The status of hepatitis B control in the African region

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Abstract

The World Health Organization (WHO) African Region has approximately 100 million people with chronic hepatitis B virus (HBV) infection. This review describes the status of hepatitis B control in the Region. We present hepatitis B vaccine (HepB) coverage data and from available data in the published literature, the impact of HepB vaccination on hepatitis B surface antigen (HBsAg) prevalence, a marker of chronic infection, among children, HBsAg prevalence in pregnant women, and risk of perinatal transmission. Lastly, we describe challenges with HepB birth dose (HepB-BD) introduction reported in the Region, and propose strategies to increase coverage. In 2015, regional three dose HepB coverage was 76%, and 16 (34%) of 47 countries reported ≥ 90% coverage. Overall, 11 countries introduced HepB-BD; only nine provide universal HepB-BD, and of these, five reported ≥ 80% coverage. From non-nationally representative serosurveys among children, HBsAg prevalence was lower among children born after HepB introduction compared to those born before HepB introduction. However, some studies still found HBsAg prevalence to be above 2%. From limited surveys among pregnant women, the median HBsAg prevalence varied by country, ranging from 1.9% (Madagascar) to 16.1% (Niger); hepatitis B e antigen (HBeAg) prevalence among HBsAg-positive women ranged from 3.3% (Zimbabwe) to 28.5% (Nigeria). Studies in three countries indicated that the risk of perinatal HBV transmission was associated with HBeAg expression or high HBV DNA viral load. Major challenges for timely HepB-BD administration were poor knowledge of or lack of national HepB-BD vaccination guidelines, high prevalence of home births, and unreliable vaccine supply. Overall, substantial progress has been made in the region. However, countries need to improve HepB3 coverage and some countries might need to consider introducing the HepB-BD to help achieve the regional hepatitis B control goal of < 2% HBsAg prevalence among children < 5 years old by 2020. To facilitate HepB-BD introduction and improve timely coverage, strategies are needed to reach both facility-based and home births. Strong political commitment, clear policy recommendations and staff training on HepB-BD administration are also required. Furthermore, high quality nationally representative serosurveys among children are needed to inform decision makers about progress towards the regional control goal.
Introduction
About 100 million persons in the World Health Organization (WHO) African Region have chronic hepatitis B virus (HBV) infection, and all countries in the Region have an intermediate (2%-7%) or high (≥ 8%) population prevalence of chronic HBV infection [1, 2]. Chronically infected individuals have a 15%-25% estimated lifetime risk of developing liver cancer or cirrhosis, dependent upon age at infection [1]. About 70%-90% of infants infected before 1 year of age will develop chronic HBV infection, compared with 20%-50% of those infected between 1-5 years of age, and with 5%-10% of those infected after 5 years of age [1]. About 90% of babies born to hepatitis B surface antigen (HBsAg) positive (a serologic marker of chronic HBV infection) and hepatitis B e antigen (HBeAg) positive (a marker of infectivity) mothers become chronically infected, compared with about 35% of babies born to HBsAg-negative chronically infected mothers [1]. In areas of intermediate or high endemicity, the majority of chronic HBV infections in the population are attributable to mother-to-child (perinatal) and early childhood transmission [1]. Childhood transmission is effectively prevented by administration of hepatitis B vaccine (HepB) in the routine childhood vaccination schedule, and perinatal transmission is effectively prevented by the timely administration of a HepB birth dose (HepB-BD). WHO recommends that all infants receive hepatitis B vaccine at birth, preferably within 24 hours, followed by two or three additional doses with a minimum interval of four weeks [1].

In November 2014, the WHO African Regional Committee endorsed a resolution for a hepatitis B control goal to reduce chronic HBV infection prevalence to < 2% in children less than 5 years of age by 2020 [8]. In this paper, we present the status of hepatitis B control in the Region, including national policies for routine childhood hepatitis B vaccination and HepB-BD, coverage estimates for the HepB series and the HepB-BD, available HBsAg prevalence data among children pre- and post-HepB introduction, and available data on the risk of mother-to-child transmission of HBV. We also describe common challenges associated with HepB-BD introduction, and propose strategies to facilitate increased HepB-BD coverage in the African Region.

Methods
For each country in the WHO African Region, we compiled data on hepatitis B vaccination (WHO-UNICEF coverage estimates) [4, 5], the number of annual births [6], the proportion of institutional births, the proportion of births attended by a skilled birth attending (SBA), and an estimate of at least one antenatal care (ANC) visit [7].

We also conducted a review of published literature from January 1995 to October 2016 using MEDLINE with the search criteria "(Country Name) AND hepatitis B". The search time frame accounted for women of childbearing age and the exponential rise of HIV cases in the 1980s and early 1990s, which could have affected the risk of HBV transmission if babies born to HBeAg-negative chronically infected mothers [1]. In areas of intermediate or high endemicity, the majority of chronic HBV infections in the population are attributable to mother-to-child (perinatal) and early childhood transmission [1]. Childhood transmission is effectively prevented by administration of hepatitis B vaccine (HepB) in the routine childhood vaccination schedule, and perinatal transmission is effectively prevented by the timely administration of a HepB birth dose (HepB-BD). WHO recommends that all infants receive hepatitis B vaccine at birth, preferably within 24 hours, followed by two or three additional doses with a minimum interval of four weeks [1].

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Current status of knowledge
Current status of Hepatitis B control in the African region
Childhood hepatitis B vaccination
All 47 countries in the WHO Africa Region have introduced HepB into the routine infant immunization schedule; 44 (94%) countries use pentavalent vaccine (diphtheria, tetanus, pertussis, Haemophilus influenzae type B and hepatitis B vaccines) and 33 (70%) countries follow a three-dose schedule at 6, 10, and 14 weeks of age (Table 1). As of December 2016, nine countries, representing 28% of the regional birth cohort, have introduced universal HepB-BD policy (Table 2). Two countries, Sao Tome and Principe and Mauritius, only provide HepB-BD for babies born to HBsAg-positive mothers [10].

Regional reported coverage with 3 doses of HepB (HepB3) increased from 5% in 2000 to 76% in 2015. However, coverage has plateaued at 70%-75% since 2009 (Figure 1) [11]. This is below the 2015 global HepB3 coverage of 84%. Country-specific HepB3 coverage estimates for 2015 ranged from 16% in Equatorial Guinea to 98% in Rwanda, The Seychelles, Swaziland, and United Republic of Tanzania; 16 (34%) countries reported national HepB3 coverage of at least 90% (Table 1) [4]. Regional reported HepB-BD coverage increased from 0% in 2000 to 10% in 2015, although coverage has plateaued at 10% since 2010 [12]. This is below the 2015 global HepB-BD coverage of 39% (Figure 1). Among countries that have introduced the birth dose, HepB-BD coverage ranged from 19% in Angola to 99% in Angola and Botswana (Table 2) [5]. Angola, Botswana, Cabo Verde, and The Gambia, all of which had introduced the birth dose over a decade ago, reported at least 90% national HepB-BD coverage (Table 2).

A recent situational report of the WHO African Region indicated HepB-BD introduction has been recommended or is under consideration in Cameroon, Cote d’Ivoire, Guinea Bissau, Mozambique, Nigeria, the Republic of Congo, Sierra Leone, South Africa, and Uganda [10]. In Ethiopia and Gabon, Hep-B-BD introduction has been proposed for the next comprehensive multi-year plan. In Rwanda, the national Expanded Programme on Immunization (EPI) reported that it has received approval from the Ministry of Health but is waiting for endorsement from the Interagency Coordination Committee (ICC). Ghana has included HepB-BD introduction in its comprehensive multi-year strategic plan for immunization and the National Viral Hepatitis Control Plan, but so far, Hep-BD introduction has been postponed due to competing priorities [10]. Countries have reported multiple barriers to Hep-BD introduction, including lack of financial support from Gavi, the vaccine alliance (10 countries), the need for evidence on the burden of chronic HBV infection and the risk of perinatal transmission in Africa (6 countries), insufficient cold chain storage (3 countries), lack of trained healthcare workers (HCW) to attend births or conduct post-natal visits (2 countries), and a high proportion of home births (2 countries) [10].

HBsAg and HBeAg prevalence estimates among pregnant women were calculated for each country using data from relevant studies. Minimum and maximum estimates are also presented.
### Table 1: childhood hepatitis B vaccine 3-dose (HepB3) coverage by country in the World Health Organization African Region, 2011–2015

| Country1 | Year Introduced2 | HepB3 Coverage %2 | 2011 | 2012 | 2013 | 2014 | 2015 |
|----------|-----------------|-------------------|------|------|------|------|------|
| Algeria  | 2001            |                   | 95   | 95   | 95   | 95   | 95   |
| Angola   | 2006            |                   | 72   | 75   | 77   | 64   | 64   |
| Benin    | 2005            |                   | 75   | 81   | 74   | 75   | 79   |
| Botswana | 1995            |                   | 95   | 95   | 95   | 95   | 95   |
| Burkina Faso | 2006 |                   | 91   | 90   | 88   | 91   | 91   |
| Burundi  | 2004            |                   | 96   | 96   | 96   | 95   | 94   |
| Cabo Verde | 2002         |                   | 90   | 94   | 93   | 95   | 93   |
| Cameroon | 2005            |                   | 82   | 85   | 89   | 87   | 84   |
| Central African Republic | 2008 |                   | 47   | 47   | 23   | 47   | 47   |
| Chad     | 2008            |                   | 33   | 45   | 48   | 46   | 55   |
| Comoros  | 2003            |                   | 83   | 86   | 83   | 80   | 80   |
| Congo    | 2007            |                   | 80   | 79   | 85   | 90   | 80   |
| Cote d’Ivoire | 2001 |                   | 62   | 82   | 80   | 76   | 83   |
| DR of Congo | 2007         |                   | 74   | 75   | 74   | 80   | 81   |
| Equatorial Guinea | 2013 |                   | -    | -    | -    | 20   | 16   |
| Eritrea  | 2002            |                   | 96   | 94   | 94   | 94   | 95   |
| Ethiopia | 2007            |                   | 65   | 69   | 72   | 77   | 86   |
| Gabon    | 2004            |                   | 75   | 82   | 79   | 70   | 80   |
| Gambia   | 1990            |                   | 96   | 98   | 97   | 96   | 97   |
| Ghana    | 2002            |                   | 91   | 92   | 90   | 98   | 88   |
| Guinea   | 2006            |                   | 63   | 62   | 63   | 51   | 51   |
| Guinea-Bissau | 2008 |                   | 80   | 80   | 80   | 80   | 80   |
| Kenya    | 2002            |                   | 96   | 94   | 93   | 92   | 89   |
| Lesotho  | 2003            |                   | 96   | 95   | 93   | 93   | 93   |
| Liberia  | 2008            |                   | 77   | 80   | 76   | 50   | 52   |
| Madagascar | 2002          |                   | 73   | 70   | 74   | 73   | 69   |
| Malawi   | 2002            |                   | 97   | 96   | 89   | 91   | 88   |
| Mali     | 2003            |                   | 66   | 68   | 71   | 77   | 68   |
| Mauritania | 2005         |                   | 75   | 80   | 80   | 84   | 73   |
| Mauritius | 1997          |                   | 98   | 98   | 98   | 97   | 97   |
| Mozambique | 2001         |                   | 76   | 76   | 78   | 79   | 80   |
| Namibia  | 2009            |                   | 82   | 84   | 89   | 88   | 92   |
| Niger    | 2008            |                   | 75   | 71   | 67   | 68   | 65   |
| Nigeria  | 2004            |                   | 46   | 42   | 45   | 49   | 56   |
| Rwanda   | 2002            |                   | 97   | 98   | 98   | 98   | 98   |
| Sao Tome and Principe | 2003 |                   | 96   | 96   | 97   | 95   | 96   |
| Senegal  | 2004            |                   | 92   | 91   | 92   | 89   | 89   |
| Seychelles | 1995        |                   | 99   | 99   | 99   | 99   | 98   |
| Sierra Leone | 2007    |                   | 89   | 91   | 92   | 83   | 86   |
| South Africa | 1995       |                   | 76   | 73   | 65   | 74   | 71   |
| South Sudan | 2014        |                   | -    | -    | -    | -    | 31   |
| Swaziland | 1996         |                   | 91   | 95   | 98   | 98   | 98   |
| Togo     | 2008            |                   | 85   | 84   | 84   | 87   | 88   |
| Uganda   | 2002            |                   | 82   | 78   | 78   | 78   | 78   |
| United Republic of Tanzania | 2002 |                   | 90   | 92   | 91   | 97   | 98   |
| Zambia   | 2005            |                   | 81   | 78   | 79   | 86   | 90   |
| Zimbabwe | 2000            |                   | 94   | 97   | 95   | 91   | 87   |

1All countries provide pentavalent (DTwPHibHepB) vaccine, except for Algeria and Mauritius which provide monovalent hepatitis B vaccine and South Africa which provides monovalent and hexavalent (DTaPIPVHibHepB) vaccines. All countries follow a 3-dose schedule at 6, 10, and 14 weeks of age, except for Algeria (0, 1, 5 months), Angola (0, 2, 4, 5 months), Botswana (0, 2, 3, 4 months), Burkina Faso (8, 12, 16 weeks), Cabo Verde (0, 2, 4, 6, 18 months), Congo (8, 12, 16 weeks), Gambia (0, 2, 3, 4 months), Mauritania (0, 6, 10, 14 weeks), Namibia (0, 6, 10, 14 weeks), Nigeria (0, 6, 10, 14 weeks), Sao Tome and Principe (0, 6, 10, 14 weeks), Senegal (0, 6, 10, 14 weeks), Seychelles (3, 4, 5 months), and South Africa (6, 10, 14 weeks, 18 months for hexavalent vaccine). 2Vaccine introduction year and annual coverage estimates were derived from WHO UNICEF Joint Reporting (updated July 2016) [http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucov_barhepb3.html](http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucov_barhepb3.html).
| Country                  | Year HepB-BD introduced | HepB-BD Coverage %<sup>1</sup> | Annual Births (1000s)<sup>2</sup> | Institutional deliveries %<sup>3</sup> | Births attended by SBA %<sup>3</sup> | >1 ANC visit %<sup>3</sup> |
|-------------------------|-------------------------|---------------------------------|-------------------------------------|--------------------------------------|---------------------------------|--------------------------|
| Algeria                 | 2004                    | 99                              | 99                                  | 99                                   | 99                              | 99                       |
| Angola                  | 2015                    | -                               | -                                   | -                                    | 19                              | 1,128                    |
| Botswana                | Pre 2000                | 99                              | 99                                  | 99                                   | 99                              | 55                       |
| Cabo Verde              | 2002                    | 99                              | 99                                  | 94                                   | 99                              | 11                       |
| Gambia                  | 1990                    | 90                              | 97                                  | 93                                   | 96                              | 83                       |
| Mauritania              | 2013                    | -                               | -                                   | -                                    | -                               | 134                      |
| Mauritius<sup>5</sup>   | n.a.                    | -                               | -                                   | -                                    | 14                              | 99                       |
| Namibia                 | 2014                    | -                               | -                                   | 1                                    | 87                              | 72                       |
| Nigeria                 | 2004                    | 31                              | 32                                  | 32                                   | 32                              | 7,133                    |
| Sao Tome and Principe<sup>5</sup> | 2002                  | -                               | -                                   | -                                    | -                               | -                        |
| Senegal                 | 2016                    | -                               | -                                   | -                                    | -                               | -                        |
| Benin                   |                         | 388                             | 87                                  | 77                                   | 83                              | 68                       |
| Burkina Faso            |                         | 717                             | 66                                  | 66                                   | 94                              | 54                       |
| Burundi                 |                         | 488                             | 60                                  | 60                                   | 99                              | 34                       |
| Cameroon                |                         | 847                             | 61                                  | 65                                   | 83                              | 92                       |
| Central African Republic|                         | 164                             | 53                                  | 54                                   | 68                              | 22                       |
| Chad                    |                         | 630                             | 22                                  | 24                                   | 53                              | 92                       |
| Comoros                 |                         | 26                              | 76                                  | 82                                   | 92                              | 93                       |
| Congo                   |                         | 167                             | 92                                  | 94                                   | 93                              | 37                       |
| Cote d’Ivoire           |                         | 838                             | 57                                  | 59                                   | 91                              | 46                       |
| DR of Congo             |                         | 3,217                           | 80                                  | 80                                   | 88                              | 40                       |
| Equatorial Guinea       |                         | 29                              | 67                                  | 68                                   | 91                              | 92                       |
| Eritrea                 |                         | 175                             | 34                                  | 34                                   | 89                              | 45                       |
| Ethiopia                |                         | 3,176                           | 16                                  | 16                                   | 41                              | 89                       |
| Gabon                   |                         | 51                              | 90                                  | 89                                   | 95                              | 34                       |
| Ghana                   |                         | 884                             | 73                                  | 71                                   | 91                              | 55                       |
| Guinea                  |                         | 460                             | 40                                  | 45                                   | 85                              | 68                       |
| Guinea-Bissau           |                         | 68                              | 44                                  | 45                                   | 92                              | 55                       |
| Kenya                   |                         | 1,571                           | 61                                  | 62                                   | 96                              | 55                       |
| Lesotho                 |                         | 61                              | 77                                  | 78                                   | 95                              | 55                       |
| Liberia                 |                         | 156                             | 56                                  | 61                                   | 96                              | 60                       |
| Madagascar              |                         | 831                             | 38                                  | 44                                   | 82                              | 55                       |
| Malawi                  |                         | 665                             | 89                                  | 87                                   | 96                              | 55                       |
| Mali                    |                         | 758                             | 45                                  | 49                                   | 70                              | 55                       |
| Mozambique              |                         | 1,087                           | 55                                  | 54                                   | 91                              | 55                       |
| Niger                   |                         | 983                             | 59                                  | 40                                   | 83                              | 55                       |
| Rwanda                  |                         | 363                             | 91                                  | 91                                   | 99                              | 55                       |
| Seychelles              |                         | 2                               | -                                   | -                                    | -                               | -                        |
| Sierra Leone            |                         | 229                             | 54                                  | 60                                   | 97                              | 55                       |
| South Africa            |                         | 1,111                           | 95                                  | 94                                   | 97                              | 55                       |
| South Sudan             |                         | 446                             | -                                   | 19                                   | 62                              | 55                       |
| Swaziland               |                         | 38                              | 88                                  | 88                                   | 99                              | 55                       |
| Togo                    |                         | 256                             | 73                                  | 59                                   | 73                              | 55                       |
| Uganda                  |                         | 1,665                           | 57                                  | 57                                   | 93                              | 55                       |
| United Republic of Tanzania |             | 2,064                           | 50                                  | 49                                   | 88                              | 55                       |
| Zambia                  |                         | 645                             | 67                                  | 64                                   | 96                              | 55                       |
| Zimbabwe                |                         | 539                             | 80                                  | 80                                   | 94                              | 55                       |

<sup>1</sup>Coverage estimates are derived from WHO UNICEF Joint Reporting (updated July 2016) http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragehepb_bd.html. <sup>2</sup>Annual birth data is derived from the WHO Immunization Monitoring System (updated May 2016) http://apps.who.int/immunization_monitoring/globalsummary. <sup>3</sup>Data derived from UNICEF (updated February 2016) www.data.unicef.org, SBA-skilled birth attendant, ANC-Antenatal care. <sup>4</sup>2015 coverage data reported to SAGE 2016 in WHO review of hepatitis B birth dose. <sup>5</sup>Sao Tome and Principe and Mauritius do not offer the birth dose universally, but follow a selective policy where infants of mothers that test HBsAg are offered vaccine.n.a.-not available.
Table 3: Hepatitis B surface antigen seroprevalence among children pre- and post-vaccine introduction by country — World Health Organization African Region

| Country                        | Year of study | Sample size | Study population | Age groups | HBsAg prevalence % | Year of study | Sample size | Study population | Age groups | HBsAg prevalence % |
|--------------------------------|---------------|-------------|------------------|------------|---------------------|---------------|-------------|------------------|------------|---------------------|
| Nigeria                        | 1996-2010     | 219         | Sabandiga-Ora town [21] | 1-4yrs     | 2001 223            | 1-4yrs        | 1.3          | 100%             |            |                     |

Table 4: Hepatitis B surface antigen and e antigen prevalence among pregnant women by country within the World Health Organization African Region, 1995-2016

| Country | No. of studies | Year of studies | Study site (no. of studies) | Study setting1 | Median No. participants per study (min, max) | Median % HBsAg prevalence (min %, max %) | Median % HBeAg prevalence among HBsAg positive women (min %, max %) |
|---------|----------------|----------------|-----------------------------|---------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------------------------|
| Western Africa | (n=75) | Single | Multiple | Urban | Rural |                                           |                                           |                                                                     |
| Benin   | 3              | 2011          | 1                        | -            | 1                | 283                                      | 15.5 (9.7)                    | 11.4 (13.7)                                      |
| Burkina Faso | 7        | 1995-2009  | 4                        | 3            | 7                | 321 (129, 917)                          | 8.1 (5.8, 17.1)               | 38 (44)                                        |
| Côte d’Ivoire | 3             | 1995-2002 | 1                        | 2            | 2                | 498 (295, 4385)                        | 8.0 (0.0, 18.2)              | 45 (47)                                        |
| Ghana   | 4              | 2000-2013    | 1                        | 1            | 2                | 727 (168, 1308)                        | 12.0 (9.5, 19.3)             | 89 (91)                                        |
| Mali    | 2              | 1994-2009    | 1                        | 1            | 2                | 2244 (829, 3595)                       | 11.8 (8.0, 16.5, 52, 53)    | -                                               |
| Mauritania | 1           | 2008-2009   | 1                        | -            | 1                | 1020                                    | 10.7 (5.4)                   | -                                               |
| Niger   | 1              | 2008         | 1                        | 1            | 1                | 499                                     | 16.2 (75)                    | -                                               |
| Nigeria | 26             | 1997-2015    | 20                       | 6            | 23               | 358 (156, 5760)                        | 6.9 (1.4, 16.5, 58, 81)      | 28.5 (6.5, 36.4) (41, 70, 72)                  |
| Sierra Leone | 4          | 2005         | -                        | 1            | 1                | 302                                     | 6.3 (6.3, 16.4)              | -                                               |
| Central Africa | (n=8) | - | - | - | - | - | - | - |
| Cameroon | 7              | 2000-2015    | 1                        | 6            | 4                | 349 (176, 7069)                        | 7.7 (4.4, 20.4)              | 83 (89)                                        |
| Gabon   | 1              | 2005         | -                        | 1            | 1                | 1186                                    | 9.2 (90)                     | 10.1 (90)                                      |

Table 5: Hepatitis B surface antigen and e antigen prevalence among pregnant women by country within the World Health Organization African Region, 1995-2016

| Country | No. of studies | Year of studies | Sample size | Study site (no. of studies) | Study setting1 | Median No. participants per study (min, max) | Median % HBsAg prevalence (min %, max %) | Median % HBeAg prevalence among HBsAg positive women (min %, max %) |
|---------|----------------|----------------|-------------|-----------------------------|---------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------------------------|
| Western Africa | (n=75) | Single | Multiple | Urban | Rural |                                           |                                           |                                                                     |
| Benin   | 3              | 2011          | 1                        | -            | 1                | 283                                      | 15.5 (9.7)                    | 11.4 (13.7)                                      |
| Burkina Faso | 7        | 1995-2009  | 4                        | 3            | 7                | 321 (129, 917)                          | 8.1 (5.8, 17.1)               | 38 (44)                                        |
| Côte d’Ivoire | 3             | 1995-2002 | 1                        | 2            | 2                | 498 (295, 4385)                        | 8.0 (0.0, 18.2)              | 45 (47)                                        |
| Ghana   | 4              | 2000-2013    | 1                        | 1            | 2                | 727 (168, 1308)                        | 12.0 (9.5, 19.3)             | 89 (91)                                        |
| Mali    | 2              | 1994-2009    | 1                        | 1            | 2                | 2244 (829, 3595)                       | 11.8 (8.0, 16.5, 52, 53)    | -                                               |
| Mauritania | 1           | 2008-2009   | 1                        | -            | 1                | 1020                                    | 10.7 (5.4)                   | -                                               |
| Niger   | 1              | 2008         | 1                        | 1            | 1                | 499                                     | 16.2 (75)                    | -                                               |
| Nigeria | 26             | 1997-2015    | 20                       | 6            | 23               | 358 (156, 5760)                        | 6.9 (1.4, 16.5, 58, 81)      | 28.5 (6.5, 36.4) (41, 70, 72)                  |
| Sierra Leone | 4          | 2005         | -                        | 1            | 1                | 302                                     | 6.3 (6.3, 16.4)              | -                                               |
| Central Africa | (n=8) | - | - | - | - | - | - | - |
| Cameroon | 7              | 2000-2015    | 1                        | 6            | 4                | 349 (176, 7069)                        | 7.7 (4.4, 20.4)              | 83 (89)                                        |
| Gabon   | 1              | 2005         | -                        | 1            | 1                | 1186                                    | 9.2 (90)                     | 10.1 (90)                                      |
Impact of hepatitis B vaccination in children

To document the impact of HBV vaccination on chronic HBV infection prevalence in the African Region, we identified HBSAg serosurveys conducted pre- and post-HepB introduction among children in seven countries: the Gambia, Nigeria, Cameroon, Ghana, Senegal, South Africa, and Tanzania (Table 3) [13-36]. All studies were limited to a few areas, districts, villages, hospitals, or clinics, resulting in HBsAg prevalence estimates that were not representative of the true burden of chronic HBV infection among children in those countries. Some studies that were conducted post-HepB introduction, only included children that had three documented doses of HepB [17, 18, 21, 28, 33]. These studies reported HBSAg prevalence among fully vaccinated children, but they do not reflect the true burden among these age groups.

Countries that have introduced the birth dose

In The Gambia, surveys conducted between 1990 and 2008, most of which were associated with the Gambia Hepatitis Intervention Study (GHIS) an initiative which progressively introduced HepB into the Gambian routine immunization program during 1986–1990, showed that HBSAg prevalence decreased from 8%-14.6% among 6 month–9 year old children to < 2% among 1–5 year old children post-HepB introduction (Table 3) [13-19]. However, two of these three post-HepB introduction studies were conducted among children that had received at least 3 doses of HepB verified by vaccination records [17, 18]. Therefore, the true HBSAg prevalence may be higher. Available data from convenience and non-representative samples in Nigeria also found a decrease in HBSAg prevalence among children after vaccine introduction (Table 3) [20-24]. However, in three of four post-HepB introduction studies that found HBSAg prevalence to be < 2%, the majority of participants had documented HepB receipt [21, 22, 24]. In the remaining study, hepatitis B vaccination history was available for 27% of the participants, thus some of the participants without vaccination history may not have received HepB, which is likely given national HepB3 coverage was 46% in 2011 in Nigeria (Table 1), resulting in the higher HBSAg prevalence of 14.1% [23].

Countries that have NOT introduced the birth dose

Studies conducted in Cameroon, Ghana, Senegal, South Africa and Tanzania, countries that did not have a HepB-BD in their schedule at the time of the surveys, reported a drop in HBsAg prevalence among children born after HepB introduction (Table 3) [25-36]. However, none of the studies were nationally representative. More specifically, estimated HBSAg prevalence among children born post-HepB introduction was less than 2% in Cameroon, Ghana, South Africa, and Tanzania [25-29, 32-36]. These estimates were derived from studies that only included children with documented verified 3 doses of HepB (Ghana, South Africa), where documented vaccination history was only available for a small proportion of participants (Cameroon), or vaccination history was not reported (Ghana, South Africa, Tanzania). In Senegal, HBSAg prevalence was > 2% in a 1993 post-HepB introduction study [30]. This study was a cluster survey conducted a year after HepB introduction in a pilot region; hepatitis B vaccination history was available for 86% of participants, of which only 40% had received 3 doses of HepB. In comparison, another study conducted in 2009 reported a HBSAg prevalence of 0.2% among hospitalized children at one hospital in Dakar; hepatitis B vaccination history was available for 43% of participants and all had received HepB [26]. Since at the time of the latter study, national HepB3 coverage would have been around 90% (Table 1) it is likely that most of the participants without vaccination history were vaccinated.

Evidence for perinatal transmission of HBV infection in Africa

Understanding the prevalence of HBSAg and HBeAg among pregnant women or women of child-bearing age helps to assess the risk of perinatal HBV transmission and the need for a HepB-BD. From 1995 to 2016, we identified 175 studies from 18 countries that reported HBSAg prevalence among pregnant women (Table 4) [37-111]. Of these, 24 reported HBeAg prevalence [37-39, 45-47, 61, 70-72, 85, 88-90, 96, 100-102, 104-106, 108, 109, 111]. Of these one third of the studies were conducted in Nigeria. Nearly all studies were cross-sectional or cohort designs that recruited participants through convenience sampling, many times at a single study site, and were subject to selection bias. Reported median HBSAg prevalence by country varied widely, from 1.9% in Madagascar to 16.2% in Niger (Table 4). For most of the countries with multiple studies, HBSAg and HBeAg prevalence estimates varied widely, reflecting the different HBV infection risks in different parts of each country and among distinct population groups, e.g. groups of differing ethnicities, socio-economic status and education levels. Although none of the studies were nationally representative, they highlight that the prevalence of chronic HBV infection among the pregnant women surveyed was intermediate to high, and that the proportion of chronically-infected mothers who were HBeAg-positive varied widely by country.

Perinatal transmission of HBV in the African region

In addition to serosurveys conducted among pregnant women, we identified four studies that assessed perinatal transmission of HBV infection [38,45,49,108]. Among women of unknown or negative HIV status in Burkina Faso, Cote d'Ivoire, and Ghana, perinatal transmission of HBV was more frequent when mothers expressed HBeAg or had a high HBV DNA viral load (≥10^4 IU/ml) [38, 45, 49]. In Cote d'Ivoire, 9 (38%) of 24 infants born to HBSAg-positive/HBeAg-positive mothers tested HBSAg-positive at six weeks of age, compared with none (0%) of 42 infants born to HBSAg-positive/HBeAg-negative mothers [45]. In Ghana, 5 (5.2%) of 97 infants born to HBSAg-positive mothers tested HBV DNA positive at two weeks of age; the relative risk of perinatal transmission associated with high maternal HBV DNA viral load (≥10^4 IU/ml) compared with low maternal HBV DNA viral load was 2.4 (95% CI:1.1-5.4, p=0.048) [49]. One study from Burkina Faso reported that 7 (32%) of 22 infants born to HBSAg-positive/HBeAg-negative and 2 (29%) of 7 infants born to HBSAg-positive/HBeAg-positive mothers tested HBSAg-positive within 24 hours of birth [38].

Challenges and strategies for improving hepatitis B vaccine birth dose coverage in Africa

Despite the introduction of HepB by all countries in the Region, for 31 countries (66%) HepB3 coverage is below the 90% recommended coverage level. Given the high chronic HBV infection prevalence throughout the Region, particularly among pregnant women, and the importance of perinatal and early childhood transmission, intermediate and high endemicity settings, countries need to improve HepB3 coverage and those without a birth dose might need to consider introducing the HepB-BD to reach the regional hepatitis B control goal by 2020. In African countries that have already introduced the HepB-BD, several challenges, including timely administration of the HepB-BD, high prevalence of home births, the lack of services available to reach infants born at home and unreliable vaccine supply have limited HepB-BD implementation. In this section we present those challenges and list some strategies that could help overcome them to improve HepB-BD coverage.

Challenges associated with birth dose implementation in Africa

HepB-BD assessments conducted in the Region have consistently identified timely HepB-BD administration (within 24 hours of birth)
as a challenge (BD workshop report, Regional Consultation on Viral Hepatitis Control, Mauritania CDC trip report, Botswana & Namibia BD assessments, unpublished reports). National policy recommendations for HepB-BD administration varied from within 24-hours in Nigeria to up to two weeks after birth in Namibia (Nigeria & Namibia BD assessments, unpublished reports). Restricting HepB-BD administration time to within 24 hours after birth, as recommended in Nigeria in February 2015, might limit coverage by preventing vaccination of infants born outside a health facility. In Nigeria, median timely HepB-BD administration was 1% (range: 0%-20%) and total HepB-BD coverage was 4% (range: 0%-22%) among health facilities visited prior to the birth dose assessment conducted in September 2015 (Nigeria BD assessment, unpublished report). HepB-BD administration among children admitted to an emergency room in Nigeria, the mean age at HepB-BD receipt was 28 days, and only 13 (32%) of 41 infants received a HepB-BD within 7 days of birth [23]. In the Gambia, a review of 10 years of district HepB-BD vaccination coverage data showed that only 1% of infants were vaccinated within 1 day of birth, 5% were vaccinated within 7 days, and 58% were vaccinated within 28 days [112]. In Botswana, 78% of the facilities visited during a birth dose assessment administered the vaccine within 24 hours of birth (Botswana BD Assessment, unpublished report).

Other challenges identified included high prevalence of home births and the lack of services available to reach infants born at home, unreliable vaccine supply and inappropriate forms to document HepB vaccination (Botswana BD workshop report, Regional Consultation on Viral Hepatitis Control, Mauritania CDC trip report, Botswana & Namibia BD assessments, unpublished reports). In The Gambia and Nigeria, where the proportion of home births was high, cultural factors such as waiting until after a child’s naming day (around 7 days) to bring him/her to a healthcare facility delayed vaccination (BD workshop report, Botswana & Nigeria BD assessments, unpublished reports). Vaccine stock outs or limited vaccination sessions hindered the provision of timely HepB-BD in Botswana, The Gambia, Mauritania, Namibia, and Nigeria (BD workshop report; Botswana, Namibia, & Nigeria BD assessment, Mauritania CDC trip report, unpublished reports) [112]. In Botswana, despite daily HepB immunization sessions, HepB stock outs lasting over one month were reported at two of 16 visited facilities; and in Namibia, two events of HepB stock outs were reported in the six months before the assessment visit. Monitoring HepB-BD coverage is dependent upon having appropriate documentation tools to record both timely and total HepB-BD coverage. For all assessed countries, documentation of HepB-BD administration was suboptimal (BD workshop report; Botswana, Namibia, Nigeria, Sao Tome and Principe BD assessments; unpublished reports). In Nigeria, only doses administered within 24 hours could be recorded, while in most other countries there was no place to record timely HepB-BD.

**Strategies for improving birth dose coverage**

Many of the challenges identified in the HepB-BD assessments in Africa can be overcome based on the experiences in the WHO Western Pacific Region (WPR) and South East Asian Region (SEAR), where several countries had high HBsAg endemicity and high home birth rates. By implementing hepatitis B vaccination strategies, including HepB-BD administration, the WPR decreased chronic HBV infection prevalence among children at least 5 years of age from 8.3% in 1990 to 0.9% in 2012 [113]. The strategies described below could help to improve HepB-BD coverage and promote the achievement of the hepatitis B control goal in the Africa Region.

**Advocate for strong political commitment**

Strong political commitment is essential to identify resources in the country’s budget or to seek financial support from donors to introduce HepB-BD. In order to engage decision makers, initial steps need to be taken, including gathering the evidence on the prevalence of chronic HBV infection in pregnant women and risk of perinatal transmission, to present to the national immunization technical advisory group or equivalent technical bodies within each country to review [114]. All potential decision makers and opinion leaders from a wide variety of organizations should be engaged, including Ministries of Health and Finance, professional societies, medical associations, donor agencies, non-governmental organizations, as well as community and religious leaders [114]. Advocacy with partners in different but related sectors, such as cancer prevention, chronic disease prevention, safe motherhood and essential newborn care, might also strengthen political commitment [114]. It will be important to highlight that monovalent HepB is affordable, varying from US $0.16 per dose for a 10-dose vial to US $0.38 per dose for a single dose vial [115]. In addition, the vaccine is 95% effective in preventing infection in newborns [1].

**Develop clear policy recommendations**

HepB-BD guidelines and policies should be consistent with the WHO Strategic Advisory Group of Experts (SAGE) recommendations. All infants should receive their first dose of HepB as soon as possible after birth, preferably within 24 hours and up until the time of the first primary dose, since vaccination up until 7 days after birth can still be effective at preventing perinatal HBV transmission [116]. Infants born to HBsAg-positive mothers vaccinated after 7 days post-birth, compared with those vaccinated 1-3 days after birth, had an increased risk of HBV infection (OR = 8.6) [1]. HepB-BD administration is needed for all infants, because selective vaccination of infants born to HBsAg-positive mothers identified by screening as is the current policy for Sao Tome and Principe and Mauritius, has been found to miss at-risk babies [117].

In China, an effective policy to ensure timely administration of the HepB-BD was to assign responsibility for vaccine administration to whoever delivered the infant (“who delivers the infant gives the birth dose”) [118]. All countries providing or considering HepB-BD introduction should ensure that staff at health facilities, hospitals, and public health departments, including MCH and perinatal care staff, are well-trained on the policy recommendations and reporting requirements to help address challenges that have been identified during the HepB-BD assessments.

**Ensure relevant documentation for monitoring birth dose administration is available**

To appropriately monitor HepB-BD coverage, countries need to record separately birth dose administered within 24 hours of birth and birth dose provided after 24 hours. Countries in the Africa Region that have introduced the birth dose and were recently assessed, had insufficient tools for documenting both timely and total birth dose. Therefore, all immunization reporting tools, including immunization cards, EPI registers, and electronic data management systems, should have a place to record the date of HepB-BD administration and to track whether it was provided within 24 hours of birth. Synergy of data collection forms across EPI and Maternal and Child Health (MCH) programs could also improve data monitoring.

**Maximize HepB-BD coverage among health facility births**

In just under one third of countries (14 out of 47) in the Region, ≥ 80% of births occurred in health facilities (Table 2). In these countries, high HepB-BD coverage can be achieved among children born in health facilities. Utilizing ANC visits to promote health facility deliveries could improve post-natal care and maternal health as well as facilitate administration of HepB-BD. In 81% of countries (38 out of 47) in the WHO African Region, ≥ 80% of pregnant women had at least one ANC visit and in 57% of countries (27 out of 47), ≥ 90% of pregnant women had at least one ANC visit (Table 2). Also, engaging local community and religious leaders to promote hospital births may be helpful. In China, increasing hospital deliveries resulted in improving timely HepB-BD coverage and contributed to decreasing maternal mortality, and eliminating maternal and neonatal tetanus [118].

Appropriate training for MCH and EPI staff is also essential and can improve timely HepB-BD coverage. In the Philippines, assessment and correction of HCWs through on-the-spot training increased timely HepB-BD coverage among hospital births [119]. In China, strong collaboration between MCH and EPI programs, supervision of low performing sites, and HCW training led to high timely HepB-BD coverage among hospitals [118]. Further improvements could be made through well-managed vaccine delivery and procurement to avoid vaccine stock outs at health facilities. Availability of HepB-BD policies on-site and standing orders for birth dose vaccination led to higher HepB-BD coverage in the Philippines [119].

**Reach children born at home within 24 hours of birth**

Across Africa, one of the major challenges for timely administration of the HepB-BD is the large proportion of home births. In nine countries, institutional births accounted for ≥ 50% of births (Table 2). In settings
where births are attended by an SBA, the HepB-BD can be administered by SBAs who have been trained to administer monovalent HepB and provided access to the vaccine. In the African Region, SBAs attend > 70% of births in 18 countries (Table 2).

In settings where births are not attended by SBAs, activities that could improve timely HepB-BD coverage include tracking pregnancies to increase HCW awareness of potential births in their community, educating pregnant women about the importance of timely HepB-BD administration during antenatal care visits and training community health workers (CHWs) or volunteers to organize outreach visits to vaccinate the newborn in a timely manner. Birth notification using village health volunteers was piloted in Lao PDR and resulted in more health facility deliveries and improved HepB-BD coverage [120]. Training CHWs or traditional birth attendants (TBAs) to vaccinate newborns with compact single-dose pre-filled auto-disable injection devices (CPAD) of monovalent HepB (Unjict™) has been conducted in Indonesia to provide HepB-BD during outreach activities for home births, improving timely access to the vaccine [121].

Storage of HepB outside the cold chain

A strategy for reaching newborn infants in areas that lack or have unreliable cold chain is to store monovalent Hep B outside the cold chain (OCC). Data from several HepB manufacturers indicate that the vaccine is thermostable for at least 4 weeks at temperatures of 37°C and 40°C–45°C and that HepB stored OCC induces a similar level of protection and seroconversion as vaccine stored between 2°C–8°C. Recently, WHO SAGE issued recommendations that support countries that choose to purchase the OCC policy for monovalent HepB vaccination [116, 122]. Storing monovalent HepB OCC has been shown to significantly improve HepB-BD coverage in Indonesia, China, Lao, and Vietnam [123-126]. Therefore, countries in the African Region, where the proportion of home births is high and/or cold chain storage might not be optimal, might want to consider storing monovalent HepB OCC to promote timely HepB-BD administration and subsequently prevent perinatal infections.

Conclusion

Substantial progress has been made to introduce routine infant hepatitis B vaccination in the WHO African Region; however, in 2015 the Region had the lowest HepB3 coverage estimate (76%) compared with other WHO Regions [11]. Only 11 (23%) countries have introduced the Hep-B-D of these, five had total HepB-BD coverage ≥ 80%. Limited data from non-representative serosurveys conducted to date suggest hepatitis B vaccination has decreased HBsAg prevalence among children born after HepB introduction in some countries. However, several studies reported > 2% HBsAg prevalence among children born after vaccination introduction. Given the HBsAg prevalence data among pregnant women and children is limited and not nationally representative, the prevalence estimates presented for each country may not reflect the true situation. High quality nationally representative serosurveys among children born after implementation of routine infant hepatitis B vaccination are needed to inform local decision makers about progress towards and actions needed to achieve the African Region hepatitis B control goal.

Competing interests

The authors declare no competing interest.

Authors’ contributions

Dr Breakwell designed the study, reviewed the literature, summarized the data and wrote the manuscript; Dr Tevi Benissan reviewed the manuscript; Ms Childs contributed to the data abstraction and analysis, and reviewed the manuscript; Dr Mihigo reviewed the manuscript; Dr Tohme contributed to the study design and reviewed the manuscript. All the authors have read and agreed to the final manuscript.

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What is known about this topic

• There is a high prevalence of chronic hepatitis B virus (HBV) infection in the African Region, resulting in 100 million people being at risk of death from liver cancer and cirrhosis; • The Africa Region has established a hepatitis B control goal to reduce the prevalence of hepatitis B surface antigen (HBsAg, a marker of chronic HBV infection) to < 2% among children aged < 5 years by 2020; • Administering a Hepatitis B vaccine birth dose within 24 hours of birth and three additional doses during infancy protects children from acquiring chronic HBV infection through perinatal transmission and during early childhood when the risk of developing chronic infection is highest.
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