The effectiveness of hepatitis B vaccine in toddlers based on the five-year period national basic health research (Riskesdas 2007, 2013 and 2018) in Indonesia

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Background. Hepatitis B is a viral infection that has a high prevalence in Indonesia. The Ministry of Health of Indonesia has conducted a national vaccination program for hepatitis B. In order to evaluate the success of the hepatitis B vaccination in Indonesia, a community study based on basic health research (Riskesdas) was performed nationwide since 2007 for five year period; in 2007, 2013, and 2018.

Methods. Further statistical analysis was performed specifically for the children under 59 months old (toddlers) immunized in both urban and rural areas in 2007, 2013, and 2018 based on certain characteristics by examining antibodies against HBsAg (anti-HBs), IgG antibodies against the core antigen (HBcAb), surface antigen (HBsAg) of hepatitis B virus (HBV). The data obtained from the data management laboratory of Ministry of Health, Indonesia, was analyzed with Bivariate analysis with continuity correction chi-square or Pearson chi-square using Stata software version 16.

Results. This study showed an increase in hepatitis B coverage of complete immunization (30% in 2007, 60.3% in 2013, and 57% in 2018), which was also influenced by mothers' level of education (Pearson chi-square, $p = 0.000$) and access to health service points within 30 minutes (OR = 1.3-2.8, $p = 0.000$). The trend of the percentage of immune status (anti-HBs) was increased (41.8% in 2007; 56.1% in 2013; and 79.1% in 2018). The higher anti-HBs was found in complete hepatitis B immunization status (OR = 1.5–2, $p = 0.000$) and in good nutritional status ($p = 0.000$). However, the anti-HBs was found decreased with increasing age ($p = 0.000$). The trend of positive HBcAb (exposure to HBV infection) showed a decrease gradually of almost ten times from 2007 (8.6%-13.5%) compared to 2013 (2.6%-11.1%) and 2018 (1.1%-2%). Urban areas were at higher risk of hepatitis B exposure (OR = 1.4–2.2) than rural areas (OR = 0.37–0.80). The HBsAg data were only available in 2013 and 2018. Riskesdas data analysis showed the prevalence of hepatitis B (HBsAg) was lower in complete immunization status than that in incomplete one ($p = 0.000$), but with an increase from 3.9% (2013) to 9.3% (2018), possibly due to inappropriate birth dose immunization schedule or a vaccine-escape mutant from the HBV variants.

Conclusions. The effectiveness of hepatitis B vaccine obtained from the three Riskesdas periods in Indonesia showed an improvement, with an increase in immune status, reduced exposure to HBV and a lower prevalence of hepatitis B in children with complete vaccination. However, there is still an increase in hepatitis B infection, especially in urban areas. Therefore, a long-term evaluation of immunization coverage especially ensuring that the initial dose of immunization was given within the first 24 hours of

birth, HBsAg and HBcAb, nutritional status, genomic surveillance of HBV, and other aspects of program quality evaluation are needed to ensure that elimination efforts have been implemented properly.

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Abstract

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Conclusions. The effectiveness of hepatitis B vaccine obtained from the three Riskesdas periods in Indonesia showed an improvement, with an increase in immune status, reduced exposure to HBV and a lower prevalence of hepatitis B in children with complete vaccination. However, there is still an increase in hepatitis B infection, especially in urban areas. Therefore, a long-term evaluation of immunization coverage especially ensuring that the initial dose of immunization was given within the first 24 hours of birth, HBsAg and HBcAb, nutritional status, genomic surveillance of HBV, and other aspects of program quality evaluation are needed to ensure that elimination efforts have been implemented properly.

Keywords: Riskesdas, hepatitis B, vaccination, anti-HBs, HBcAb, HBsAg

78

Introduction

80   In order to evaluate the Health program in Indonesia, the Ministry of Health through the National

81   Institute of Health Research and Development conducted basic health researches (Riskesdas) with the aim

82   of providing health data in Indonesia and is carried out 5 years periodically, since 2007, 2013 and 2018.

83   The prevalence of infectious diseases, the health status of infant and toddler, nutritional status, and results

84   of serological examination of diseases preventable by immunization were included in the health data

85   obtained through this nationwide research program. A clear description picturing of the success of the

86   health program in Indonesia hopefully could be obtained from the implementation of Riskesdas. One of

87   the research programs which will be evaluated and discussed in this research article is the Hepatitis B

88   controlling program (Kementerian Kesehatan RI 2018).

89   Hepatitis B is the main cause of chronic hepatitis, cirrhosis and liver cancer worldwide. World

90   Health Organization (WHO) estimated that 296 million people were living with chronic hepatitis B

91   infection in 2019 with 1.5 million new infections annually and an estimated 820,000 deaths, mostly from

92   cirrhosis and hepatocellular carcinoma (primary liver cancer) (WHO 2022a, 2022b). As an anticipation of

93   increasing cases of chronic hepatitis and mortality due to hepatitis B, WHO in 2012 recommended

94   implementing universal immunization coverage where 95% of children have been immunized and 180

95   countries have adopted this step (Podlaha et al. 2019; WHO 2012, 2017). Hepatitis B is still a health

96   problem in Indonesia, this can be seen from a study in Banjarmasin involving healthy young adults where

97   at the time the children had not received Hepatitis B immunization, and the results obtained were that the

98   prevalence of HBsAg, anti-HBc, and anti-HBs was 9 (4.6%) respectively, 62 (31.8%), and 96 (49.2%)

99   (Darmawan et al. 2015). Indonesia has carried out a national Hepatitis B immunization program since

100   2005 where hepatitis B immunization should be administered at 0 months and will be completed once the

101   immunization has been given 3 times until the baby is 11 months old (Kementerian Kesehatan RI 2005).

102   Then, in order to break the chain of transmission from the mother to the infant or child, the national

103   program for Hepatitis B immunization administration was revised to be given at 0 day, for 4 times

104   administration according to the announced decisions of Minister of Health (Kementerian Kesehatan RI

105   2015).

106   The prevalence of hepatitis B in Indonesia varies from 1.9 to 11.2% according to the region and

107   year of study (the highest is Yogyakarta 11.2% and the lowest is Bali 1.9%) (Utsumi et al. 2014). The

108   prevalence rate in Indonesia is still high when being compared to several countries in Asia such as China

109   (in children aged 1-4 years old 0.97%) (Zhu et al. 2018), Philippines (children aged 5-7 years 0.8%)

110   (Minta et al. 2021), Lao PDR (Anti HBs 0.7%) (Kowalczyk, Wiktor, and Stępień 2019). Further analysis

111   of Riskesdas data for 2007, 2013 and 2018 on serological examination of Hepatitis B was carried out to

112   obtain an overview of the success trend of the hepatitis B immunization national program and the factors

113   that influenced it. Furthermore, the analysis results can be used as an input for recommendations for

114   national program in hepatitis B prevention in Indonesia.

115

116   Material and Method/ Methodology

117   Study design

118   This study is a further analysis of the data collected in Basic Health Research (Riskesdas) in

119   2007, 2013 and 2018, when at that time Indonesia consisted of 33 provinces (in 2007 and 2013) and 34

120   provinces (in 2018). Riskesdas is carried out using a cross-sectional research design, which represents

121   community data nationally. Data was obtained from the data management laboratory of the Health

122   Development Policy Agency, Ministry of Health, Indonesia.

123   Samples

124   The sampling frame was designed based on calculations from the Indonesian Central Statistics

125   Agency (BPS) by means of multistage sampling through the stages in accordance with those in the 2007,

126   2013, 2018 Riskesdas national reports (Kementerian Kesehatan RI 2008, 2013b, 2018). Data from

127   structured interviews and measurements on selected household and individual samples were then

128   subjected to further analysis. Blood sampling and serological examination was carried out in the selected

129   samples that were aged over 1 year old. The sub-sample used for the further analysis process was children

130   aged 1-4 years old whom owned the complete record of immunization. The total number of samples for

131   children aged 1-4 year old at Riskesdas 2007, 2013 and 2018 respectively are as follows 1486 subjects,

132   568 subjects and 992 subjects. The 2007 sample data represents national urban areas, while 2013 and

133   2018 represent national urban and rural areas.

134   Assessment of serological hepatitis B indicators

135   Blood samples for Hepatitis B serological examination were examined at the research laboratory

136   of the Health Research and Development Agency, Ministry of Health, Indonesia. The serological

137   examination for hepaptitis in 2007 Riskesdas was performed by using the Enzyme Linked

138   Immunosorbant Assay (ELISA) method with Murex-Abbot laboratories reagent. Meanwhile, the 2013

139   and 2018 Riskesdas was performed by using the commercial chemiluminescence immunoassay (CLIA)

140   kit method (DiaSorin LIAISON® anti-HBs II and DiaSorin LIAISON® anti-HBc. The interpretation of the

141   results of the serological examination is stated as follows: anti-HBs $\geq$ 10 IU/L is considered

142   positive/protective, hepatitis B core antibody (HBcAb) at a value of < 1 IU/L, hepatitis B surface antigen

143   (HBs Ag) $\geq$ 0.05 IU/ml (CLIA), $\geq$ mean negative control + 0.05 (ELISA) is positive.

144   Operational Definitions

145   Complete hepatitis B immunization for data analysis in 2007 Riskesdas, namely hepatitis B

146   immunization with 3 doses given to infants aged 0 months, 2 months and 3 months in accordance with the

147   Regulation of the Minister of Health of the Republic of Indonesia number 53 of 2005 (Kementerian

148   Kesehatan RI 2005). Meanwhile, complete hepatitis B immunization for 2013 and 2018 Riskesdas,

149   namely 4 doses given to infants aged 0-7 days, then continued for 2, 3, 4 months together with the DTwP

150   vaccine in the form of the DTwP-HB combo in accordance with the 2011 Technical Guidelines which

151   was then stipulated/written in Permenkes no 12 of 2017 (Kementerian Kesehatan RI 2017). Meanwhile,

152   complete hepatitis B immunization for 2013 and 2018 Riskesdas, namely 4 doses given to infants aged 0-

153   7 days, then continued for 2, 3, 4 months given with the DTwP vaccine in the form of the DTwP-HB

154   combo (2011) which was replaced by DTwP-HB-Hib pentavalent (2015) (Kementerian Kesehatan RI

155   2011, 2015, 2016, 2017). The effectiveness of hepatitis B vaccine was based on the results of the

156   measurements of anti-HBs, HBsAg and anti-HBc levels.

157   The immunization service facilities are health facilities that provide immunization services for

158   infants and toddlers, such as hospitals, health centers, auxiliary health centers, practicing doctors,

159   practicing midwives, integrated service posts (posyandu), village health posts, village maternity posts in

160   villages. Economic status was measured by expenditure quintiles, namely the grouping of expenditures

161   into 5 equal groups after being sorted from smallest to largest expenditure. Quintiles 1-2 are classified as

162   poor, quintiles 3-4 as middle class and quintile 5 as rich.

163   The nutritional status of children under five was measured based on the weight/age index, which

164   then converted into a standardized value (Z-score) using the 2005 WHO anthropometric standard

165   (Kementerian Kesehatan RI 2011; WHO 2005). Furthermore, based on the Z-score value of each of these

166   indicators, the nutritional status of children under five was determined with the following limitations:

167   malnutrition is a combination of malnutrition and undernutrition with Z-score < -2.0, good nutrition with

168   Z-score ≥ -2.0 to Z-score ≤ 2.0, and over nutrition with Z-score > 2.0.

169   **Statistical analysis**

170   In this further analysis, the samples taken were children aged 1-4 year old. At the time of

171   analysis, weighting was carried out on the data every year, the value of which has been determined by

172   Central Agency of Statistic Republic of Indonesia. Weighting was done to ensure that there is no

173   imbalance in the samples taken because they come from different years and so that they were surely close

174   to the population taken.

175   The descriptive analysis was carried out to identify the characteristics of the respondents and

176   factors that might influenced the effectiveness of hepatitis B vaccination using the variables available in

177   the main Riskesdas questionnaire, namely age, sex, mother's education, hepatitis immunization status,

178   hepatitis immunity status, respondent's travel time to the nearest health facility, and economic level.

179   Grouping is done on several research variables to answer the purpose of further analysis. Analysis was

180   performed using Stata software version 16. Bivariate analysis with pearson chi square was performed to

181   assess the relationship of the research variables namely hepatitis immune status, immunization status,

182   nutritional status and characteristics of the respondents. The significance level was 0.05 for all statistical

183   analyses used in this study.

Data limitation

185   In 2007 Riskesdas, serology data collection was only carried out in urban areas due to limited

186   field laboratory facilities and human resources. Not all the required variables are available in the

187   main data, so the data analyzed is limited to the available variables.

Ethical consideration

189   This studi analyzed sets of publicly available data, therefore ethical clearance was not

190   compulsory. Permission to use and analyze the dataset was obtained by submitting a proposal to the

191   Centre of Data and Information, Health Policy Agency (Indonesia: Pusat Data dan Informasi, Badan

192   Kebijakan Pembangunan Kesehatan), Ministry of Health, Indonesia via email: datin.bkpk@kemkes.go.id.

193

Results

195   The results of the further analysis showed that in the 2013 and 2018 Riskesdas data, which

196   included both rural and urban, most samples included were obtained from urban areas, with 50.1% and

197   71.6% in the respective Riskesdas periods. Meanwhile, based on gender and age, the distribution was

198   almost even. For the education level, the highest distribution was among respondents who had graduated

199   from high school. In both 2007 and 2018, the majority of people (49.2% and 43.8%, respectively) came

200   from low-income families. while in 2013, the highest distribution was medium (46.7%). For travel time to

201   immunization services, most distributions take less than 30 minutes. The most distribution of nutritional

202   status is good nutrition.

203   For complete immunization status, there was an increase from 2007 to 2013, from 30% to 60.3%,

204   but in 2018, there was a slight decrease to 57%. For hepatitis immune status (positive anti-HBs antibody),

205   there was an increase from 2007 to 2018, namely 41.8%, 56%, and 79.1%. While the prevalence of

206   hepatitis B (HBsAg) increased more than twice as much in 2013, rising from 3.9% in 2013 to 9.3% in

207   2018. However, the history of hepatitis B infection (HBcAb) has decreased from 10.1% in 2007 to 7.8%

208   in 2013 and 1.3% in 2018. All the data above can be seen in **Table 1**. The relationship between

209   immunization status and the education status of mothers showed that that the higher the status of mother's

210   educational level, the higher the percentage of complete immunization status analyzed with *p < 0.05*

211   (**Table 2**).

212 In **Table 3**, the relationship between hepatitis B immunization status and the length of travel time
213 taken by respondents to immunization service facilities nationally showed that complete immunization
214 status is higher when travel time is less than 30 minutes compared to travel time that is more than 30
215 minutes. All tests showed significant results ($p < 0.05$) with an increase in the completeness of
216 immunization between 1.3 and 2.8 times (OR around 1.3-2.8) at a travel time of less than 30 minutes
217 compared to a travel time of more than 30 minutes.

218 Trends in the effectiveness of hepatitis B vaccination from the 2007, 2013 and 2018 Riskesdas
219 data based on age show that the older the age, the lower the percentage of hepatitis protective antibodies
220 (anti-HBs antibodies) (**Figure 1A**). From **Figure 1A**, the trend of increasing hepatitis B protective
221 antibodies was observed quite high, about 5 times and 6 times respectively from 2007 to 2013 and 2018.
222 Meanwhile exposure to HBV, there was a trend of percentage of positive HBcAb that had decreased by
223 almost ten times from 8.6% -13.5% in 2007, then 2.6% -11.1% in 2013, finally to 1.1% -2% in 2018
224 (**Figure 1B**). The prevalence of hepatitis B, as assessed by positive HBsAg examination results, showed
225 both in the 2013 and 2018 Riskesdas that the highest was in the 2-year-old group (6.3%), and there was
226 an increase in prevalence of about 2 times, from 0.7% (6.3%) in 2013 to 5.8% (14.7%)% in 2018 (**Figure
227 1C**).

228 Hepatitis B immunization immunity in the 2007, 2013 and 2018 Riskesdas data based on the
229 completeness of hepatitis B immunization status showed that the percentage of protective immunity (anti-
230 HBs antibody) was higher in complete immunization status than incomplete, around 1.5 to 2 times ($p <
231 0.05$. OR : 1.5-2), as shown in **Table 4**. From the 2007, 2013 and 2018 Riskesdas on positive HBc Ab
232 data indicating that they have been exposed to hepatitis B infection, show that the risk is higher (OR: 1.4-
233 2.2), while rural areas/ villages in 2013 and 2018 show a low risk OR: 0.366-0.804. The percentage of
234 HBc Ab positive was lower in complete immunization status compared to incomplete in rural areas. In
235 urban areas, however, the percentage of positive HBc-Ab is even higher with complete immunization
236 status than with incomplete immunization status, as shown in **Table 4**.

237 While the prevalence of hepatitis B (HBsAg positive) in urban areas is higher in the incomplete
238 immunization status (2.7%) than in the complete (1%), On the contrary, in rural areas, the complete
239 immunization status (8.9%) is higher than the incomplete (3.8%), while the anti-HBs is higher in the
240 complete immunization status (65.3%) than the incomplete (46.8%). As shown in **Table 4**, the prevalence
241 of hepatitis B is higher in those with an incomplete immunization status than in those with a complete
242 one, in both urban and rural blood.

243 The trend of protective anti-HBs immune status for children under the age of five with complete
244 hepatitis B immunization shows that the older the toddler, the lower the percentage of immunity, both in
245 the 2007 and 2013 Riskesdas data and in the 2018 Riskesdas data (**Figure 2**). The effectiveness of the

246   hepatitis B vaccine showed an improvement based on three periods of Riskesdas, namely with an

247   increase in immune status (anti-HBs), a decrease in the percentage of exposure to infection (HBV) and

248   lower HBsAg in complete hepatitis B immunization status compared to incomplete (**Figure 1 A, 1 B ,**

249   **and Table 4**). Based on data from the 2007, 2013, and 2018 Riskedas demonstrated that nutritional status

250   affecting the immune system against hepatitis B, it can be seen that the percentage of positive anti-HBs in

251   poor nutrition is lower than in good nutrition and more ($p < 0.05$), as shown in **Table 5**.

252

Discussion

254   The hepatitis B virus is a major cause of hepatitis infection which contributes to the high rate of

255   morbidity and mortality. WHO has announced one dose of hepatitis B vaccination for newborns followed

256   by two additional doses for infants to prevent vertical transmission from infected mothers to infants,

257   thereby preventing the occurrence of chronic hepatitis B and reducing the prevalence of hepatitis B. WHO

258   also recommends universal immunization for infants, which has a greater impact in populations with

259   reduced hepatitis B prevalence by 34 compared to immunization of newborns born to mothers infected

260   with hepatitis B (Hutin, Desai, and Bulterys 2018). In 2016, there were only 101 countries providing

261   routine vaccinations to all newborns; 20 countries have targeted programs, and the remaining countries do

262   not provide newborn vaccinations (Hutin et al. 2018; Li et al. 2018). The highest proportion of babies

263   who do not receive a birth dose is in the WHO African region (Hutin et al. 2018). Indonesia has

264   implemented a universal hepatitis B vaccination program for infants since 1997, and has used a prefilled

265   single-use injection device of hepatitis B vaccine that is stable even outside the cold chain since 1999

266   (Purwono et al. 2016). Furthermore, hepatitis B immunization has begun to be given to newborns since

267   2000, and has also been given a follow-up immunization schedule in the form of a combination of DTwP-

268   HB-Hib and measles at the age of 18–24 months since 2017, according to the WHO's call to achieve the

269   virus elimination target of hepatitis in 2030 (Kementerian Kesehatan RI 2017).

270   Analyzing Riskesdas data is one way to learn about hepatitis B infection control. Some of the

271   variables discussed in this analysis are directly related to immunization coverage and effectiveness of

272   hepatitis B immunization, namely the education status of mothers, the distance or travel time needed to

273   get to immunization service facilities, and the nutritional status of children. While the success of the

274   hepatitis B immunization program is demonstrated by the frequency and effectiveness trend of hepatitis B

275   vaccination observed by age group during the 2007-2013 and 2018-2019 Riskesdas.

276   Data obtained from the Riskesdas studies showed a nearly 2-fold increase in immune status

277   (protective-level anti-HBs) in 2018 (41.8% in 2007, 56.1% in 2013, and 79.1% in 2018) (**Table 1**,

278   **Figures 1A and 2**), which is also in line with increasing vaccination coverage and strengthening

279   vaccination programs. In addition, completeness of immunization status also affected the increase in the

280   protective level of immune status (**Table 4**) to 1.5–2 times higher ($p < 0.05$; OR: 1.5–2), which of course

281   is necessary to reduce HBV transmission. The immune status decreases with increasing age (**Figure 2**), so

282   booster vaccinations are still required at an older age to ensure protection against hepatitis B infection

283   (Bruce et al. 2016).

284   The timing of the hepatitis B vaccination at the initial dose also contributed to the reduced risk of

285   HBV exposure, which was originally given to infants from 0–1 months of age in 2005 but has been given

286   at birth since 2015 (Garcia et al. 2018). In addition, the hepatitis vaccine preparation in combination with

287   Diphteria Tetanus whole Pertusis (DTwP) or DTwP-Hib (Haemophillus Influenzae type b) vaccine

288   provided convenience when injecting it into infants, thereby reducing the dropout rate for subsequent

289   doses (Kementerian Kesehatan RI 2013a, 2015). Although the three Riskesdas periods showed a decrease

290   in HBcAb levels, the percentage of HBcAb was actually higher in those with complete immunization

291   status (11.4% in 2007 compared to 3.6% in 2013 and 1.3% in 2018) compared to those with incomplete

292   immunization status (8.5% in 2007 compared to 2% in 2013 and 0.6% in 2018). There could be other

293   factors that affected the exposure to hepatitis B virus infection such as population density which affects

294   the transmission of hepatitis B virus infection (Genowska et al. 2015). While 2013 Riskesdas, HBsAg

295   was found to be lower in the completed vaccinated group (1%) than that in incomplete vaccinated group

296   (2.7%) ($p < 0.05$). However, in rural areas, HBsAg was higher in complete immunization status (8.9%)

297   than incomplete immunization status (3.8%), possibly due to the delay of vaccination at the initial dose

298   for the newborn. This delay might cause the transmission from mother to infant (vertical HBV

299   transmission) which could be the risk factor of chronic hepatitis B, for HBV infection acquired as a baby

300   will have a risk of becoming chronic around 95%, while infection acquired as an adult has a risk of

301   becoming chronic less than 5% (WHO 2022b).

302   Riskesdas 2013 for children under five, which describes the immunization program 4 years

303   earlier, starting in 2009, in rural areas, the scope of newborn vaccination may not be as wide due to

304   geographical conditions that make it more difficult to get access to immunization services, compared to

305   urban areas, besides strengthening the routine immunization program for all infants for hepatitis B with 4

306   new doses starting in 2015 (Kementerian Kesehatan RI 2015). The 2018 Riskesdas data showed that the

307   prevalence of hepatitis B (HBsAg) in both urban and rural areas was lower in the group with complete

308   hepatitis B vaccination (7.6% urban, 9.4% rural) compared to incomplete immunization (11.1% urban,

309   10.9% rural, $p < 0.05$). The effectiveness of hepatitis B vaccination had shown improvement with a

310   decreasing trend towards exposure to HBV infection (anti-HBc), lower HBV infection (HBsAg) in the

311   fully vaccinated group and an increasing trend towards hepatitis B immune status.

312 Unfortunately, the prevalence of hepatitis B (HBsAg) in infants showed an increase from 3.9% in
313 2013 to 9.3% in 2018, which was also in line with an increase in immune status (positive anti-HBs) from
314 56.1% (2013) to 79.1% (2018). However, HBcAb decreased from 7.8% (2013) to 1.3% (2018) (**Table 1**).
315 Positive anti-HBs indicated an immune response that is formed either due to hepatitis B vaccination or
316 due to HBV infection. The possibility of an increase in anti-HBs indicated an increase in HBV infection,
317 which was shown by an increase in HBsAg, because 2/3 of those infected with HBV were asymptomatic
318 and can become carriers. This could be a source of transmission both vertically from mother to baby and
319 horizontally from people around them who are infected with HBV (Garcia et al. 2018; Genowska et al.
320 2015). This was also consistent with several other studies in Indonesia, which show that Indonesia is
321 moderate to high endemic with an HBsAg value of around 2.5% to 10% (Lusida and Yano 2016;
322 Wijayadi et al. 2018; Yano et al. 2015). So it is very important to ensure that the first dose of
323 immunization is given in the first 24 hours when the baby is born. In addition, it could be also due to the
324 presence of a variant HBV mutation that caused vaccine-escape mutants that had occurred in several
325 regions in Indonesia, which had been reported in several studies. In Indonesia, 4 genotypes (A,B,C,D)
326 have been identified and the most distributed are genotypes B and C. HBV subtype adw3 which is part of
327 genotype C was a new subtype found in West Timor. Another mutation in genotype B, T126I
328 substitution, combined with T143 found in East Java, can affect the antigenicity of HBsAg. Mutations of
329 T140I amino acid substitution and M133T substitution, which are known as vaccine-escape mutations
330 during immunization, also occur in unvaccinated children in Taiwan and Korea. Pre-S2 start codon
331 mutations that occurred in Indonesia and other Asian countries were associated with chronic hepatitis
332 (Lusida and Yano 2016). The hepatitis B vaccine that has been used in the world today is the yeast-
333 derived S-HBsAg which comes from 2 genotypes. The two types of vaccines have the ability to induce
334 strong neutralizing antibodies with a good safety profile. However, about 10% have a low or no humoral
335 immune response in vaccinated adults. The existence of polymorphisms from the S-HBs antigenic region
336 influenced the ability to neutralize HBV vaccine antibodies.
337 The government, in this case the Indonesian Ministry of Health, is also working to prevent the
338 transmission of HBV infection from mother to child through early detection of hepatitis B from mother to
339 child with the HBsAg rapid diagnostic which has been carried out since 2013. Starting from DKI Jakarta
340 and continuing to other provinces the following year. Based on the Hepatitis and Gastrointestinal
341 Infection Information System (SIHEPI) 2018-2019, the number of pregnant women tested for hepatitis B
342 was 1,643,204 in 34 provinces. As a result, as many as 1.88% (30,965 pregnant women) were reactive
343 (infected with hepatitis B virus), and 15,747 newborns from reactive hepatitis B mothers had been given
344 Hepatitis B Immunoglobulin (HBIg) in less than 24 hours and routine immunizations (Kementerian
345 Kesehatan RI 2019). Apart from that, the anti-viral drug tenofovir will also be given to pregnant women

346 infected with HBV at 28 weeks' gestation. This program has been implemented at the Wahidin Hospital in
347 Makassar, South Sulawesi and Karyadi Hospital in Semarang, Central Java and will be expanded to 6
348 provinces, namely DKI Jakarta, Lampung, East Java, South Kalimantan, South Sulawesi and East Nusa
349 Tenggara (Kementerian Kesehatan RI 2016).
350   The further analysis results showed that the education background of the mother has a significant
351 effect on the completeness of the child's immunization status, including hepatitis B immunization. If the
352 baby has received four doses of hepatitis B immunization, the immunization is complete. Complete
353 hepatitis B immunization coverage was still low for all levels of education of mothers in 2007, but it had
354 increased in 2013 and 2018 Riskesdas. Before 2007, DTwP and vaccine HB was initially given separately
355 – which was given at the same time for baby aged 0, 2, and 3 months. Since mid 2015, the HB vaccine
356 was administered 4 doses. The single dose purposed for newborn which was followed by the other three
357 doses of HB vaccine combined with DTwP and *Haemophyllus influenza* type b vaccines become one-shot
358 pentavalent vaccine (DTwP-HB-Hib) (Kementerian Kesehatan RI 2013a). It is possible that this is
359 related to the implementation of the new immunization program schedule, namely the first dose of
360 hepatitis B immunization for newborns, which was announced starting in 2011.
361   The different number of dose of hepatitis B vaccine was given according to WHO
362 recommendations. By distributing hepatitis B vaccine as many as 3 doses can provide protection from
363 HBV infection of more than 95% in healthy infants, children and young adults (Jain et al. 2021).
364 Vaccination can also reduce HBV infection in newborns of infected mothers by 3.5 times. However, the
365 efficacy of the vaccine in preventing perinatal transmission decreases as the length of time the first dose is
366 administered at birth increases (Potsch et al. 2010). The risk of HBV infection in newborns was found to
367 be 8 times higher when the first dose was given after 7 days of birth compared with giving within 3 days
368 after birth (Jain et al. 2021; Potsch et al. 2010). In areas where chronic infection is endemic, timing of the
369 first dose of hepatitis B vaccine is critical with minimal delay after birth. In countries with low
370 endemicity, administration of the first dose at birth is also necessary to prevent early transmission.
371 Resolution 63.18 of the World Health Assembly, which focused on viral hepatitis, recommends that all
372 infants in the world receive the first dose of hepatitis B vaccine immediately after birth, preferably within
373 24 hours (WHO 2013). Several other studies have also shown that the average seroprotective rate is
374 higher in those given 4 doses of the HB vaccine compared to 3 doses in both children and adults (Jain et
375 al. 2021; Potsch et al. 2010). Because Indonesia is included in an area with a high prevalence, the
376 program is carried out according to WHO recommendations, by carrying out 4 doses of vaccination to
377 prevent transmission of HBV infection as early as possible and ensure a person's protection against
378 horizontal transmission (World Health Organization 2013).

379   Concerning mother education and the completeness of babies receiving complete basic

380   immunizations, including hepatitis B, several studies in Indonesia show that knowledge and education of

381   mothers have a significant impact on child immunization compliance and completeness (Kibreab,

382   Lewycka, and Tewelde 2020; Nanda Kharin et al. 2021). Studies in several countries in Africa, such as

383   Nigeria and Eritrea, also show that mothers who are literate and educated will have better reading skills

384   and health-seeking behaviors, including seeking immunization (Balogun et al. 2017; Kibreab et al. 2020).

385   Apart from being influenced by the mother's education, immunization status is influenced by the

386   household wealth index, the mother's ANC visits, region, and ownership of the vaccination card (Kibreab

387   et al. 2020). A literature study conducted by Kaufman (2018) shows that face-to-face education about

388   immunization can improve immunization status in infants. This is related to the increased knowledge,

389   attitudes, and motivation of mothers to immunize their babies. The same thing happens if the mother

390   receives immunization education during her pregnancy (Saitoh et al. 2013). Ignorance about the need for

391   immunization is the main cause of an incomplete or even unimmunized children's immunization status

392   (Ratta and Meshram 2020).

393   In addition to the educational status of the mother, the access to health care facilities as defined

394   by travel time, both in urban and rural areas also showed a significant effect on the completeness of

395   hepatitis B immunization status, based on the data of 2007, 2013 and 2018 Riskesdas. This travel time is

396   related to the distance to where you live and the ease of transportation to health services. The 2013

397   Riskesdas analysis shows that proximity, convenience, and knowledge about access to health services

398   affect the completeness of a child's immunization status (Nainggolan, Hapsari, and Indrawati 2016). One

399   of the efforts of Indonesian government to facilitate access to community-based health services is to

400   establish posyandu, poskesdes, and polindes, one of whose health services is immunization. This is very

401   useful, especially for rural areas. In countries in the poor-middle category, the factor of ease of access to

402   health services plays a very important role, the same is also found in rural India (Ratta and Meshram

403   2020). However, based on an analysis of immunization coverage data from 2013 on 45,095 children aged

404   2-3 years in China, the maternal education and access to health services was shown to have no effect on

405   children's complete immunization status. Other factors that actually have an effect are: sons, a father's

406   education that did not finish high school, being born in a house, and living in a suburb or mountain area

407   (Cao et al. 2018). The existence of differences in the dominant factors affecting the completeness of

408   immunization status in several countries may be due to, among other things, the availability of health

409   facilitation, socio-economic differences, and cultural and geographical cultures. In Sub-Saharan Africa,

410   based on 23 demographic and health surveys involving 26,241 children between 2010 and 2018, it shows

411   that the existence of a socio-economic gap between urban and rural areas greatly influences children's

412   immunization status. Another factor is the number of births and the distance to health facilities (Ameyaw

413   et al. 2021).

414   The nutritional status was one of important factors affecting the immune system against hepatitis

415   B in this study based on the data obtained from 2007, 2013, and 2018 Riskesdas. Besides, nutritional

416   deficiencies were reported to strongly affect patients diagnosed with liver diseases, such as HBV-caused

417   hepatitis and cirrhosis, especially in children. Yu, R. et al. had examined and reported prevalence of

418   malnutrition and malnutrition risks in the hospitalized children with liver diseases (Yu et al. 2017).

419   Previous study which analyzed the 2013 Riskesdas data had highlighted and well discussed that the

420   failure in to get sufficient nutrition intake was related to challenging life environment, socioeconomic

421   status, and infectious diseases in children under five year old (Kusrini, Mulyantoro, and Supadmi 2020).

422   Meanwhile, another previous study comparing the progression of cirrhosis caused by hepatitis B virus

423   infection in malnourished patients and nourished patients reported that there were no significant

424   difference in liver-specific complications, such as variceal bleeding, ascites, and hepatic encephalophathy

425   in these two different nutrional status groups of patients (Chen et al. 2021). However, the relationship

426   between hepatitis vaccine effectiveness and nutritional status in children was still unraveled. Based on our

427   knowledge and readings, there was only one previous study reported the antibody responses toward

428   hepatitis B vaccine in adult patients under hemodialysis (Afsar 2013). The nutritional and immunological

429   factors were also assayed in this previous study and shown to positively influence the seroconversion

430   towards hepatitis B vaccination.

431   Defects in cellular and humoral immunity as well as phagocyte function disorders can be caused

432   by protein energy malnutrition (PEM). In addition, reductions in the levels of the complement (except

433   C4), secretory immunoglobulin A and cytokines can result. Malnutrition, secondary to deficiencies in

434   proteins, metal elements or vitamins, can lead to changes and severe atrophy in the thymus gland because

435   of apoptosis-induced thymocyte depletion. This can lead to a persistent lymphocyte reduction, particularly

436   in the immature CD4þ CD8þ cells, and to a decrease in cell proliferation. It is noteworthy that these

437   conditions can be reversed following proper diet rehabilitation (Savino 2002). PEM also reduces the

438   concentrations of IgA, IgM and IgG and the production of cytokines (Scrimshaw and SanGiovanni 1997).

439   PEM-associated micronutrient deficiencies also have adverse effects on the immune response. Deficiency

440   in zinc, iron, copper, vitamins plays an important role in reduced immune response as a result of

441   malnutrition (Keusch 2003). Zinc, copper and selenium are needed to maintain and reinforce immune and

442   antioxidant systems (Mocchegiani et al. 2014). Vitamin A stimulates cell differentiation and cytokine

443   secretion by macrophages, including tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-12 (Mohty et

444   al. 2003).

445   In this study based on the data obtained from 2007, 2013, and 2018 Riskesdas demonstrated that

446   nutritional status was one of important factors affecting the immune system against hepatitis B. It can be

447   seen that the percentage of positive anti-HBs in malnourish children is lower than in normal nutritional

448   status (*p=0.000*), as shown in **Table 5**. This is similar with a study in Senegal and Cameroon, they found

449   the percentages of protected children were lower among children with moderate to severe malnutrition

450   versus normal nutritional status (60% vs 85%) and nutritional status was significantly correlated with the

451   response to HBV vaccination ($p < 0.001$) (Rey-Cuille et al. 2012). In Iran, Karimi found a significant

452   decrease in the immune response to HBV vaccination in malnutrition children (60.2%) (Karimi et al.

453   2013). Nutritional status is major influencing factor in immunologic response; and is major factor of

454   immunodeficiency. Protein energy malnutrition (PEM) was found to cause a decrease in cellular and

455   humoral immunity and phagocyte function disorders; complement level (except C4), secretary IgA, and

456   cytokine production (Cantani 2000; Keusch 2003; VanLoveren et al. 2001). PEM also reduces the

457   concentrations of IgA, IgM and IgG and the production of cytokines (Scrimshaw and SanGiovanni 1997).

458   Micronutrient deficiency in zinc, selenium, Fe, copper, vitamins A, B, C, E, B6, and Folic acid play

459   important role on the immune response in malnutrition (Mocchegiani et al. 2014; Scrimshaw and

460   SanGiovanni 1997). This study showed a significant association between anti-HBs levels and the normal

461   nutritional status, the higher anti-HBs was found in normal nutritional status (*p < 0.05*). Protective rates

462   in children with malnutrition versus normal nutrition based on the data obtained from 2007, 2013, and

463   2018 was 8.5%, 44%, 73.7% vs 10,4%, 56,1%, 79,6%, respectively, with a statistically significant

464   difference (*p < 0.05*) (**Table 5**).

465   The 2007 Riskesdas study, conducted in 21 of 33 provinces in Indonesia, found an HBsAg

466   prevalence of 9.4% in all age groups (Muljono 2017), which dropped nearly threefold to 3.9% in 2013

467   and then rose again to 9.3% in 2018 (**Table 1**, **Figure 1C**). The results of the 2018 Riskesdas are almost

468   identical to the meta-analysis of 26 cohort studies (20 studies from China, 2 each from Gambia and Italy,

469   and 1 each from Australia and Fiji) which assessed the long-term impact of hepatitis immunization. When

470   the prevalence of hepatitis B infection is compared to the prevalence of HBV infection (HBsAg positive

471   or HBc positive or both are positive), the unvaccinated group showed a prevalence of 0.6%-16%, while

472   the vaccinated group showed a prevalence of 0.3-8.5% (Whitford et al. 2018). However, **Table 1** and

473   **Figure 1B** showed a significant decrease of almost 10 times for HBc Ab positives (10.1% in 2007; 7.8%

474   in 2013; and 1.3% in 2018). This result indicated that the immunization program in Indonesia has

475   succeeded in reducing transmission of hepatitis B both vertically from mother to baby, as well as

476   horizontally or in the surroundings because immunity has been formed, which is quite good according to

477   the results of studies on immune status in the 3 periods of Riskesdas. This result is in accordance with the

478   improvement in the policy for the hepatitis B vaccination program for all infants in Indonesia which has

479   an increasingly wider coverage, which was originally given in 2005 with 3 doses, then since 2015 it has

480   become 4 doses (Kementerian Kesehatan RI 2005, 2015).

481

Conclusions

483   There was a fairly good increase in complete immunization status (from 30% to 57%) and

484   immune/anti-HBs status (from 41.8% to 79.1%) with exposure to HBV (HBc Ab), which decreased

485   significantly from 10.1% to 1.3% over the three Riskesdas periods in 2007, 2013, and 2018. This

486   indicateed the effectiveness of the hepatitis B vaccine was also getting better. The higher immunization

487   coverage was also influenced by the higher education level of the mother and the travel time to the

488   immunization service which was less than 30 minutes. Meanwhile, the better immune response is

489   influenced by good nutritional status. The routine hepatitis B immunization program for all babies in

490   Indonesia has been getting better with the provision of vaccination to newborns, 4 doses with a

491   combination preparation with the DTwP vaccine and Hib vaccine, which has been implemented since

492   2015, and an increasingly wide program coverage area in Indonesia. However, there were still hepatitis B

493   infection cases reported that vary from low to high. Therefore, long-term evaluation of HBV prevalence

494   (HBsAg and HBcAb), immunization coverage, immune status, nutritional status, timeliness of vaccine

495   delivery schedules especially the accuracy of giving the first dose before 24 hours after birth, and other

496   aspects of program quality are surely needed. To ensure that elimination efforts have been carried out

497   correctly, adolescents and young adults with a history of vaccination must be evaluated.

498

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503

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507

508 **Competing Interest**

509   The authors clearly stated that there is no conflict of interest.

510

511 **Authors Contributions**

512 ●   Christina Safira Whinie Lestari conceived and designed the study and experiments, performed the

513   experiments, analyzed the data, prepared figures and tables, authored or reviewed drafts of the

514   article, and approved the final draft.

515 ●   Rita Marleta Dewi conceived and designed the study and experiments, performed the experiments,

516   analyzed the data, prepared figures and tables, authored or reviewed drafts of the article, and

517   approved the final draft.

518 ●   Sunarno Sunarno conceived and designed the study and experiments, performed the experiments,

519   analyzed the data, prepared figures and tables, authored or reviewed drafts of the article, and

520   approved the final draft.

521 ●   Armedy Ronny Hasugian conceived and designed the study and experiments, performed the

522   experiments, performed the statistical analysis, analyzed the data, prepared figures and tables, and

523   approved the final draft.

524 ●   Sarwo Handayani analyzed the data, prepared figures and tables, authored or reviewed drafts of the

525   article, and approved the final draft.

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527   of the article, and approved the final draft.

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529   drafts of the article, and approved the final draft.

530 ●   Nathalia Ningrum authored or reviewed drafts of the article, and approved the final draft.

531 ●   Meiriani Sari authored or reviewed drafts of the article, and approved the final draft.

532 ●   Firda Fairuza conceived and designed the study and experiments, obtained the funding for the study,

533   prepared figures and tables, analyzed the data, authored or reviewed drafts of the article, and

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545

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547

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725

Distribution of the respondents based on characteristics

1   **Table 1.** Distribution of the respondents based on characteristics.

Characteristic	Percentage (%)		
	Riskesdas 2007	Riskesdas 2013	Riskesdas 2018
Demographic			
Area			
Urban	100	50.1	71.6
Rural		49.9	28.4
Sex			
Boy (M)	50.3	49.7	50.4
Girl (F)	49.7	50.3	49.6
Age (years old)			
1	17.8	14.7	20.4
2	25.9	22.7	24.4
3	30.8	26.2	25.8
4	25.5	36.4	29.4
Educational level of the mother			
Unfinished Senior high school	10.6	11.6	7.9
Senior high school	82.8	83.3	84.2
College	7.3	5.1	8
Family economy status			
Poor	49.1	34.0	43.8
Middle class	38.9	46.7	36.4
Rich	12.0	19.3	19.8
Travel time to immunization services			
< 30 minutes	99.1	94.8	93.6
≥ 30 minutes	0.9	5.2	6.4
Toddler Nutritional status			
Undernutrition	15.2	7.6	8.5
Good nutrition	67.8	80.1	79.7
Overnutrition	17.0	12.3	11.8
Complete hepatitis B immunization status based on the toddler age (years old)			
1	37.0	69.4	75.2

2	32.2	65.4	59.7
3	28.9	56.0	54.0
4	23.7	56.4	44.0
1-4	30.0	60.3	57.0
Immune Status to Hepatitis B (Anti HBs)			
Positive	10.1	56.1	79.1
Prevalence of hepatitis B (HBsAg)			
Positive		3.9	9.3
Have ever been infected with Hepatitis B (Anti-HBc)			
Positive	0.2	7.8	1.3

Relationship between immunization status and mother's education (Riskesdas 2007, Riskesdas 2013, Riskesdas 2018).

*Pearson Chi-Square

1 **Table 2.** Relationship between immunization status and mother's education (Riskesdas 2007,

2   Riskesdas 2013, Riskesdas 2018).

Survey years	Hepatitis B Immunization Status	The educational background of toddler's mother (%)			
		Unfinished senior high school	Senior high school	College	*P* value
Riskesdas 2007 (urban area)	Completed	15.6	31.3	28.0	0.000
	Uncompleted	84.4	68.7	72.0	
Riskesdas 2013 (urban & rural areas)	Completed	50.0	60.5	69.5	0.000
	Uncompleted	50.0	39.5	30.5	
Riskesdas 2018 (urban & rural areas)	Complete	48.3	56.8	70.8	0.000
	Uncompleted	51.7	43.2	29.2	

3 *Pearson Chi-Square

The correlation between hepatitis immunization status and respondent's travel time to immunization service facilities.

* Continuity Correction

1   **Table 3.** The correlation between hepatitis immunization status and respondent's travel time to immunization service facilities.

The year of Riskesdas implementation	Area	Travel time to health facilities (minutes)	Hepatitis B Immunization Status (%)				
			Completed	Uncompleted	*P** value	OR	95% CI
Riskesdas 2007	Urban	< 30 min	29.9	70.1	0.000	0.813	0.75–0.88
		≥ 30 min	34.5	65.5			
Riskesdas 2013	Urban and rural areas (national)	< 30 min	61.1	38.9	0.000	1.883	1.81-1.96
		≥ 30 min	45.5	54.5			
	Urban	< 30 min	61.6	38.4	0.000	2.78	2.56-3.05
		≥ 30 min	36.5	63.5			
	Rural	< 30 min	60.5	39.5	0.000	1.68	1.60-1.75
		≥ 30 min	47.7	52.3			
	Urban and rural areas (national)	< 30 min	57.5	42.5			
		≥ 30 min	51.0	49.0	0.000	1.30	1.27-1.33
Riskesdas 2018	Urban	< 30 min	57.2	42.8	0.000	0.61	0.58-0.64
		≥ 30 min	68.7	31.3			
	Rural	< 30 min	58.4	41.6	0.000	1.754	1.70-1.80
		≥ 30 min	44.5	55.5			

* Continuity Correction

Effectiveness of hepatitis B immunization (anti-HBs antibody, HBsAg and HBc antibody) based on immunization status in children under five in Riskesdas 2007, 2013 and 2018 data.

1 **Table 4.** Effectiveness of hepatitis B immunization (anti-HBs antibody, HBsAg and HBc antibody) based on immunization status in

2 children under five in Riskesdas 2007, 2013 and 2018 data.

The year of Riskesdas implementation	Area	Positive markers	Hepatitis B Immunization Status (%)				
			Completed	Uncompleted	P value	OR	95% CI
Riskesdas 2007	Urban	Anti-HBs	11.4	8.5	0.000	1.390	1.36 – 1.42
		HBcAb	0.0	0.1	0.000	1.451	1.45 – 1.46
Riskesdas 2013	Urban	Anti-HBs	59.1	48.8	0.000	1.516	1.47-1.56
		HBsAg	1.0	2.7	0.000	0.356	0.32-0.39
		HBcAb	3.6	2.0	0.000	1.806	1.61-2.02
	Rural	Anti-HBs	65.3	46.8	0.000	2.138	2.08-2.20
		HBsAg	8.9	3.8	0.000	2.509	2.37 – 2.66
		HBcAb	7.1	17.3	0.000	0.366	0.35-0.39
Riskesdas 2018	Urban	Anti-HBs	86.4	77.1	0.000	1.893	1.86-1.93
		HBsAg	7.6	11.1	0.000	0.669	0.65-0.69
		HBcAb	1.3	0.6	0.000	2.273	2.08-2.29
	Rural	Anti-HBs	84.9	72.6	0.000	2.127	2.06-2.19
		HBsAg	9.4	10.9	0.000	0.851	0.82 – 0.89
		HBcAb	1.4	4.5	0.000	0.804	0.76-0.85

Relationship between hepatitis B immune status (anti-HBs antibody marker) and nutritional status (Riskesdas 2007, 2013 and 2018).

1 **Table 5.** Relationship between hepatitis B immune status (anti-HBs antibody marker) and

2   nutritional status (Riskesdas 2007, 2013 and 2018).

Antibody marker	The year of Riskesdas implementation	The nutritional status of toddlers (%)			P value
		Undernutrition	Good nutrition	Overnutrition	
Anti HBs positif (%)	Riskesdas 2007	8.5	10.4	11	0.000
	Riskesdas 2013	44.0	56.1	56.3	0.000
	Riskesdas 2018	73.7	79.6	79.6	0.000

Figure 1

Trends in the effectiveness of hepatitis B immunization (markers for anti-HBs, anti-HBc and HBsAg) based on the age of the toddler (Riskesdas 2007, 2013 and 2018) with *p = 0.000*.

(A) Percentage of protective hepatitis B immunity (anti-HBs anti body) based on age in 2007, 2013 and 2018. (B) Percentage of positive anti-HBc based on age in 2007, 2013 and 2018.

(C) Percentage of positive HBsAg based on age in 2013 and 2018.

(A)

(B)

(C)
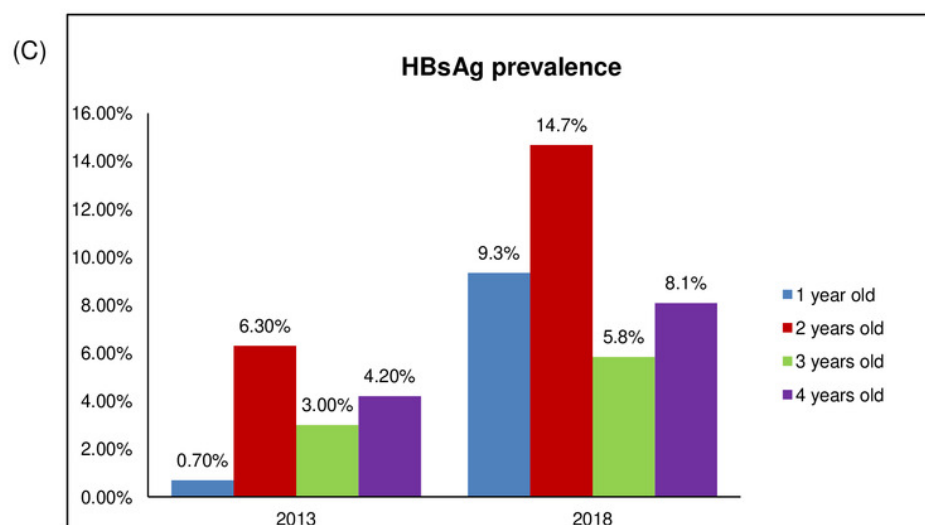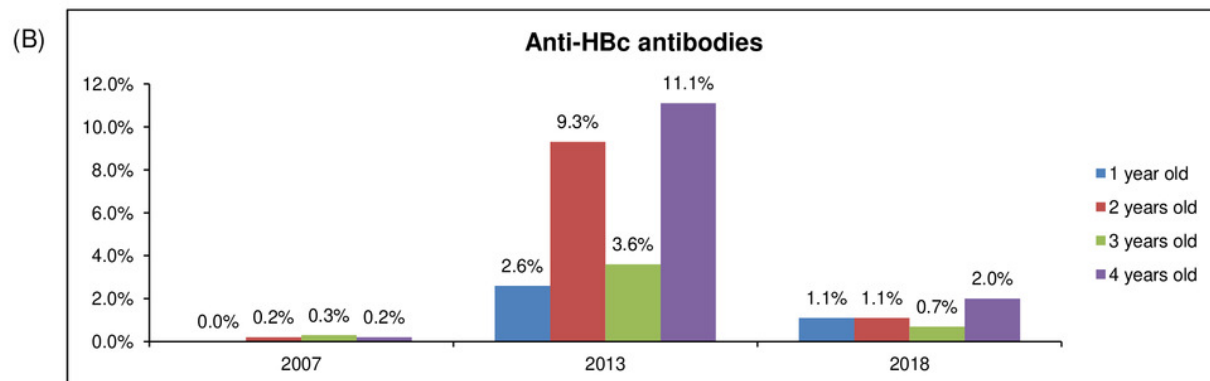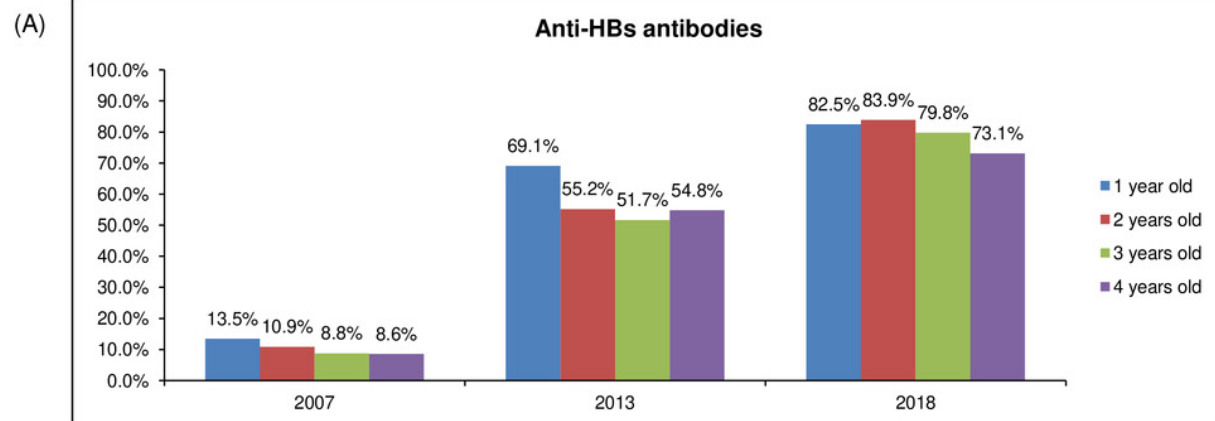
Figure 2

Figure 2. Trends in hepatitis B immune status (anti-HBs) in infants with complete hepatitis B immunization status based on age.