supplement. Nevertheless we believe that the essence of the meeting is conveyed and that this supplement demonstrates the need to bring HepA prevention again to the attention of public health doctors. The abstract book and most of the presentations of the meeting are available at http://www.havmeeting.info.

HEPATITIS A VIRUS INFECTION

In 1973, HAV particles were first isolated from human stool samples and identified as the aetiological agent of HepA. New technologies supported subsequent seroepidemiological studies as well as patient studies and outbreak investigations to define the period of virus shedding, characterize the virus and understand the natural history of HepA.

Children infected with HAV tend to have mild or no clinical disease while older HAV-infected persons tend to have more severe disease and an increased HAV-associated mortality infection can cause fulminant hepatitis in developing countries [1].

Increased access to safe water and adequate sanitation, usually in urban but not rural areas, has decreased HAV infections among children resulting in growing populations of susceptible persons. As a consequence of this epidemiological shift, countries have reported an increased incidence of symptomatic and fulminant HepA with significant morbidity and mortality among susceptible children from urban populations [1–6]. In some developing countries circulation of HepA virus is enhanced due to the co-existence of populations with low and high socio-economic conditions.

In both industrialized and developing countries, broader use of HepA vaccine would have a major impact on future hospitalizations due to symptomatic and fulminant HepA. As presented at the meeting, for the USA [7], Israel [8] and Argentina, declines in the incidence of hospitalizations and clinic visits followed the adoption of routine children HepA vaccination programmes.

SURVEILLANCE

Disease-specific epidemiological data are needed to inform decisions regarding appropriate prevention and control measures, including the use of vaccines. Two types of epidemiological surveillance are needed: seroprevalence data characterizing the pattern of immunity or infection in the population and incidence data on acute disease providing an assessment of the burden of disease and allowing to identify individuals, groups and regions at increased risk of disease. Incidence data also provide better information for monitoring trends in transmission and risk factors for disease that, in turn, are critical not only in deciding on vaccination strategies but also in measuring their impact on disease reduction strategies (see Table 1).

The value of acute disease incidence data is highly dependent on its quality (completeness and validity) and requires consistent application of standardized case definitions, including both clinical evaluation and laboratory confirmation, and surveillance systems that ensure the systematic identification, investigation and reporting of cases. There are multiple approaches to how surveillance can be implemented and these can be tailored to the available resources and relevant epidemiological questions of a particular setting.

Worldwide, multiple seroprevalence studies show that due to improved water, sanitation and socio-economic conditions, many countries are experiencing a shift in HAV epidemiology: the overall force of infection has decreased, especially among young children, resulting in a higher HAV incidence among older age groups who are at risk of more severe disease following HAV infection, as well as increased heterogeneity within regions (urban *vs* rural) and within socio-economic classes. This shift towards lower endemicity among young children has also increased the potential for community-wide outbreaks as large cohorts of older children, adolescents and adults have become susceptible to circulating virus. [5,9]. These changes in HAV epidemiology reflect the need for updated vaccination strategies. In 2005, the WHO issued *Vaccine Introduction Guidelines*, outlining key issues to be considered prior to adding a vaccine into a national immunization programme [10]. In order to support the decision-making process regarding new vaccine recommendations, improved data on burden of disease are needed to document the shift in global HAV epidemiology and to estimate the economic impact of the disease. Reliable surveillance data on HAV morbidity and mortality at global, regional or country level should be made available in order to obtain representative global HAV disease burden data required to adequately place HAV disease as a public health item on the agenda of national authorities.

The first major comprehensive effort to estimate the global burden of disease in 1990 failed to address the significant burden resulting from HAV infections. The new *Global Burden of Diseases, Injuries, and Risk Factors Study* is led by a consortium including the Harvard Initiative for Global Health at Harvard University, the Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, the University of Queensland and the WHO. This new study will address HepA and other diseases

Table 1 Country and regional examples of HAV epidemiology and prevention strategies

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
South Africa (AFRO)	Burden underestimated due to lacking data Large differences between lower and upper socio-economic classes: exposure higher in Black, followed by Coloured (mixed race), Asian and White	**Intermediate** to **high** with pockets of **low** endemicity (where improved sanitary conditions) >90% anti-HAV+ among 5–10 years in lower class (mainly Black) Increasing seroprevalence with age in upper class (White, Asian)	Outbreaks almost every year in schools, day care centres and closed institutions with compromised hygiene	Targeted risk group vaccination recommended No short-term planning for universal national immunization, mainly due to competing health priorities, such as new childhood vaccines	NA	NA
Argentina (PAHO)	*Pre-vaccination*: **high** incidence: 139/100 000 in 2003 and 172/100 000 in 2004 (due to large outbreaks) Incidence highest among 5–9 year olds, followed by 2–4 year olds *Post-vaccination*: 28.3/100 000 in 2006 and 7.76/100 000 in 2007 (calculated up to week 39) High number of acute liver failure (ALF) cases among children: 87% < 10 years and the aetiology was HAV in 61% with a high mortality rate (25% of HAV ALF cases are fatal)	*Pre-vaccination*, (before 2005): **Intermediate** with areas of **high** endemicity 54% anti-HAV+ among 1–15 year olds for whole country and lower prevalence among young children and high socio-economic class	Large outbreaks in 2003 and 2004	Universal HepA vaccination introduced in mid-2005 with a **single dose** at 12 months of age (mandatory, free of charge) Evaluation of second dose ongoing, depending on new disease surveillance data	95% coverage in 2006, with regional variation from 60% to >90%	Substantial decrease in 2006–2007 incidence in all age groups and regions (83.7% reduction *vs* 2004) Most important impact is reduced number of fulminant hepatic failures due to HAV in children and no new large outbreaks (80% reduction in ambulant and hospitalized HAV cases)

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
Brazil (PAHO)	Lack of national incidence data; no pre-1994 data; data with underreporting 1994–1999 In 2000–2005: 7.5–11/100 000 Progressive decline in mortality rates over 1980–2002, suggesting decline in HAV circulation HAV is the most frequent cause of ALF, with high mortality rates (69%)	Shift from **high** to **intermediate** endemicity *North:* high exposure early in life *South-east:* decline in seroprevalence with several outbreaks and <5 year olds mostly unprotected MoH population-based seroprevalence study ongoing in four regions	1999–2004 outbreaks in public schools, orphanages and day care centres; increasing susceptibility with declining immunity among children, from 47–49% in 1999 to 16–17% in 2000 and 2004	No routine vaccination policy Prevention approach: plans for providing better standards of sanitary conditions at poorest regions	NA*	NA
Chile (PAHO)	In 1990s: ~30–60/100 000 Increasing incidence among adolescents/adults: 40% among 10–24 year olds in 2002 Low incidence after national 2002–2003 outbreak: 6/100 000 in 2006 4/100 000 in 2007	Shift from **high** (1980s) to **intermediate** (1990s) thanks to improved sanitation (e.g. cholera campaign) Reduction in seroprevalence	Increasing number of cyclic outbreaks Last nationwide outbreak in 2002–2003 (with national incidence rate of 70/100 000) Since then, persisting local outbreaks in poor villages	HepA vaccine available in private sector (mainly high socio-economic class) Prevention approach: improved sanitation + outbreak control	NA	NA
Mexico (PAHO)	NA	Shift from **high** to **intermediate** endemicity Increasing susceptibility: decreased seroprevalence in children <3 years from 1973 to 1987 In 2000: 97–99% anti-HAV + among >20 year olds Large cohort of pre-school children susceptible	NA	Decision on introduction of HepA vaccine based on cost–benefit analysis Competition with other, equally important childhood vaccines	NA	NA

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
United States (PAHO)	*Pre-vaccination* (before 1999): incidence >10/100 000 with peaks in 1971 (~30/100 000 and in 1989 (~15/100 000). Incidence highest among children 2–9 years old and in Western States *Post-vaccination:* in 2006, incidence 1.2/100 000	Overall **low** endemicity, pre-vaccination there were higher rates in Western regions. Anti-HAV+ in 1988–1994: 8.1% in 6–19 years; 30.7% in >20 years; and higher among children aged 6–19 years living in Western States (14.3%) compared with children living in other regions (~6%)	*Pre-vaccination* (before 1999): large outbreaks every 10–15 years	Incremental recommen dations: In 1996, targeted high-risk-groups. In 1999, children living in 17 high-incidence Western states. In 2006, all children nationwide, at 12–23 months of age	Modest coverage rates. In 2005 (for at least one dose): in 11 States with recommended vaccination: 13–71%; In six states with vaccination to be considered: 2–58%	Significant declines when comparing 1996–1997 to 2004: Hospitalizations: −69% Ambulatory visits: −42%. Over period 1990–2004: 32% reduction in HAV mortality rates. Considerable out-of-cohort effects among unvaccinated children and adults
India (SEARO)	In 1982–1998: almost 100% exposure of children in low socio-economic class In 1999–2004: increasing incidence among adolescents and adults, highest in 13–20 years followed by 21–30 years High rate of fulminant hepatic failure cases due to HAV, with high mortality rates	Shift from **high** to **inter mediate**, mainly in higher socio-economic class, co-existing with highly endemic low socio-economic class (even within the same city) In 2006: >90% anti-HAV + in rural adults Serosurvey to be started in 2008	Several large outbreaks across the country in 2002–2007 among children and/or adults	Formulation of national policy for the control of HAV is desirable, with optimal age for vaccination at 9 months	NA	NA
Thailand (SEARO)	MoH data during 2003–2006: 0.58–3.89/100 000 (but underreported) Incidence increasing with age (>15 year olds)	Shift from **high** to **inter-mediate** endemicity since mid-1980s thanks to improved sanitation In 2004 anti-HAV+: 5.4% in <10 years; 11.9% in 10–20 years; 35.8% in 20–30 years; 59.4% in 30–40 years; 70.6% in 40–50 years; 74.8% in 50–60 years 91.4% in >60 years Overall: 27.4%	Several outbreaks across the country over 2001–2005 among children, adolescents and adults	Cost–benefit analysis (2002) did not justify implementation of HepA vaccination programme at current HepA vaccine cost	NA	NA

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
Belarus (EURO)	Increasing national incidence (almost twofold) since 1999, with rates up to 95/100 000 in 2001, with more adult and more severe cases involved	**Intermediate** endemicity Anti-HAV+ in Minsk City in 2007: 10–17 years: 11% **18–24 years**: 22% (most susceptible age group) 25–29 years: 46% 30–39 years: 45% 40–45 years: 70% > 45 years: 85%	NA	Minsk City: 2003: universal vaccination of 6 year olds 2004: vaccination of adults and children for outbreak control 2005: risk group vaccination	Minsk City: 97–99% of 6 year olds	Minsk city: Decreasing incidence in all age groups (herd immunity) to <6/100 000 in 2005–2006
Israel (EURO)	Mean overall incidence in 1993–1998: 50.4/100 000 (Jews: 46.8/100 000 non-Jews: 65.1/100 000)	**Intermediate** endemicity until 1999	Average 10 outbreaks/year pre-vaccination No outbreaks reported 2 years after start of universal vaccination in day care centres and schools	Free of charge universal vaccination since 1999 for toddlers only (at 18 and 24 months of age) as part of the routine immunization program	~90% Dose 1 >85% Dose 2	Important incidence decrease in all age groups (herd immunity effect) to 2.3/100 000 in 2002 and 1.1/100 000 in 2006 (=98% reduction)
Italy (EURO)	Incidence data collection system SIEVA Incidence decrease from 4/100 000 in 1995 to 1.4/100 000 in 2006 Incidence highest in 15–24 year olds, followed by 0–14 year olds HAV most frequent cause of ALF: 54% (1991–2001) and 50% (2001–2006)	Shift to **low** endemicity Increasing susceptibility among young adults	Large outbreak in 1996–1997 in south Italy (shellfish consumption) and outbreak among IVDU in 2003	Targeted risk group vaccination + surveil – lance of shellfish retail Universal vaccination not considered for whole population (see also Puglia region)	NA	NA
Italy, Puglia (EURO)	Average incidence 25/100 000 in 1989–1995 Ranging between 4 and 138/100 000 with epidemics in 1992, 1994 and large epidemic in 1996 and 1997 (>5000 cases/year)	Shift from **intermediate** to **low** endemicity High population susceptibility sustains epidemics Medium age of infection 16 years in 1993, 20 years in 1998	Cyclic outbreaks, often starting with raw seafood consumption	Universal HepA vaccination started in 1998: toddlers at 15–18 months+ catch-up programme for adolescents at 12 years until 2002 to prevent future outbreaks	~60–70% among 12 year olds	Substantial decline in incidence in all age groups (herd immunity effect) to levels lower than rest of Italy: from 20 to 0.7/100 000 during 1998–2006

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
Russian Federation (EURO)	Decreasing incidence from 170–200/100 000 in 1990 to <50/100 000 in 2006 in all age groups, but most importantly among 0–6 years, resulting in highest incidence shifting to older age (11–29 years) The shift is mostly connected with the dramatic decline in HAV immunity	Shift from **high** to **intermediate** endemicity Important decrease in immunity during 1986–2005: from 62% to 30% among 20–29 years and from 88% to 70% among 40–49 years	Periodic large outbreaks 2000–2005	Increased susceptibility requires preventive measures, including extension of HepA vaccination	NA	NA
Spain, Catalonia (EURO)	Incidence (whole population Catalonia): *Pre-vaccination* 5.51/100 000 in 1992–1998 *Post-vaccination* 2.98/100 000 in 1999–2005	Shift from **intermediate** to **low**	NA	1995: risk group HepA vaccination 1998: universal pre-adolescent vaccination with combined HepA/HepB vaccine at 0, 1, 6 months	NA	Limited impact of HAV risk group vaccination Important incidence reduction after universal HepA/HepB vaccination: 73% in 10–19 years and >45% in 5–9 years (herd immunity)
The Netherlands (EURO)	Decreased incidence from 12 to 2/100 000 during last decade Import through travelling immigrants (Turkey, Morocco) + ongoing transmission among MSM	**Low** endemicity Anti-HAV+ <10% among individuals born after 1960 *vs* 77% for those born before 1945 Seroprevalence among children/adolescents originating from Morocco, Turkey (*vs* Dutch) is higher but the majority are susceptible	Limited number of outbreaks thanks to effective source contact tracing + ongoing pre-travel vaccination efforts	Favourable cost-effectiveness profile of vaccination but not included in NIP Organized, annual pre-travel vaccination sessions offered at low cost MSM vaccination with combined HepA/HepB vaccine (since 2000)	Pre-travel vaccination programme: uptake < 40%	Pre-travel vaccination: decreased import through immigrant travel Outbreaks limited

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
Turkey (EURO)	Progressive incidence decrease since 1995 No reliable national data, 2004 MoH data range 6.6–19.7/100 000 depending on region but underreported Incidence highest in age group 5–14 years and still high in >15 years Acute viral hepatitis caused by HAV in 27.5% adults *vs* 63.1% in children	Overall **intermediate** but high variability from **low** to **high** endemicity, depending on regions with different socio-economic conditions Seroprevalence increase at school age (5–9 years) with peak in late adolescence (20–24 years) By the age of 10 years, 50% are anti-HAV+ Overall seropositivity 71.3% (2002)	NA	HepA vaccine available but only in private sector HepA vaccine not included in NIP	NA	NA
Ukraine (EURO)	Decreasing incidence during 2001–2006: from ~145 to 40/100 000 in children <14 years and from ~65 to 20/100 000 in adults	Shift from **high** to **intermediate** endemicity Anti-HAV+ in 2007 (Kiev): 9% in <11 years; 16% in 11–17 years; 42% in 18–50 years; 82% in >50 years. High susceptibility in children and young adults Overall anti-HAV+: 32%	Several outbreaks in 2003–2007 effectively controlled by HepA vaccination	HepA vaccination of children planned to be included in NIP by 2011, with optimal age between 12 months and 3 years	NA	NA
Saudi Arabia (EMRO)	14/100 000 in 1992 9/100 000 in 2003	Shift from **high** to **intermediate** endemicity Anti-HAV+: *before 1990*: 50–92% among children 1–18 years *during 1990s:* 25–30% among children 1–15 years with higher prevalence in older children *in 2005:* 7.1% in <8 years; 14.5% in 8–11 years; 30.6% in 12–15 years; 52.0% in >16 years	Several outbreaks in various regions in 1997, 2002, 2003, 2004 with 63–114 cases/outbreak (control method: IG)	*Since 2000:* targeted risk group vaccination + childhood immunization schedule in private sector *Since Jan 2008:* universal HepA vaccination introduced into NIP (18 and 24 months)	NA	NA

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
Australia (WPRO)	*Pre-vaccination:* higher incidence among Indigenous Australians (2% of population): 1997: up to 75.2/100 000 1999–2002: 6.6/100 000 in Indigenous *vs* 3.1/100 000 in non-Indigenous populations *Post-vaccination:* 2003–2005: country average: 1.8/100 000	In 1998: overall prevalence 38.3%, higher with increasing age (~50% in age group >30 years) Increasing rates of susceptibility	Point-source and community-wide outbreaks in 1990s Large outbreak in 1997 (oyster consumption) Outbreaks among MSM, IVDU and in day care centres	Targeted risk group vaccination Vaccination programme for Indigenous children: Since 1999 in North Queensland (at 18 months and 2 years old) Since 2005 nationwide in high incidence states for children aged 12–24 months Economic analyses required for decision on universal vaccination	NA	Important reduction in incidence in Indigenous population (>95% in some regions)
China (WPRO)	*Pre-vaccination:* >50/100 000 in 1990–1992 Cyclic epidemics Highest incidence among 5–9 year olds *Post-vaccination:* 5/100 000 in 2005–2006	Shift from **high** to **intermediate** endemicity	Largest outbreak in Shanghai, 1988 (>310 000 cases) *Post-vaccination:* out breaks still reported in less developed regions with low vaccination coverage	Vaccination since 1992, mainly with live attenuated vaccine (inactivated vaccine available since 2002 but more expensive) Plan to include HepA vaccine in some regional routine immunization plan as of December 2007 (age 18 months)	High coverage in some cities and counties with high endemicity Low coverage in less developed regions Correlation between coverage and incidence among 1–15 year olds	Progressive incidence decrease Cyclic epidemics disappeared 90% decline in HAV risk for infection, but mainly correlated with improved socio-economic conditions

Table 1 *Continued*

Country (WHO region)	Incidence Burden of disease	Level of endemicity Age-specific seroprevalence	Outbreaks	HepA vaccination		
				Policy	Coverage	Impact
South Korea (WPRO)	Decreasing incidence since mid-1980s but increase after large outbreak in 1996 Incidence up to 9.8/100 000 in 2004 (among soldiers aged 19–27 years) Age group with highest incidence shifted from 10–20 to 20–39 years Prevalence of acute HepA is region dependent	Shift from **high** to **Intermediate** endemicity Anti-HAV+: In early 1980s: 85–90% in >10 year olds Mid 1990s: <20% in 0–20 year olds In 2006: 57% in 1–9 years; **11% in 10–19 years** (most susceptible age group); 16% in 20–29 years; 73% in 30–39 years; 96% in 40–49 years; 100% in >50 years		HepA vaccines available since 1997 Vaccination at >12 months + 6 months later (recommended by paediatricians but no universal vaccination) Plan to consider universal vaccination with catch-up programme for adolescents/adults, depending on the results of cost-effectiveness evaluation	~40% in 2006	NA

Data based on presentations from meeting session 5: *Country and regional studies of hepatitis A epidemiology* and session 9: *Country and regional examples of hepatitis A prevention*. The abstract book and most presentations are available on the scientific programme page of the meeting website (http://www.havmeeting.info).
*NA: data not presented.

and injuries, and produce comprehensive and comparable estimates of the burden of diseases, injuries and risk factors for two time periods, 1990 and 2005. By November 2010 the project will produce a final set of estimates.

In Europe, a feasibility study called EUROHEP.NET was funded by the European Commission to establish a common network of surveillance and prevention of vaccine-preventable hepatitis at the European level. Among the 24 participating European countries, the survey showed a wide diversity of surveillance systems in place to estimate HAV burden of disease, revealing the need for a standardized system of data collection at the enlarged European Union level, while respecting current practices in the different countries. This database has now been handed to the European Centre for Disease Prevention and Control that will set up a European viral hepatitis surveillance system in the near future.

HAV MOLECULAR EPIDEMIOLOGY

Excellent serological anti-HAV antibodies (IgM/IgG) diagnostic tests with high sensitivity and specificity are available worldwide, for use among persons with symptoms suggestive of hepatitis. However, such tests are not widely used in countries where HAV is endemic due to its elevated costs. Also, more sensitive serological assays are needed for the assessment of response to HepA vaccination due to lower levels of antibody following vaccination.

The development of molecular tools for the study of HAV epidemiology increased the knowledge of HAV transmission patterns and virus evolution, and helped identify the source of HAV outbreaks (e.g. 2004 outbreak due to orange juice consumption among travellers to Hurghada, Egypt). Such diagnostics have been used to assess the efficacy of universal HepA immunization. A study in Jerusalem, Israel, conducted between 1999 and 2004 demonstrated that genotype 1a HAV cases were practically extinct following immunization of toddlers while genotype 1b cases still occur, in other populations with different epidemiology of HAV transmission. HAV molecular surveillance in the USA conducted by CDC between 1996 and 2006 has shown a limited number of HAV strains to be responsible for most outbreak-associated cases and facilitated linking phylogenetic and epidemiological patterns.

Experience from several countries indicates that there is a need for data on circulating strains to be shared and that more attention should be drawn to the link between molecular diagnosis and clinical relevance.

HEPATITIS A VACCINES

Hepatitis A vaccines became available in the early 1990s. While it was demonstrated in animal models that attenuated strains were effective in providing protection, most manufacturers opted for the development of inactivated vaccines, avoiding the potential risk of reversion to virulence.

Four inactivated vaccines are currently widely available – in addition to other vaccines with more limited distribution – with well-documented data showing these vaccines to be safe and highly immunogenic, with rapid seroconversion [11–13], proven protective efficacy and demonstrated field effectiveness. The use of these HepA vaccines is interchangeable with flexible schedules and they can be co-administered or used in combinations. A full primary (i.e. two-dose) schedule confers long-lasting protection in terms of antibody persistence documented for at least 5 years in children and 12 years in adults [14–16]. In addition, indirect evidence exists that immune memory persists even after the loss of detectable anti-HAV levels [17]. In 2002, the International Consensus Group on HAV immunity concluded that booster vaccinations are unnecessary for healthy persons who complete primary vaccination course (two-dose schedule) [18]. However, further investigations are needed to decide whether boosters can be omitted in special patient groups [e.g. patients with chronic liver disease (CLD), chronic hepatitis B or hepatitis C infection, or human immunodeficiency virus]. Also, attention should be paid to a reduced humoral immune response due to the presence of maternal antibodies when vaccinating during the first year of life. In these situations it was seen from the robust anamnestic response to a booster dose even up to 6 years post-primary vaccination that priming and immune memory was adequate.

Furthermore, vaccine performance in terms of long-term protection and alternative schedules (e.g. one-dose, accelerated, etc.) should be further studied. Argentina has opted for a one-dose HepA vaccination schedule. A single dose of live attenuated vaccine has been shown to provide long-term antibody persistence and effectiveness. Although there are good indications of an excellent anamnestic response to a second dose even if delayed up to 5–8 years, the longer term duration of protection with one dose needs further investigation (ongoing in Argentina), especially when vaccinating young children and/or in conditions of low endemicity where no natural boosters occur [19–22]. The outcome of such studies will have important economic implications for Ministers of Health in developing countries and for the national capacity to sustain vaccine introduction financially.

Impact of paediatric hepatitis A vaccination

Hepatitis A childhood vaccination programmes have shown to be effective in several countries, including Argentina, Australia, Israel, Italy (Puglia), Spain (Catalonia), and United States, as confirmed by substantially reduced HAV incidence, outbreaks, mortality rates and hospitalizations (see Table 1). Furthermore, accumulating evidence indicates that routine vaccination programmes have also proved

successful in protecting non-vaccinated cohorts by inducing herd immunity [23].

Since 1996, HepA vaccination was recommended in the US for individuals belonging to groups at increased risk of HepA, including international travellers, men having sex with men (MSM) and intravenous drug users (IDU) and children living in communities with high rates of HepA. However, this initial approach did not substantially reduce national disease rates as most cases occurred among persons with no identified risk factor and outside high-rate communities. Based on epidemiological data available in the US at that time, a recommendation was made in 1999 to begin vaccinating at least children living in 17 western states with high rates of HepA that contributed the majority of cases to the national disease burden. In the years following this recommendation, national incidence of HepA declined with the greatest declines observed in the 17 western states. In 2005, HepA vaccine was licensed for use in children aged 12–23 months which allowed the integration of this vaccine with others in the routine childhood vaccination schedule. To further reduce the incidence of HepA, vaccine recommendations were expanded in 2006 to include all US children 12–23 months of age.

Targeted vaccination strategies for persons at increased risk of HAV infection

Adult risk group vaccination strategies are also implemented in Canada, Australia and some countries in Europe, mainly targeting MSM, IDU, travellers and CLD patients. However, cyclical outbreaks still occur in these risk populations, as shown from US data. These outbreaks are often of sustained duration (months to years) and contribute to large community outbreaks.

Recent data have shown that the overall risk ratio for HAV in travellers from industrialized to developing countries has decreased from 1:300 to 1:3000 in unimmunized travellers per month of stay [24]. However, the potential of common source outbreaks and subsequent person to person transmission in developing countries with shifting epidemiology continues to expose unprotected travellers to HAV. Cross-sectional surveys conducted at various airports have demonstrated that <50% of travellers to developing countries are protected against HAV despite the WHO recommendation for HepA vaccination for all travellers to areas with moderate to high risk of infection [25]. Hence, efforts to improve the vaccination of travellers to developing countries remain a priority.

Vaccination strategies need to take into account the increased risk in order to better protect groups at risk. Although HepA vaccination is effective, it is often underutilized and low vaccine coverage needs to be improved [26–28], e.g. by integrating HepA vaccination programmes in settings serving adults at risk [29] or using public health surveillance to detect risk populations and guide vaccine policy development.

For over 50 years, immune globulin (IG) has been the only option for outbreak control and post-exposure prophylaxis to limit spread in risk populations and general community. IG has been shown to be >85% efficacious in post-exposure prophylaxis. More recently, HepA vaccines have also been successfully used. A recent study in Almaty, Kazakhstan, compared the efficacy of HepA vaccine and IG in the prevention of symptomatic HepA, when given within 14 days of exposure to an HAV-infected household or day care contact. The study concluded that HepA vaccine had a high efficacy, which was similar to that of IG [30]. No data are available in individuals older than 40 years or those with underlying medical conditions. The choice of IG *vs* HepA vaccine for post-exposure prophylaxis has evolved with time and resulted in implementation of different policies in different countries.

ECONOMIC ASPECTS OF HEPATITIS A VACCINATION

Economic evaluation and modelling can assist vaccine policy decisions, taking into account the uncertainty associated with the input parameters, as well as the structure of the simulation model (with main distinction between static *vs* dynamic models) [31]. Depending on the country under investigation, studies have shown HepA risk-based vaccination strategies to be cost-effective if target populations are sufficiently exposed while results from many cost-effectiveness studies of routine vaccination strategies have tended to be inconclusive [32]. However, recently published analyses have shown more favourable results in industrialized countries [33,34] when marginal vaccination costs were low [e.g. through the use of the combined HepA/hepatitis B (HepB) vaccination]. This is illustrated in the example of Canada where the cost-effectiveness of HepA routine vaccination compared to continuing current risk-based strategy is expected to be poor, while universal vaccination of 9-year olds with a combined HepA/HepB vaccine might be more economically attractive [35].

Also, dynamic transmission modelling has shown routine vaccination of 1-year olds to be the best strategy to control HAV in the USA, with substantial herd protection after 10 years of vaccination [36] and >80% reduction in incidence. The parameters of such models could be adapted to other countries where HepA is endemic, in terms of their demographic, epidemiological and healthcare characteristics in order to inform local policy [31].

Introduction of new and underutilized vaccines remains a challenge, in terms of budgetary requirements and ensuring financial sustainability. PAHO provides support to Latin American and Caribbean nations (LAC) for the introduction of new vaccines through a number of initiatives. The ProVac initiative (http://www.paho.org/English/AD/FCH/IM/

provac.htm) consists of training and data collection to enable economic evidenced-based decision-making regarding introduction of new vaccines according to national health priorities. The work being done by Pro-Vac is in alignment with a 2006 Resolution of PAHO's Directing Council (a yearly PAHO meeting of all Ministers of Health of countries of the Americas). This policy forum requested PAHO to provide technical support to countries for developing evidence that would allow them to make informed decisions on the introduction of four priority vaccines: influenza, rotavirus, pneumococcal and human papillomavirus. HAV vaccine is not included on this list of priority vaccines [37].

So far, two LAC countries (Argentina and Panama) have included HepA vaccine in their universal childhood immunization programmes while Cuba, El Salvador and Mexico are planning to follow the example of Bermuda and introduce the vaccine in the public sector in the near future. To enhance the national capacity for evidence-based policy decisions, PAHO promotes strengthened disease surveillance and improved reporting systems. Given the importance of sustaining the introduction of new vaccines, PAHO is conducting reviews of existing vaccine legislation in LAC countries to assess the potential for increasing fiscal space and national immunization budgets to purchase new vaccines. In this context, PAHO's Revolving Fund is a critical regional mechanism to promote price reductions through bulk purchasing of vaccines pre-qualified by WHO, such as HepA.

Similarly, one of the strategic goals of the Global Alliance for Vaccines and Immunization (GAVI Alliance) is to accelerate uptake and use of new and underused vaccines, and to improve safety of vaccine supply [38]. Specific activities regarding new vaccine introduction include the Accelerated Development and Introduction Plans for Pneumococcal and Rotavirus, the Hib initiative, the Advanced Market Commitment as well as plans for overall vaccine investment strategy. However, HepA is not listed in the GAVI Alliance 'Vaccine investment strategy' for near-term or future consideration.

COUNTRY PRESENTATIONS: HAV EPIDEMIOLOGY AND PREVENTION STRATEGIES

A majority of countries present at the meeting, mainly from Latin America, Asia and Eastern Europe, described a HAV epidemiology shifting from high to intermediate endemicity with an increasing number of outbreaks and higher incidence in older ages, with more severe cases (see Table 1). Most countries reported lacking accurate national surveillance data and underlined the need for adapted national vaccination and prevention policies.

MEETING CONCLUSIONS

The meeting concluded with a round table discussion on lessons learnt from countries that planned or have already introduced routine HepA vaccination in their national immunization programme with a view to understanding the actions required to make HepA a globally supported priority.

The most relevant approaches to control the changing epidemiology of HAV infection were reviewed, focusing on the primary need for improved surveillance in order to produce accurate burden of disease data and document the increased number of susceptible persons due to a shift from high to intermediate endemicity in many countries. In this context, the use of simple and low cost surveillance methods, such as cross-sectional data, as well as reporting from wider sources including clinicians and hepatologists were encouraged, particularly in developing countries with limited infrastructure and resources.

HepA vaccination strategies should be implemented taking into account the level of endemicity, socio-economic development and sanitation, and the risk of outbreaks. Consensus was reached on the need for countries to adopt a stepwise strategy for the introduction of HepA universal immunization of children, as illustrated in the following model:

Conduct accurate surveillance of cases and document outbreaks with standardized case definition (jaundice, icterus, anti-HAV IgM antibodies)

↓

Document vaccine use to control outbreaks and secure political support on the basis of good results

↓

Conduct cost-effectiveness studies

Several critical factors supporting HepA vaccination were also identified, such as the importance of public perception and the need to raise disease awareness. The severity of HAV disease is underestimated: although it affects primarily children 2–14 years old, an important number of fulminant cases are observed, in particular in Latin American and Caribbean nations with intermediate endemicity and co-existing populations with high and low socio-economic conditions. Media and lobbying activities may be used to influence decision makers and present the vaccine as an investment.

The need to place HAV disease in the context of global health priorities was also emphasized, targeting elimination, but also taking into account the national context, i.e. using existing vaccination programmes to improve logistics and lower costs. Likewise, the conduct of cost-effectiveness analyses of a strategy including an early one-dose with a delayed second dose after 10 years to lower costs was encouraged, while urging PAHO and other international funds to support studies on the long-term effectiveness of one dose. This strategy was presented as the preferred alternative to vaccination of young adolescents, which leaves younger children at risk and infections.

In terms of vaccine supply, diversification was recommended in order to make the vaccine less expensive while purchase mechanisms, such as PAHO's Revolving Fund, may be used to lower the cost of vaccines.

Closing remarks reinforced the need to control HAV globally justified by the specific complications of the disease, as well as its changing epidemiology leading to visible clinical consequences. Hence the requirement for WHO-adapted guidelines to be made operational with the support of UNICEF, GAVI and other programmes in countries lacking appropriate expertise and infrastructure. The results of this meeting were seen as a first step towards the recognition of the need for increased investment in HepA vaccines.

The time has come for the international public health community to match HepA prevention strategies to the changing epidemiology. Thanks to the existence of safe and efficacious vaccines global control of HepA should be feasible.

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CONFLICT OF INTEREST

K. van Herck and P van Damme have been principal investigators of vaccine trials for several vaccine manufacturers, for which the University of Antwerp receives research grants; all other authors declare no conflict of interests.

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