South African National Advisory Group on Immunization (NAGI)

Hepatitis B birth dose

November 2018 meeting

Summary

The National Advisory Group on Immunization (NAGI) is an academic advisory body appointed by the Minister of Health to advise on issues related to vaccines and immunizations. In 2018 NAGI was asked to consider whether South Africa should implement a birth dose of hepatitis B vaccine. The World Health Organization recommends a birth dose hepatitis B vaccine for all countries [1, 2]. The guidelines do not distinguish between countries where horizontal transmission (acquisition during childhood) was the major route of transmission and countries with predominantly vertical transmission (from mother-to-child during pregnancy or post-partum.

South Africa introduced hepatitis B vaccine into its routine Expanded Programme on Immunization (EPI) in 1995. The vaccine is administered at 6, 10 and 14 weeks of age. A booster dose at 18 months was introduced in 2015 as part of a hexavalent preparation. South Africa has not introduced a birth dose of hepatitis B vaccine. Available evidence suggests good impact of the current EPI schedule, with large gains made towards elimination of hepatitis B. Although there is no national active surveillance for hepatitis B, evidence reviewed below suggests that prevalence of hepatitis B surface antigen positivity in children has decreased substantially over 23 years since the hepatitis B vaccine was introduced into the EPI programme.

NAGI has particularly considered South African evidence related to vertical transmission of hepatitis B. Vertical transmissions have been reported, however NAGI is of the opinion that introduction of a birth dose of hepatitis B vaccine would not hasten time to national hepatitis B elimination as vertical transmission is not the major mode of hepatitis B transmission in the country. NAGI is of the opinion that local epidemiology should be used by South Africa to tailor its own vaccination schedule rather than following blanket recommendations for all countries.

Rationale

Hepatitis B virus (HBV) is the most common viral infection of the liver. Infection can be acute with mild symptoms or severe with life-threatening liver failure. Some patients go on to develop chronic disease with complications such as liver cirrhosis and hepatocellular carcinoma. Hepatitis B can be transmitted through blood and body fluids. Major routes of transmission are through unprotected sexual intercourse or sharing of needles amongst intravenous drug users. Horizontal transmission in childhood is also common, most likely via exposure to saliva or other postulated mechanisms [3-8]. Vertical transmission may occur from infected mothers to their unborn children at the time of delivery or post-partum.

Prior to vaccine introduction, South Africa was considered a country of high hepatitis B endemicity (>8% prevalence of Hepatitis B surface antigen). Hepatitis B surface antigen (HBsAg) is used as a marker of hepatitis B infection and Hepatitis B e antigen (HBeAg) as a marker of active viral replication. Before introduction of hepatitis B vaccine in South Africa in 1995, rates of 5-16% for

HBsAg were seen in rural black men, with lower rates in females, urban populations and other races [4, 9-11]. In the late 1980s, HBsAg prevalence of 18.5% in rural and 10% in urban black children were reported, with rates of 2.5% in urban children under 6 years [5]. Geographic heterogeneity was apparent with prevalence of 1% in urban children 1-19 years of age in Soweto, Gauteng province [12] but 10% in children less than 6 years old Eastern Cape in the 1990's [13].

The World Health Organisation recommends that children born to Hepatitis B infected mothers receive a birth dose of hepatitis B vaccine and hepatitis B immune globulin within 24 hours of birth. Many mothers however do not know they are asymptomatic carriers of hepatitis B and therefore their children are not identified as being at risk. There has been global and national advocacy to introduce a birth dose[14].

Recommendations

As a general principle, global guidelines should recommend tailoring of immunization schedules according to local epidemiology where evidence is available. Birth dose vaccination is not a one-size-fits-all solution and may not be the most appropriate intervention for countries with low rates of mother-to-child hepatitis B transmission.

Within the next 10 years, most women in South Africa of child-bearing age would themselves have been eligible to receive vaccine in childhood per the South African schedule introduced in 1995. The opinion of NAGI is that sharp reductions in maternal hepatitis B prevalence can be anticipated within the next 5-10 years, using the current immunization schedule. NAGI does not believe that the current schedule requires adjustments targeted specifically at vertical transmission. Vertical transmission was not a major mode of hepatitis B transmission in the country even before 1995, and evidence suggests that even with high South African HIV prevalence, rates of vertical hepatitis B transmission remain low.

Research Evidence

A summary of original South African research articles related to hepatitis B since vaccine introduction is included in Table 1 (adults) and Table 2 (children). We focused on hepatitis B serology in order to standardize comparison between studies. Occult hepatitis B infection (presence of Hepatitis B DNA without serological markers of hepatitis B) is described in the literature will not be discussed further in this document. We will discuss surface antigen (HBsAg) as a marker of hepatitis B infection and e antigen (HBeAg) as a marker of active viral replication that increases the risk of hepatitis B transmission.

Much of the South African literature has focused on HIV infected populations, as HIV and hepatitis B share common modes of transmission in adolescence and adulthood, including sexual exposure. In 2012, HIV prevalence in South Africa was estimated at 12% overall, with prevalence of 2.4% in children 2-14 years [15]. Studies in adults from HIV clinics have found HBsAg positivity ranged from 0.4-9.4% [16-25]. Studies using residual laboratory sera have reported higher figures of up to 22.9%[26-28] (Table 1).

In pregnant women, hepatitis B prevalence ranged from 0.4% to 5.8% in HIV-uninfected women and from 2.1% to 7.4% in HIV-infected women [29-33]. HBeAg was positive in 0% to 37.5% of HBsAg-positive HIV-uninfected women (equating to HBeAg positive in up to 0.5% of overall cohorts) and in

18.9% to 47% of HBsAg-positive HIV-infected women (equating to HBeAg positive in up to 3.2% of overall cohorts).

Two studies have directly investigated vertical hepatitis B transmission rates in South Africa. Hoffmann *et al* enrolled HIV-infected mothers and followed up their infants for one year [33]. 63% of the women had received antiviral therapy that included Tenofovir. Among the pregnant women, HBsAg positivity was 7% and HBeAg positivity was 43% in those who were HBsAg positive (3.2% HBe positive of overall cohort). Of the children, one child acquired hepatitis B, equating to 7% of children born to HBsAg positive mothers or 0.5% of babies in the overall cohort. The transmitting mother had received Lamivudine but not Tenofovir. Chotun *et al* tested residual samples from 1000 infants born to HIV infected mothers. Mothers had not received Tenofovir nor Lamivudine antiretroviral therapy during pregnancy. Three infants were HBsAg positive (0.3%), but only 2 had persistently positive HBsAg results on follow up, bringing prevalence to 0.2% of this cohort born to HIV-infected mothers not on antiretroviral therapy [34]. There have been additional case reports of vertical transmission [35].

Although there is no national active surveillance for hepatitis B, evidence suggests that childhood hepatitis B prevalence has decreased substantially over the 23 years of the vaccine programme (Table 2). Regarding rates in children, in residual sera collected collected through febrile rash surveillance, Prabdial Sing et al found that the prevalence of HBsAg in children under 15 years of age was 0.4% [36]. Other studies have found HBsAg prevalence of 0.4% in children under 2 years old in out-patient clinics [37] and 0.8% in HIV-infected children and adolescents under 16 years of age [38].

Table 1: Hepatitis B surface antigen prevalence in South African adults from 1995

Reference	Study population	Sample number	HBsAg in HIV+	HBsAg in HIV-	Comments
Hoffmann 2014 [33]	antenatal	189	7% (14/189)		
Thumbiran 2014 [32]	antenatal	570	7.4% (16/215)	4.7% (14/294)	HBsAg 5.2%(30/570) overall
Diale 2015 [31]	antenatal	2368	2.1% (10/486)	0.4% (8/1882)	HBsAg 0.8% (18/2368) overall
Burnett 2007 [30]	antenatal	1420	6.2% (44/710)	5.8% (41/710)	
Andersson 2013 [29]	antenatal	3089	3.4% (53/1543)	2.9%. (44/1546)	HBsAg3.1% (97/3089) overall
Venter 2017 [16]	HIV clinic	771	8.0%		
Di Bisceglie 2010, [17] Firnhaber 2008 [18]	HIV clinic	502	4.8%		

Hoffman 2012 [19]	HIV clinic	998	4.2%		
Lodenyo 2000 [20]	HIV clinic	100	6.0%		
Boyles 2011 [21]	HIV clinic	1765	7.1%		
Hamers 2013 [22]	HIV clinic	569	6.7%		
Bell 2012 [23]	HIV clinic	298	9.4%		
Barth 2011 [39]	HIV clinic	258	0.4%		
Mayaphi 2012 [25]	HIV clinic	400	6.5%	2.0%	case control study following HIV testing
Mphahlele 2006 [26]	Residual sera	295	16.2%	35.2%	residual sera from routine hepatitis B testing
Lukhwareni 2009 [27]	Residual sera	192	22.9% (44/192)		residual sera from hiv clinic
Ayuk 2013 [28]	Residual sera	380	20.0%		residual sera, laboratory based

HBsAg Hepatitis B surface antigen; HIV+ HIV positive; HIV- HIV negative; Antenatal implies study population was pregnant women; HIV clinic implies study participants were all HIV infected except for Mayaphi et al, who included HIV positive and negative groups, as indicated in the relevant columns.

Table 2: Hepatitis B surface antigen prevalence in children in South African from studies since 1995, excluding vaccine efficacy trials

Reference	Study population	age	sample number	HBSAg+ overall	Comments
Chotun 2015 [34]	Infants born to HIV infected mothers	<18 months	1000	0.2%	0.3% (3/1000). One baby became HBsAg negative on follow up ie 0.2% remained sAg positive
Hoffmann 2014 [33]	Infants born to HIV infected mothers	<1 year	189	0.5%	7% of those born to HBsAg pos mothers (1/14), 0.5% overall (1/189)
Simani 2009 [37]	children 5-24 months in a vaccination clinic	5-24 months	303	0.4%	1.2% in vaccination clinic, 0% in outpatient clinic

	and outpatient clinic				
Jooste 2016 [38]	HIV infected children and adolescents	<16 years	625	0.8%	0.8% (5/625)
Prabdial- Sing	residual sera from febrile rash surveillance <15 years	<15 years	450	0.4%	all samples previously tested negative for measles
Amponsah-Dacosta 2014 [40]	residual sera, hospital based	1-16 years	635	1.4%	1-5 years 0.5%; 6-10 years 1.3%; 11-16 years 2.2%

HBsAg Hepatitis B surface antigen; < less than

Additional Key Information

Since 2015, HIV infected pregnant women in South Africa were eligible for the same antiretroviral therapy as non-pregnant women, regardless of CD4 count, with Tenofovir, Emtricitabine and Efavirenz as first line agents, of which Tenofovir and Emtricitabine are active against hepatitis B [41].

Preference and Values

Our opinion is that introduction of birth dose for any vaccine should require a higher threshold of evidence than introduction of a vaccine at a later age, due to vulnerability of the newborn and mother shortly after birth. In South Africa, oral polio vaccine and injected BCG are administered at birth. Should birth dose hepatitis B vaccine be introduced, it would be a second injection for newborns. Increasing the number of antigens administered at birth could increase vaccine hesitancy. In addition, a birth dose would increase cost of current EPI schedule and add workload and cold chain demands on health facilities. Such considerations need to be weighed against the potential benefits of the vaccine dose for disease burden in the country.

Hepatitis B testing of mothers during pregnancy has been recommended in draft national hepatitis B guidelines. Hepatitis B laboratory testing is more expensive than vaccination. Testing of maternal hepatitis B status, however, has potential benefits of allowing full investigation and follow- up of the mother's hepatitis B infection. Identified neonates at risk could be offered both birth dose vaccine as well as immune globulin. There is no South African literature regarding whether mothers would prefer maternal screening rather than neonatal vaccination if given the choice.

In the South African situation, proposed hepatitis guidelines include both maternal HBV screening and birth dose. If maternal screening becomes standard of care, the need for universal birth dose would fall away. Targeted birth dose vaccination of those born to HBV infected mothers would be a feasible approach. Ethics of including a birth dose vaccine for infants whose mothers are known to be hepatitis B negative (that is infants not at risk of vertical hepatitis B infection) require consideration.

Resources and Other considerations

Hepatitis B third dose immunization coverage in South Africa ranged from 66-85% from 2006 to 2017, requiring programmatic strengthening [42]. Birth dose hepatitis B vaccination should not be used as an alternative to strong routine coverage of childhood doses for prevention of horizontal hepatitis B transmission. Strengthening routine immunization should be prioritized.

Full costing of maternal hepatitis B screening as a national programme is recommended in order to assess feasibility of the approach of adding hepatitis B screening to maternal care. Price per test always depends on test volume and could perhaps decrease substantially from current prices if scaled up nationally.

Practical Information

Regarding maternal HIV, studies of vertical hepatitis B transmission following treatment of mothers with Tenofovir in pregnancy, per current HIV guidelines would be of assistance. Transmission is likely to be lower than that in the cited literature due to increased access by pregnant HIV-infected women in recent years to Tenofovir.

In summary, NAGI feels there is no compelling evidence to introduce universal birth dose hepatitis B vaccination in South Africa. Routine childhood immunization coverage should be strengthened. Maternal HIV screening should be costed and implemented on a national scale, allowing targeted birth dose vaccination and immune globulin to infants born to hepatitis B infected mothers.

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