Appendix

Annex A: Search Strategy

We searched for English language publications with the use of broad search terms: “hepatitis B virus” AND (“child” OR "adolescent") together with (AND) either “epidemiology”, “transmission”, “natural history", “prevention", “diagnosis", or “treatment" from January 1st, 2010, to December 31st, 2017. The age limit “birth-18 years” was applied. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports. Animal studies and in-vitro studies were excluded. We also searched reference lists of articles identified through this strategy and included additional relevant studies. The final list of eligible studies was based on an assessment by co-authors of those of direct relevance to the key topics of this review.

Table 1A. Phases in natural history of chronic hepatitis B virus infection in adults, adolescents and children[1]

	HBeAg positive[§]	HBeAg negative[§]	HBsAg negative
Infection (normal ALT)	**HBsAg**: high **HBV DNA**: $>10^7$ IU/ml **Liver disease***: none/minimal **Progression to cirrhosis**: none or slow **Old terminology**: immune-tolerant **Treatment**: not generally indicated **Notes**: Stage seen in most of the children infected at birth (90%) or in the first few 5 years of life (20-60%); young adults infected in the perinatal or early childhood period are in this phase	**HBsAg**: low **HBV DNA**: <2 000 IU/mL **Liver disease**: none **Progression to cirrhosis**: none **Old terminology**: inactive carrier/immune-control **Treatment**: not indicated **Notes**: anti-HBe positive; risk of cirrhosis and HCC reduced; may develop HBeAg negative hepatitis; monitoring required for reactivation and HCC; the rate of spontaneous seroconversion to anti-HBe is < 2% per year in children younger than 3 years of age and 8% and during puberty; the rate of spontaneous seroconversion to anti-HBe is 12% per year in adults	**HBV DNA**: undetectable by commercial kits **Liver disease**: none **Progression to cirrhosis**: none **Old terminology**: occult HBV infection **Treatment**: not indicated **Notes**: anti-HBc positive, anti-HBs positive or negative
Hepatitis (abnormal ALT)	**HBsAg**: high **HBV DNA**: >2 000 IU/ml (constantly raised or fluctuating) **Liver disease**: moderate to severe **Progression to cirrhosis**: possible **Old terminology**: immune-active **Treatment**: may be indicated **Notes**: pediatric guidelines recommend treatment in this phase; may develop anti-HBe with normalization of ALT leading to "immune-control" phase	**HBsAg**: intermediate **HBV DNA**: >2 000 IU/mL **Liver disease**: moderate to severe **Progression to cirrhosis**: more rapid than in other phases **Old terminology**: immune-escape **Treatment**: may be indicated **Notes**: HBeAg-negative chronic hepatitis progresses slowly in children. The overall annual incidence of HBeAg-negative hepatitis was 0·37% (95% CI 0·35-0·39) in spontaneous HBeAg seroconverters. HBeAg seroconversion during childhood predicts a lower risk of HBeAg-negative hepatitis in later life[2].	

Legend: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; ALT, alanine aminotransferase; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; *necroinflammatory changes; [§]according to the old terminology "reactivation" or "acute-on-chronic hepatitis" (characterized by HBeAg positive or negative hepatitis, moderate to high levels of HBV DNA, seroreversion to HBeAg positivity if HBeAg negative, with high risk of decompensation in presence of cirrhosis) is now classified as HBeAg positive or negative hepatitis. Reactivation can occur spontaneously or be

precipitated by immunosuppression (chemo- or immunosuppressive therapy, human immunodeficiency infection or transplantation), development of antiviral resistance, or withdrawal of antiviral therapy.

Table B. Summary of main findings of large prospective (>90 children enrolled and >10 years of follow up) and other relevant studies evaluating the natural history of hepatitis B infection in children

Author	n	Duration of follow up, years [mean ± SD; median (range)]	Type of study	HIV Status	Population HBeAg +	Route of acquisition	Region	Main characteristics and findings
Wu, 2016 [2]	434	14·4 (8·7-20·5)	prospective	negative	434	NP	Taiwan	79% presented spontaneous HBeAg seroconversion (median age 13·93 years, interquartile range 8·76-20·59); in spontaneous HBeAg seroconverters annual incidence of HBeAg-negative hepatitis was 0·37% (95% CI 0·35-0·39); HBeAg-negative hepatitis in HBeAg seroconversion was predicted by male gender (HR = 3·15), HBV genotype C (HR = 4·40), HBeAg seroconversion after 18 years of age (HR = 2·46), and lamivudine therapy prior to HBeAg seroconversion (HR = 1·42)
Wu, 2012 [3]	104	23·7 (14·5-33·3)	prospective	NP	104	vertical 75% horizontal 25%	Taiwan	serial ALT levels in chronic HBV-infected subjects offer a predicted effect on the occurrence of spontaneous HBeAg seroconversion (median times to seroconversion were 8·35, 5·14, 4·25, 3·95, and 2·8 years after the ALT levels crossed 20, 30, 40, 60, and 150 IU/L, respectively); ALT levels above 30 IU/L served as a cutoff of the inflammatory phase in chronic genotype B and C HBV-infected patients.
Roushan, 2012 [4]	139	18 ± 6·6	prospective	NP	139	vertical 100%	Iran	59% presented spontaneous HBeAg seroconversion: 25% in the first, 63·4% in the second and 70·5% in third decade (p<0·001); seroconversion rate was higher in children of anti-HBe-positive mothers (75% vs· 33·9%, p<0·0001); time to seroconversion in children who received hepatitis B vaccine and HBIG was shorter than those who did not (HR=6·35, p<0001).
Tseng, 2011 [5]	185	20·2 (4·2-3·1)	prospective		185	vertical 74% other 26%	Taiwan	65·4% presented spontaneous HBeAg seroconversion; during similar infection duration seroconversion was achieved in 83·3% of children with non-carrier mothers, 73·7% of children with HBeAg-negative chronic HBV-infected mothers and 48·8% of children with HBeAg-positive mothers; positive maternal HBeAg was associated with delayed spontaneous HBeAg seroconversion in multivariate analysis (p=0·01)

Bortolotti, 2006 [6]	99	14·5 ± 6·1	prospective	negative	91	NP	Italy	97·8% presented spontaneous HBeAg seroconversion after a mean period of 5·2 +/- 4 years; 4 patients were cirrhotic (2 developed HCC and 2 became inactive carriers); 85 patients were not cirrhotic (84 became inactive carriers and 3 developed HBeAg negative hepatitis; 2 of the 8 children who were HBeAg negative at the enrolment developed HBeAg negative hepatitis
Wen, 2004 [7]	426	14.9 (5.1-27.2)	prospective	NP	386	NP	Taiwan	2/426 children with chronic hepatitis B prospectively followed during 6250 person-years of observation, developed HCC; the incidence of HCC was 32 per 100 000 person-year
Ni, 2004 [8]	460	NP; >10 years	prospective	NP	398	NP	Taiwan	in Taiwan HBV genotype B was more common than C overall and in the specific group of children with HCC; genotype C was shown to delay HBeAg seroconversion in paediatric chronic HBV infection
Marx, 2002 [9]	174	4·9 (4 weeks - 16)	prospective	negative	174	vertical 19·5% horizontal 12·7% unknown 67·8%	Canada	40·2% presented spontaneous HBeAg seroconversion after a mean period of follow-up of 4·5 years; seroconversion rates were lower in Asian-born and vertically infected children (as compared with those born in Canada and horizontally infected); the cumulative persistence of HBeAg after 13 years was 25% in Asian-born children, versus 6% in all others (p<0·05)
Fujisawa, 2000 [10]	52	11 (3-22)	prospective	NP	52	vertical 77% horizontal 8% unknown 15%	Japan	50% presented spontaneous HBeAg seroconversion; 1 child developed HCC 16 years after seroconversion; another child developed HCC 6 years after interferon-induced HBeAg seroconversion
Chang, 1995 [11]	415	7·1 ± 2·9	prospective	NP	365	NP	Taiwan	38·3% presented spontaneous HBeAg seroconversion; 30 anti-HBe positive children underwent liver biopsy: 16 had minimal histologic changes, 9 mild activity and mild fibrosis, 2 inactive cirrhosis, 2 mild activity and moderate fibrosis, and 1 chronic hepatitis with marked fibrosis
Popalis, 2013 [12]	252	6·9 ± 4·2	retrospective	negative	252	vertical 60% horizontal 15% unknown 25%	Canada	41·7% presented spontaneous HBeAg seroconversion over 0·5-19·1 years of follow-up; transmission route, gender, and nor treatment did not affect e-seroconversion rate; 49% achieved inactive chronic infection by age 19 years
Ni, 2007 [13]	58	NP; >10 years	retrospective	NP	58	vertical 78% other 22%	Taiwan	all the patients were HBeAg seroconverters; their mean age at HBeAg seroconversion was 17·2 +/- 5·8 years; peak ALT was achieved at 23·7 +/- 4·1 years; HBV genotypes had no effect on the viremia profiles; after HBeAg seroconversion, none had persistent abnormal ALT levels.

Iorio, 2007 [14]	180	12·1 (5-23)	retrospective	negative	103	NP	Italy	69·3% presented spontaneous HBeAg seroconversion after a mean period of follow-up of 12·1 years; 9·7% untreated patients became anti-HBs positive; 57 children underwent liver biopsy: 91·2% presented mild-to-moderate disease
Ruiz-Moreno, 1999 [15]	103	6·3 (0·6-12·5)	retrospective	NP	0	vertical 36% horizontal 39% unknown 25%	Spain	all the patients were HBeAg seroconverters; follow up was 0·6 to 12·5 years (mean, 6·3 years); 79% had persistently normal ALT levels throughout the follow-up; 2·9% became anti-HBs positive; 83 underwent paired liver biopsies (before and after seroconversion): significant improvement (p <·001) was found in the histological activity index and in the necrosis, cytolysis, inflammation, and fibrosis scores

Legend: SD, standard deviation; HIV, human immunodeficiency virus; NP, not provided; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ration; ALT, alanine aminotransferase; HBIG, hepatitis B immunoglobulin; HCC, hepatocellular carcinoma.

Table C. Summary of results of clinical trials of hepatitis B antiviral therapy in children

	interferon-α-2b [16]	**lamivudine [17]**	**adefovir [18]**	**tenofovir DF[19]**	**entecavir[20]**	**pegylated-interferon-α-2b a[21]**
number treated	144	191	173	52	120	101
dose	6 MU/m^2 thrice weekly	3 mg/Kg daily (max 100 mg)	2-7 years: 0·3 mg/kg daily > 7-12 years: 0·25 mg/kg > 12-18 years: 10 mg	300 mg daily	0·015 mg/kg daily (max 0·5 mg)	180 µg/1·73m^2
duration of treatment (weeks)	24	52	48	72	48	48
age, median (range)	5 (1-17)	9 (2-17)	11	15·5 (12-17)	12 (2-17)	11 (3-7)
virological response (HBeAg negative; HBV DNA undetectable) (% treated *versus* placebo)	26% (*vs* 11%)	23% (*vs* 13%)	10·6% (*vs* 0)	21·2% (vs 0)	24·2% (vs 3·3%)	19·8% (vs 2%)
HBsAg negative (% treated *versus* placebo)	10% (*vs* 1%)	2% (*vs* 0)	0·8% (*vs* 0)	1·9 % (vs 0)	5·8% (vs 0)	8.9% (vs 0)

Legend: HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBsAg, hepatitis B s antigen.

Note: there is no data on the use of TAF in HBV infected children

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