

**Prevention and control of viral hepatitis in Latin America and Brazil:
lessons learnt and the way forward**

BRASÍLIA, BRAZIL

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The Brazilian Ministry of Health in conjunction with the Viral Hepatitis Prevention Board (VHPB), PAHO and the Brazilian Association of Hepatology organized a meeting on the prevention and control of viral hepatitis in Latin America (LA) and Brazil in Brasília on 19-21 March 2014, attended by more than 110 participants. Its objectives were: to review the epidemiological situation in Latin America generally and the epidemiology, disease burden, prevention and control measures in Brazil in particular: to discuss progress in prevention, control and treatment; to identify specific issues in Latin America that need further attention; and to present an assessment of the work of VHPB and discuss its possible role as a model approach for the region.

The context of the meeting was that, despite considerable progress (especially the introduction of routine universal childhood vaccination against hepatitis B, the successful use of single-dose vaccination against hepatitis A in a few countries and a secure blood supply), the burden of disease and death in the region due to viral hepatitis remains heavy, posing a public health challenge.¹ Morbidity and mortality due to viral hepatitis infections (especially hepatitis B and C) and their consequences are forecast to rise over medium term.

Globally, prevention and control responses appear to be fragmented and incomplete. Knowledge and awareness of viral hepatitis across all sectors of society remain poor, and the visibility of viral hepatitis in governments' priorities, and thus programmes and budgets, is generally low. Indeed, few governments have a plan to tackle viral hepatitis, although in Latin America Argentina, Brazil and Peru do. A recent global survey revealed that only 33 governments self-reported having a written strategy for viral hepatitis that included components for prevention, treatment and care, 5 out of 18 responding Latin American countries have a written strategy, but only Argentina has a plan that focuses exclusively on viral hepatitis.² Most people infected with hepatitis viruses are undiagnosed, implying a large volume of cases of undetected chronic disease. Policies for clinical management of those

whose infections have been diagnosed are lacking. Moreover, patients' perspectives are frequently neglected.

Recent events mark a turning point. Worldwide, health systems are moving towards universal health coverage with equity of access to care. Efforts are being made to include viral hepatitis as an indicator in the putative post-2015 sustainable development goal related to health being discussed by the United Nations. A trend has begun towards coalescing programmes and integrating viral hepatitis into HIV/AIDS programmes, as has occurred in Argentina, Brazil and Peru. This move has resulted partly in response to growing unease at the disparate institutional and governmental responses to disease burdens that match or outweigh those in the well-funded AIDS, tuberculosis and malaria sectors. The move raises expectations of synergies between programmes and an increased availability of resources for viral hepatitis (although concerns were raised that it would be subsumed and lost in HIV/AIDS programmes). Partnerships with civil society are strengthening and growing. Also, in November 2013, two new direct-acting antiviral agents for hepatitis C were licensed, heralding the prospect of effective new oral, interferon-free treatments - but at unaffordable prices, a scenario that is reminiscent of what happened with HIV/AIDS 20 years ago.

Brazil, which aspires to international and regional leadership, has played an important role in raising awareness of viral hepatitis at the intergovernmental level, in particular through sponsoring draft resolutions for consideration by the governing bodies of the World Health Organization (WHO). In 2010 it sponsored with Colombia a resolution on viral hepatitis adopted by the World Health Assembly (resolution WHA63.18) that designated a World Hepatitis Day, and in January 2014 WHO's Executive Board decided to recommend to the World Health Assembly in May 2014 the adoption of another Brazilian-sponsored resolution on viral hepatitis. In 2012 WHO established its Global Hepatitis Programme (which was recently incorporated into the HIV/AIDS department) and published its framework for global action on prevention and control of viral hepatitis.³ In June 2013 the Pan American Health Organization (PAHO) established a new unit that includes HIV, sexually transmitted infections, tuberculosis and viral hepatitis in order to create synergy. WHO's focus of viral hepatitis will continue with meetings of global partners and the newly established Strategic and Technical Advisory Committee later in March 2014.

The discussions underscored the heterogeneity between and within countries in Latin America and the Caribbean – the enormous differences in size and geography, the social disparities and inequalities in access to health care, the diversity of cultures, ethnicities, policies and strategies, epidemiology and disease burden, and the varied role of civil society and patients' organizations. These contrasts underlined the need for cooperation between countries, sharing of experiences, and optimal use of resources.

VHPB

As an independent forum and neutral provider of broad range of multidisciplinary expertise, VHPB has the convening power to bring together interested parties and disparate groups for frank and open discussions. It has organized more than 40 meetings in different countries and regions, and some 600 presentations (including those of the present meeting) are accessible through the VHPB's website.* The meetings consider European, national and technical aspects of prevention and control of viral hepatitis.

Country meetings catalyse communication, interaction and networking. They are conducive to influencing policy and legislation, and facilitate the sharing of best practices. They provide a trigger for high-level advocacy, assist with prioritization and aid generation of political commitment. Experiences reported by three countries (Bulgaria, Israel and Portugal) demonstrated the impact of VHPB, including recognition of successes and failures as well as the shaping of policy and legislation.

Technical meetings have resolved topical questions (such as whether booster doses of hepatitis B vaccine are needed) and provided recommendations for action at national, regional and global levels. The Board drafts guidelines and issues consensus statements.

Given that there have been great achievements in Latin America but activities are not necessarily coordinated nationally or regionally and that Europe's mosaic of epidemics, policies and diversity of countries is mirrored in the region, the question was raised as to whether there was a role for a VHPB-like group in Latin America.

* <http://www.vhpb.org/>

EPIDEMIOLOGY OF VIRAL HEPATITIS IN LATIN AMERICA

Liver disease is the third cause of mortality in the Americas but overall the disease burden due to viral hepatitis is not accurately known in Latin America and the Caribbean. The prevalence rates are generally intermediate, but high rates are seen in various areas and subpopulations. Few national studies in the general population have been conducted. Despite numerous small epidemiological studies in selected populations and some ongoing mathematical modelling of the impact of prevention and control, the paucity of data and their limited reliability and coherence constrain comparisons, with the result that data for policy are derived often from literature reviews.

According to the latest data from PAHO, for the period 2008-2010, 10% of all deaths in the region attributable to liver disease were due to causes related to viral hepatitis. In a third of those deaths the cause was hepatocellular carcinoma (HCC, globally the second most common cause of cancer mortality and described as a “real problem” for Latin America). The epidemiological, clinical and societal burden of HCC is recognized and acknowledged to be likely to increase in the short- to medium-term. The incidence rate of HCC in Brazil is put at 5/100,000 population but that is certainly an underestimate.

Lack of, and delays in, diagnosis and treatment of viral hepatitis mean that many patients present in the late stages of disease. A study in 9 countries of LA showed that hepatitis C is the most frequent etiology of HCC (38%) in the region, with an important proportion of patients being diagnosed at their sixties⁴ (Fassio et al, 2010).

Screening policies vary from compulsory for specific groups in 7 countries to being available free for all individuals in 12 countries. Only some 40% of countries report having policies for surveillance of chronic hepatitis B and C. Although people who test positive should be referred to health services, less than half the countries in Latin America and the Caribbean have a referral policy.

Hepatitis A. Generally intermediate rates of endemicity are reported. More than 50% of individuals are (naturally) immunized by the age of 15, with rates up to 96% in the Andean region. In Argentina the disease had been highly endemic until the introduction of universal single-dose vaccination of people at risk in 2005, since when cases and reported incidence rates have dropped

dramatically to practically zero ⁵(Vizzotti et al, 2014). Panama and Uruguay have also adopted that vaccination policy.

Overall, improved sanitation is reducing prevalence. As a consequence of that and vaccination, the epidemiological patterns are changing with the pool of susceptible people increasing and cases shifting from children to young adults, increasing the danger of more severe disease and the likelihood of outbreaks.

Hepatitis E: Few data exist, but it is certainly present in Latin America and causes some morbidity and mortality. Different routes of transmission (oro-fecal and zoonotic) have been identified for different genotypes. A vaccine developed in China has been licensed.

Hepatitis B. Overall, low or low/intermediate prevalence rates (for instance 2.2% carriage rate for HBsAg in Peru, where hepatitis B is included in the national health strategy) are reported in the region but wide variations are seen in different groups and populations. Some 11 million people may be infected with hepatitis B virus. Superinfection with hepatitis D virus is a problem in parts of Brazil (see below) and Colombia.

All countries have introduced routine childhood vaccination against hepatitis B. Few data on coverage rates and serological monitoring were presented, but those for Peru indicated that difficulties were being seen in practice in reaching the target rate of 95% coverage; only in one year in the period 2000-2013 had that figure been attained.

Genotype F is the most frequent in Amazonian part of Brazil (and in a study reported from Buenos Aires, Argentina⁶); elsewhere other genotypes, mainly A and D, are circulating.

Co-infection with HIV is a serious problem; it causes more rapid disease progression and poorer outcomes. At least 5% of HIV-infected subjects are infected with hepatitis B virus and a further 1% infected with hepatitis D virus as well. Many of those infected with hepatitis B virus were not vaccinated against hepatitis B.

Hepatitis C: Some 8 million people are thought to be infected in the region, with 4 million in Brazil and Mexico together⁷ (Szabo, et al., 2012). Data for Central America and the Caribbean were described as scarce, inadequate and not published or easily accessible. HCV and to a lesser extent HBV are the major causes of HCC and result in the need for liver transplants, and the

limited data available indicate a varied but heavy burden. Even if prevalence rates stay constant in most countries, without active disease management, hepatitis C could put considerable pressure on health systems in the future.

The rates of co-infection in HIV-infected people (for both HBV and HCV) are probably higher than the official figures portray, and such patients were described as a “priority for treatment”.

Health-care related infections (with both hepatitis B and C viruses) still occur.

THE CASE OF BRAZIL

- Health System

Brazil’s federal constitution of 1988, which established the unified public health system, guarantees health as a right of every citizen and a duty of the State through provision of health services with universal access to health care. Subsequent laws and decrees have covered health promotion, the regional organization of health services, a strategy to strengthen links between the administrative layers of the State for the implementation of health policies, the participative management of the health system by the community, and citizens’ rights. The health system is decentralized, with complex links between the federal, state and municipal levels and primary health care at its base. A unique feature is public participation (social control), institutionalized as health councils and conferences, and the encouragement of dialogue between directors of health services and systems on the one hand and parliamentarians, members of the judiciary and civil society on the other.

The health ministry invests through a public institution, the Butantan Institute, for the development and production of vaccines (hepatitis B – the entire domestic production - and, imminently, hepatitis A vaccine). Considerable improvements in health have been recorded in recent years, with the national immunization programme one of the major successes. Vaccination is free with policy, procurement and payment resting with the Ministry of Health but responsibility for administration of vaccine devolved to municipalities.

Areas in which challenges remain include financing, human resources, targeting universal health care (some 80% of the population depends on the public health system, the rest using private medicine), managing the mix of public and private health care, national networks for surveillance, and inequalities in health care (for instance, between population groups and regions, with fragmentation of care in both cities and less developed areas of

the country). The health ministry recognizes many of the challenges and is said to be responding accordingly.

- **burden of disease**

The prevention and control of viral hepatitis are seen as highly cost-effective measures. As part of the response, a law in 2003 provided for universal access to treatment for hepatitis B and C. The estimated number of hepatitis C patients treated in Brazil increased from 1.200 in 2006 to more than 12.000 in 2012, and about 14.000 hepatitis B patients were treated that year. Since 2004-2005 the network of more than 250 HIV testing centres has been used to expand diagnosis of viral hepatitis, and in 2009 the national programme on viral hepatitis (launched in 2002) was integrated into the health ministry's Department of STDs and AIDS. High rates of infection are seen in vulnerable groups such as prisoners and people who inject drugs. Concern was expressed that purchase and delivery of medicines for HIV/AIDS were reportedly more rapid than for viral hepatitis. Civil society is active but faces many obstacles in trying to influence policy. The country is seeing a growing use of the internet for information about viral hepatitis and of telemedicine.

As in other countries in the region, liver disease poses a heavy and rising burden in Brazil. The country boasts one of the highest rates of liver transplantation in the world, and the service is almost exclusively provided by the state health system. Waiting lists are long, and more than half of the 62 city-based transplant teams are located in the south-east of the country. In the period 2001-2010, one study showed that viral hepatitis and its consequences accounted for about 10% of admissions to hospital for liver disease and at least 8% of deaths therefrom, and the main causes (1999-2009) were hepatitis A (40%), hepatitis B (35%) and hepatitis C (24%) ⁸(Nader LA et al, 2014)

In the Amazonian region ("Legal Amazon"), which accounts for 60% of the territory of Brazil but only about 10% of the population, viral hepatitis shows particular characteristics, for instance in terms of ethnic factors, intrafamilial transmission, dental treatment as a risk factor for infection, clinical presentation, and difficulties for logistics, immunization, treatment and access to care. More work is needed on hepatitis B, C and D and viral genotypes in the region – the D genotype 3 found there is unique.

Hepatitis A. Variations in epidemiology are seen between the various regions of the country, as well as a changing pattern with decreasing prevalence and increasing susceptibility (especially in children of low socioeconomic status). Outbreaks still occur. The Ministry of Health is reviewing Argentina's experience of single-dose vaccination.

Data on hepatitis E in Brazil are scarce but indicate that the virus is present although at a low level. Seroprevalence studies (IgG anti HEV) in healthy populations report prevalence rates between 0 to 7.5%, depending on the region and the study population. From 1999 to 2011, 967 cases of hepatitis E were reported in the country, representing less than 1% of notified viral hepatitis cases.

The prevalence of **hepatitis B** is generally low but high prevalence rates of HBsAg of more than 5% have been detected in some locations. High rates are particularly reported for the Amazon region, where superinfection with **hepatitis D** virus is a major problem; reported rates of infection with hepatitis D virus range from 0% to 60% of HBsAg carriers in western Amazonia.

An estimated three million people are infected with **hepatitis C virus** (70% genotype 1) but the prevalence in western Amazonia is three times higher than in the rest of the country. Whereas previously people who inject drugs were at high risk for infection with hepatitis C virus, that practice has declined and now proportionately more people who use crack are being infected. Both hepatitis C and to a lesser extent B viruses co-infect people infected with HIV. A meta-analysis indicates that about 20% of people with HIV/AIDS were infected with hepatitis C virus (although figures ranged from 3% in serum samples to 82% in injecting drug users)⁹. Given that many infected people are unaware of their hepatitis C status (one report estimated that in 2007 only 10% were diagnosed and only 0.8% treated), a media campaign has been proposed to encourage 35-year olds to ask their doctors to test them for infection.

SOME BARRIERS IN LATIN AMERICA

A major obstacle to preventing and controlling viral hepatitis in Latin America and the Caribbean continues to be poor access to diagnosis and treatment. In part that is due to costs (of both antiviral treatment and case management) and the scarcity of human resources. Furthermore, hepatologists, health care workers and even referral centres are unevenly distributed across countries in the region and within countries. Health ministries and other stakeholders are

working on equitable mechanisms for the purchase and distribution of antivirals at best prices.¹⁰ Nevertheless, at the moment the recently licensed directly acting antiviral agents against hepatitis C are unaffordable to the overwhelming majority of patients at US\$ 84,000 for a course of treatment; even access to the standard treatment with pegylated interferon and ribavirin is limited because of its cost (up to US\$ 30,000).

The good-quality up-to-date surveillance data, including molecular biological information on the viruses, that are needed for evidence-based decisions are lacking. Under-reporting of all viral hepatitis is probably considerable.

Few countries have written national prevention and control strategies or clinical management guidelines. Low prioritization and lack of vision about viral hepatitis at governmental level leads to inadequate budgeting and funding, often aggravated or coupled with limited awareness and knowledge of the public and in the media can result in a range of consequences from stigmatization to lack of incentive to be diagnosed. A recent editorial identified the need for a global plan for hepatitis C as imperative, noting that countries were only likely to develop national plans when treatments became more affordable.¹¹

In the absence of fully implemented national plans, services and programmes are often fragmented and uncoordinated. While merging of viral hepatitis into the well-established programmatic platform of HIV programmes could offer significant advantages for expanding the response to viral hepatitis, but there are also concerns that viral hepatitis will lose its already-low visibility.

SOME LESSONS LEARNT

While it is encouraging to note the steps undertaken in Argentina Peru and Brazil, most countries are not yet moving as decisively as the situation may request. The cost of inaction can be high and needs to be reflected in all plans and strategies for the prevention and control of viral hepatitis. National plans are necessary, but they need to be implemented and backed with appropriate budgetary allocations and authority. The recent global survey of policies and responses provided valuable insights and a spur to action (not all countries in the region responded).

Regional networking is in its infancy, but a start has been made. The Latin American Liver Research, Education and Awareness Network (LALREAN) currently links 15 academic centres in 10 countries. Its first initiative was to

create an electronic patient management system to help to standardize epidemiological data, costs and treatment outcomes for hepatitis C. Existing networks for HIV/AIDS provide a foundation on which to build. Indeed, in several areas opportunities were evident to learn from the experiences of HIV/AIDS programmes and policies.

Different communities need different approaches; one size does not fit all. Cultural diversity indicates the need for sensitivity in outreach, whether to indigenous people, vulnerable groups or people with risk behaviours.

Good-quality surveillance and laboratory data are essential, but concerns were expressed about the reliability and quality of serological and molecular biological tests in some remote centres. Blood screening data are neither representative nor an indicator of prevention programme performance. Monitoring the status and real-life performance of programmes (for example through vaccine coverage rates attained) is essential.

The valuable contributions of speakers from Argentina, the Caribbean, Mexico and Peru indicated the usefulness of continuing to sharing policy development and implementation practices. Progress has been made in the region, but overall work is just at an early stage and the meeting touched on many of the challenges to be faced.

POSSIBLE WAYS FORWARD

Comprehensive plans are needed for prevention and control of viral hepatitis at national and regional levels. These plans must be based on solid epidemiological principles, including robust surveillance of acute and chronic disease and vaccination coverage rates and on solid data so as to enable the setting of priorities and rational resource allocation. Plans need to recognize subcomponents of viral hepatitis programmes (including blood screening, preventive medicine, and prevention, access to screening, diagnosis and treatment). Furthermore, plans need to be harmonized at national (and where appropriate international) level and include performance indicators and targets.

In the rest of the region outside Brazil, prevention policies and activities (from improved sanitation to blood safety and safe injection campaigns) as well as monitoring need further development, reinforcement or better structuring. Cost-benefit analyses are essential for policy-making but often the results need interpretation for policy-makers. In Brazil and other countries as appropriate,

multidisciplinary meetings at regional, state and municipal levels should be held to discuss plans to implement and prioritize public health policies, including cross-border issues. Access to treatment represents a topic of great urgency and complexity that would require further attention and discussion.

For those and other issues including prices of medicines, vaccines and diagnostic tools, intercountry collaboration and networking should be stepped up. With the prospect of increasing access to care, policies need to be formulated on screening and treatment as well as funding; concerns were raised by both medical specialists and patients' groups. There exists an impressive array of treatments in some locations in the region, but questions included how therapy will be monitored, how to expand access to treatment, and who pays? Regional mechanisms for improving access to medicines and diagnostics for viral hepatitis similar to PAHO Strategic Fund, a mechanism based on the success of the Revolving Fund for Vaccines, currently including priority disease control commodities or a body such as the GAVI Alliance, both with successful experiences in vaccine procurement, should be considered. Another proposal was for countries to compare the prices they paid for antivirals and diagnostic tools and to pool their tendering. The current price of newly licensed antiviral medicines is unaffordable in the region and patient advocacy groups will need to keep the profile of viral hepatitis high and to fight for realistic prices.

The proposal for the creation in Latin America of a neutral advisory body on viral hepatitis that is independent of health ministries and pharmaceutical industry needs to be evaluated and followed up as appropriate. The publication of WHO Guidelines for the diagnosis and management of persons with hepatitis C infection expected in April 2014 and other normative guidance on Hepatitis B as well as on screening and surveillance for later this year are all expected to increase the urgency of such development.

To try to ensure the international comparability of data, harmonized coherent indicators and monitoring tools need to be adopted and applied. It would be useful to have more information on, for example: surveillance since 2009; the breakdown of the proportion of transmission by different routes; programmes for prevention among pregnant women, people who inject drugs, sex workers, refugees, migrants, and health care workers (including safe injection); and the organization of vaccination programmes and coverage for different target

groups - all vital elements of a coherent comprehensive plan. No evidence was presented of any implementation strategy for a national plan for prevention and control.

Calls were made for further medical education, more networking, more human resources including hepatologists, more equitable distribution of health workers (e.g. in remote areas) and a greater number of referral centres (especially away from cities). WHO was urged to appoint a focal point for viral hepatitis in all its six regional offices.

At the public health level, the outstanding questions were how to set priorities, what is needed to guide public health interventions, what are the best strategies to increase access to care, and how can any action plan be monitored? What is evident is that the greater the investment in primary prevention, the more treatment of chronic viral hepatitis will be feasible and affordable.

¹ Diez-Padriza N, Castellanos LG, PAHO Viral Hepatitis Working Group. Viral hepatitis in Latin America and the Caribbean: a public health challenge. *Revista Panamericana de Salud Pública/Pan American Journal of Public Health*, 2013, 34(4):275-281
(http://www.paho.org/journal/index.php?option=com_docman&task=doc_view&gid=648&Itemid=&lang=en, accessed 27 March 2014).

² World Health Organization. Global policy report on the prevention and control of viral hepatitis in WHO Member States. Geneva: World Health Organization, 2013
(http://apps.who.int/iris/bitstream/10665/85397/1/9789241564632_eng.pdf?ua=1, accessed 25 March 2014).

³ World Health Organization. Prevention and control of viral hepatitis infection: framework for global action. Geneva: World Health Organization, 2012 (document WHO/HSE/PED/HKP/GHP 2012.1)
(http://www.who.int/csr/disease/hepatitis/GHP_framework.pdf, accessed 25 March 2014).

⁴ Fassio E, Díaz S, Santa C, Reig ME, Martínez Artola Y, Alves de Mattos A et al. Etiology of hepatocellular carcinoma in Latin America: a prospective, multicenter, international study. *Ann Hepatol*. 2010 Jan-Mar;9(1):63-9.

⁵ Vizzotti C, González J, Gentile A, Rearte A, Ramonet M, Cañero-Velasco MC, Pérez Carrega ME, Urueña A, Diosque M. Impact of the single-dose immunization strategy against hepatitis A in Argentina. *Pediatr Infect Dis J*. 2014 Jan;33(1):84-8

⁶ Pezzano SC, Torres C, Fainboim HA. Hepatitis B virus in Buenos Aires, Argentina: genotypes, virological characteristics and clinical outcomes. *Clin. Microbiol. Infect*. 2011;17(2):223-31.

⁷ Szabo SM, Bibby M, Yuan Y, Donato BM, Jiménez-Mendez R, Castañeda-Hernández G, Rodríguez-Torres M, Levy AR. The epidemiologic burden of hepatitis C virus infection in Latin America. *Ann Hepatol*. 2012 Sep-Oct;11(5):623-35.

⁸ Nader LA, de Mattos AA, Bastos GA. Burden of liver disease in Brazil. *Liver Int*. 2014 Jan 15. doi: 10.1111/liv.12470

⁹ Kuehlkam VM, Schuelter-Trevisol F. Prevalence of human immunodeficiency virus/hepatitis C virus co-infection in Brazil and associated factors: a review. *Brazilian Journal of Infectious Diseases*, 2013, 17(4): doi.org/10.1016/j.bjid.2012.10.023 (http://www.scielo.br/scielo.php?pid=S1413-86702013000400012&script=sci_arttext, accessed 26 March 2014).

¹⁰ *The Lancet* recently published a call for UNITAID to include treatment of hepatitis C in its new strategy: see Von Schoen-Angerer T, Cohn J, Swan T, Piot P. UNITAID can address HCV/HIV co-infection. *The Lancet*, 2013, 381:628, doi:10.1016/S0140-6736(13)60346-3 ([http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60346-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60346-3/fulltext), accessed 26 March 2014.)

¹¹ Only just the beginning of the end of hepatitis C. Editorial. *The Lancet*, 2014, 383:281, doi:10.1016/S0140-6736(14)60087-8 ([http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(14\)60087-8/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60087-8/fulltext), accessed 26 March 2014).