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Review

Prevalence of chronic hepatitis B virus infection in Thailand: a systematic review and meta-analysis

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SUMMARY

Objective: To estimate the number of people living in Thailand with chronic hepatitis B (CHB), a major cause of liver cirrhosis and cancer, in view of the implementation of programs to prevent CHB complications.

Methods: Using PubMed/Medline and ScienceDirect, all studies reporting hepatitis B surface antigen (HBsAg) seroprevalence estimates conducted in Thailand and published between 1975 and 2015 were reviewed systematically. Pooled prevalence estimates and their 95% confidence intervals (CIs) were calculated, and potential sources of heterogeneity investigated.

Results: A high heterogeneity was observed between prevalence estimates. There was a significant decrease in the 150 estimates of HBsAg prevalence with more recent decades of birth ($p < 0.001$), even before the implementation of the national universal immunization program in 1992. When restricted to the general population, the pooled prevalence estimate was 5.1% (95% CI 4.3–6.0%), which would translate to an estimated number of individuals with CHB living in Thailand in 2015 as high as three million.

Conclusions: The high burden of CHB in Asian countries is a major challenge for the incorporation of national programs to prevent CHB complications within health care systems.

1. Introduction

Chronic infection with the hepatitis B virus (HBV) affects an estimated 240 million persons worldwide.[1] It is believed to cause liver cirrhosis and hepatocellular carcinoma (HCC) in at least 25% of affected people, resulting in 780 000 deaths annually,[2] most of them in low- and middle-income countries.[3] In 2012, the World Health Organization (WHO) re-emphasized the need to estimate the burden of viral hepatitis and improve the assessment of their global and regional economic impacts.[4] Nearly 75% of people chronically infected with HBV worldwide are from the Southeast Asia and Western Pacific regions,[5] where chronic hepatitis B (CHB) infection is 30 times more prevalent than HIV and represents a major public health issue.

In 1992, the Department of Disease Control of the Ministry of Health incorporated HBV universal immunization (starting with a birth dose) in the Expanded Program on Immunization (EPI). Since 2011, the EPI has been managed by the National Health Security Office as a vertical program, with the Government Pharmaceutical Organization in charge of the distribution of all vaccines to public hospitals. The vaccines are administered free of charge. The coverage rate increased from 15% in 1992 to 95% in 2000 and has reached levels of 99% since 2013. However, immune globulin is not always available for infants born to hepatitis B surface antigen (HBsAg)-positive mothers.[6] As observed in all settings where such programs have been implemented, this has resulted in a dramatic reduction in the prevalence; for example, 0.3% in Thai children born before 2015.[7] However, the prevalence is still high in people

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born before 1992, and the increasing incidence of associated complications in relation to the increase in life expectancy has become a major concern.[8] Currently, only pregnant women are screened routinely for HBsAg during antenatal care and only a small proportion of those with CHB who meet the criteria for treatment do receive antiviral treatment. To plan for national programs, information on CHB prevalence by birth year is needed.

A systematic review and meta-analysis was conducted to synthesize CHB prevalence data in the general population in Thailand, overall and by birth year.

2. Methods

2.1. Literature search strategy

A systematic review of the peer-reviewed literature for HBsAg prevalence data was conducted following the 2009 PRISMA statement guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[9] by searching PubMed/MEDLINE and ScienceDirect (Elsevier) with a combination of medical subject heading (MeSH) terms and free text words used in research equations with 'OR' and 'AND' logical operators (**Supplementary Material**, Checklist S1). All relevant articles were reviewed and their reference lists hand-searched to identify additional studies. The references cited by review articles were also examined. Additionally, sources in the Thai language were investigated. All duplicate entries were removed and all citations managed with the bibliographic management tool Zotero. The literature was last searched on January 19, 2016.

2.2. Eligibility criteria

All articles meeting the following criteria were screened and then assessed for eligibility: peer reviewed publications published from 1975 to December 2015, reporting HBsAg seroprevalence estimates, specifying the period over which the study was conducted, and providing a description of the population involved and the number of people tested for HBsAg. Review articles, conference abstracts, editorials, and case reports were excluded. Reports of analytical studies (cross-sectional studies, prospective or retrospective) and clinical trials were included, with no restriction on age or type of population.

2.3. Data extraction and study outcomes

After study selection, the following data were extracted by two independent reviewers (CL and PA) using a data extraction form (**Supplementary Material**, File S1): study identification (first author, publication year, journal of publication), period over which the study was conducted, population, design, direct or indirect information on participant years of birth, numerator and denominator for estimated HBsAg estimates, and sex distribution. Data were entered into a table and imported into Stata version 13.1 (StataCorp, College Station, TX, USA) for analysis. Each of the two experts independently checked and compared the extracted data. Discrepancies or disagreements were resolved by consensus; a third expert was consulted if needed (GJ).

The primary study outcome was the proportion of subjects with HBsAg considered as affected by chronic infection, as in high prevalence countries the vast majority of transmissions occur perinatally or during early childhood and are followed by chronic infection.

The populations were categorized into general population, new blood donors and unspecified blood donors (new and regular blood donors pooled when unspecified), health care workers, people living with HIV, people who use drugs, and men who have sex with men (MSM). Medical students were considered as health care workers and pregnant women as part of the general population.

Participant years of birth were calculated using the mean or median age and the period over which the study was conducted. The year of birth was imputed for one study on Thai workers going abroad based on national statistics on age at migration of such workers; in another study on blood donors, the year of birth was based on the average age known for this population. When a study was conducted over several years, the mean year of the study was used. Whenever possible, estimates were extracted by age group or by study period. Birth year was categorized into five classes: $\leq$1960, 1961–1970, 1971–1980, 1981–1991, and $\geq$1992 (in Thailand, individuals born in or after 1992 could have been immunized through the national program).

2.4. Quality assessment

The quality of the studies was assessed using a score varying from 0 to 4, with 1 point awarded in each case if the number of participants screened was 1000 or more, selection of the participants screened was random, information on age and sex was available, and the recruitment period was provided. In the meta-regression analysis, the effects of each criterion and that of the total quality score on the prevalence estimates were assessed.

2.5. Data synthesis and analysis

The estimated prevalence of CHB infection was calculated as the number of HBsAg-positive subjects divided by the total number of subjects screened.

Overall and sub-group-specific prevalence estimates were computed using a random-effects meta-analysis (*metaprop* procedure, Stata)[10] to account for uncertainty in pooled estimates due to between-study heterogeneity (e.g., patient characteristics, location of study, study design). The 95% confidence intervals (CI) for the individual studies included were estimated by exact or Clopper–Pearson confidence limits for a binomial proportion.[11] The Freeman–Tukey double arcsine transformation was performed to compute the weighted pooled estimate.[12] The inter-study heterogeneity and the heterogeneity across studies were assessed using the I^2 measure.[13]

2.6. Test for publication bias

The presence of publication bias was assessed graphically by funnel plot and formally by its direct statistical analogue, the Egger adjusted rank correlation test,[14] using the *metabias* program in Stata.[15]

2.7. Additional analyses

Potential effects of demographics (birth year, proportion of men, type of population, and age) and methodological characteristics (study period, sample size, and quality score) on HBsAg prevalence estimates were explored with random-effects meta-regression using the *metareg* procedure in Stata.[16] The overall p-value was estimated for each variable using a Monte Carlo permutation test to address multiple testing. Only covariates identified as possibly associated ($p < 0.25$) in a first-step univariable analysis were included in the multivariable model, and a backward selection process was then used ($p < 0.05$). In addition, the probability plot of standardized shrunken residuals was estimated to check the quality of the final model.

The absolute prevalence of CHB by age in 2015 in the general population was computed using the prevalence rates and the age

group distribution in Thailand in 2015, as published by the United Nations (UN) Population Division.[17]

3. Results

3.1. General scope

Of 341 references identified through database searching and 27 additional records identified through other sources, 288 articles were excluded after screening titles and abstracts. Of the remaining 80 articles, 54 eligible articles were included in the systematic review and meta-analysis (Figure 1). The characteristics of the studies are summarized in the **Supplementary Material**, Table S1.

In terms of population, 26 studies were conducted in the general population (including one in pregnant women),[7,18–42] six in new blood donors,[43–48] four in unspecified blood donors,[49–52] seven in people living with HIV,[53–59] seven in health care workers,[60–66] two in people who used drugs,[67,68] one in MSM,[69] and one in both the general population and people living with HIV.[70] In terms of design, 34 studies were cross-sectional,[7,18–37,43,44,49,50,53,54,60–65,70] 13 were retrospective analyses of medical records,[38–41,45–48,51,52,55,56,66] four were prospective cohort studies,[42,57,58,69] and three were clinical trials.[59,67,68] In terms of sex distribution, 47 studies (87%) were conducted in both sexes, five in females, and two in males. In terms of quality, 25 of the 54 studies (46%) had a total quality score ≥3. Most studies reported the age and sex distribution of the population (85%), as well as the period of recruitment (90%), but only 22% were based on a randomly selected population sample and only 37% had a sample of at least 1000 individuals (**Supplementary Material**, Table S1).

The median year of publication was 2006 (interquartile range (IQR) 1999 to 2012). There was no evidence of a publication bias, as shown by the funnel plots (**Supplementary Material**, Figure S1) (Egger test, $p = 0.33$).

3.2. Overall and subgroup prevalence estimates

In the 54 studies, there were 150 age-, year-, and/or sex-specific prevalence estimates of HBsAg status from a total of 989 574 persons in Thailand. Figure 2 presents each study prevalence estimate and the overall pooled prevalence estimates for each population obtained through meta-analysis in a forest plot. The pooled prevalence estimates ranged from 0.6% (95% CI 0.0–3.1%) to 14.7% (95% CI 7.3–27.4%), with high heterogeneity between studies ($I^2 = 99.3\%$).

Subgroup pooled prevalence estimates with no adjustment are shown in Figure 3. The meta-analysis showed that the prevalence differed significantly across populations ($p = 0.002$). When restricted to general population studies, the estimate was 5.1% (95% CI 4.3–6.0%). It was higher in MSM (8.1%, 95% CI 6.6–9.7%) and people living with HIV (8.1%, 95% CI 6.4–9.9%) compared with the general population. The lowest prevalence was found in unspecified blood donors (2.8%, 95% CI 1.7–4.0%), but the prevalence in new blood donors was close to the general population prevalence (5.8%, 95% CI 5.4–6.3%). In health care workers, it was 5.2% (95% CI 3.5–7.2%). The prevalence was lower in children (<15 years) compared to those in the older groups ($p = 0.02$). Significant differences were noted depending on the study design ($p = 0.001$): the estimates were as high as 10.4% in cohort studies and 7.5% in clinical trials, but 5.6% in cross-sectional studies and 3.6% in retrospective studies. The prevalence was lower in studies with a quality score ≥3 (4.0%, 95% CI 3.5–4.7% vs. 6.2%, 95% CI 5.8–6.6%; $p < 0.001$).

3.3. Prevalence of HBsAg according to birth year

The 150 groups had a median birth year of 1965 (IQR 1952–1983). The meta-analysis showed that the pooled prevalence decreased significantly in groups born during the more recent years ($p = 0.002$): from 6.3% (95% CI 5.7–6.8%) in those born before

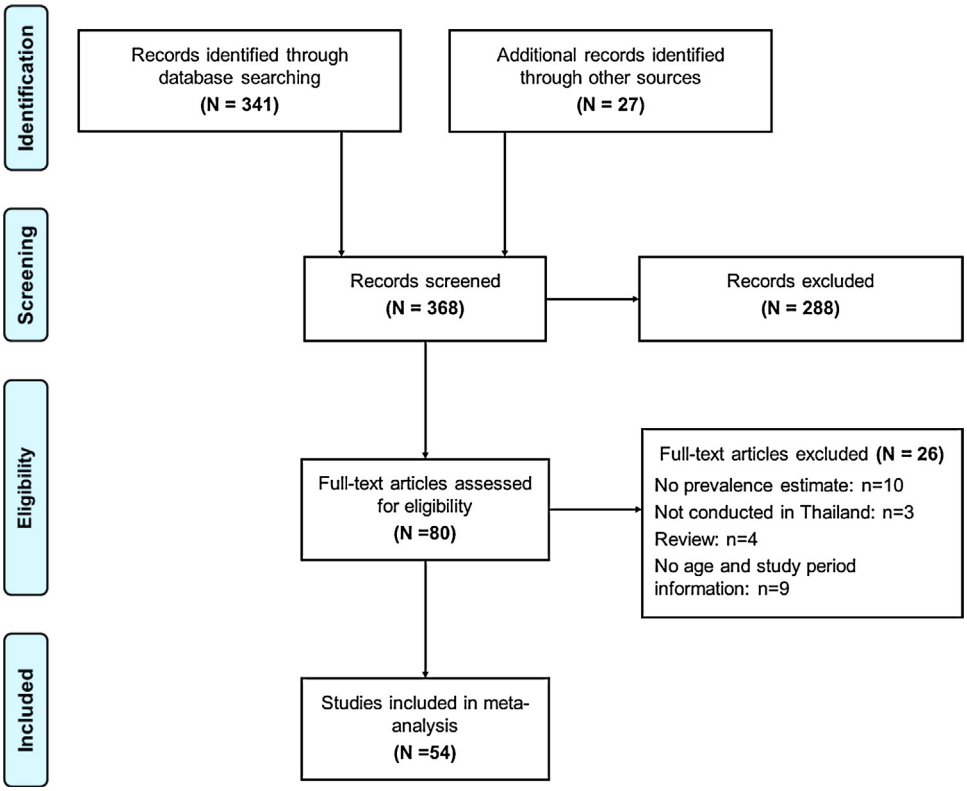

Figure 1. Flow diagram of the systematic review, Thailand, 1975–2015.

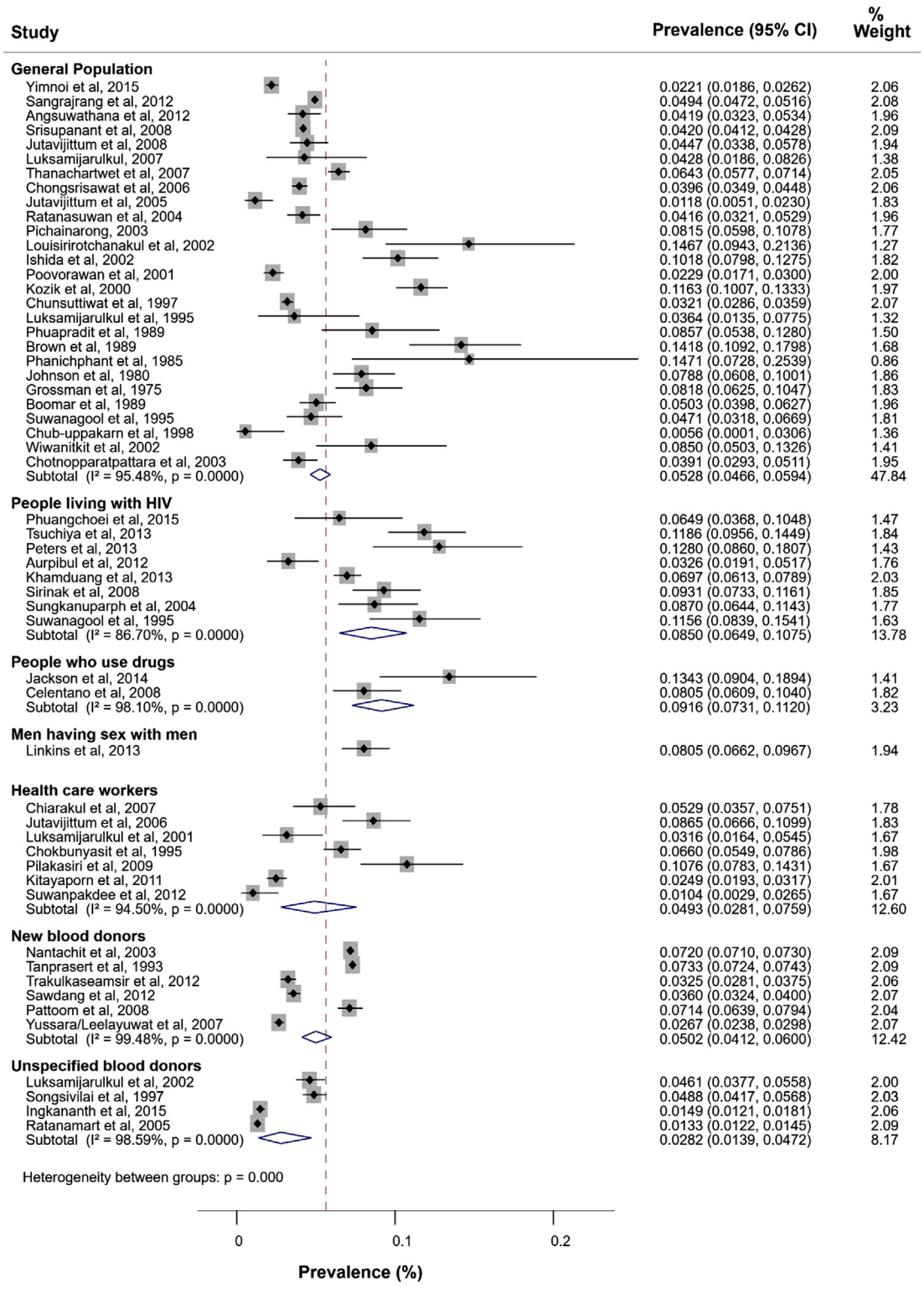

Figure 2. Forest plot of the prevalence estimates for the different populations, Thailand, 1975–2015. Meta-analyses with random-effects models. Abbreviations: CI, confidence interval; ES, estimated prevalence.

1961 to 4.1% (95% CI 3.0–5.3%) for the period 1981–1991, and to 1.3% (95% CI 0.3–2.7%) after 1992 (when the national immunization program started) (Figure 4). A significant decline in HBsAg prevalence in the more recent birth years was observed in the general population ($p < 0.001$), as well as in all other groups (Figure 4), including people living with HIV who consistently carry the greatest HBV burden across all birth periods.

3.4. Factors of heterogeneity

The type of population ($p = 0.002$), age ($p = 0.018$), birth year ($p = 0.002$), study design ($p = 0.001$), availability of information on age and sex ($p < 0.001$), and quality score ≥ 3 ($p < 0.001$) were associated with the prevalence estimate. Adjusting for the type of population and study design, the prevalence tended to decrease in

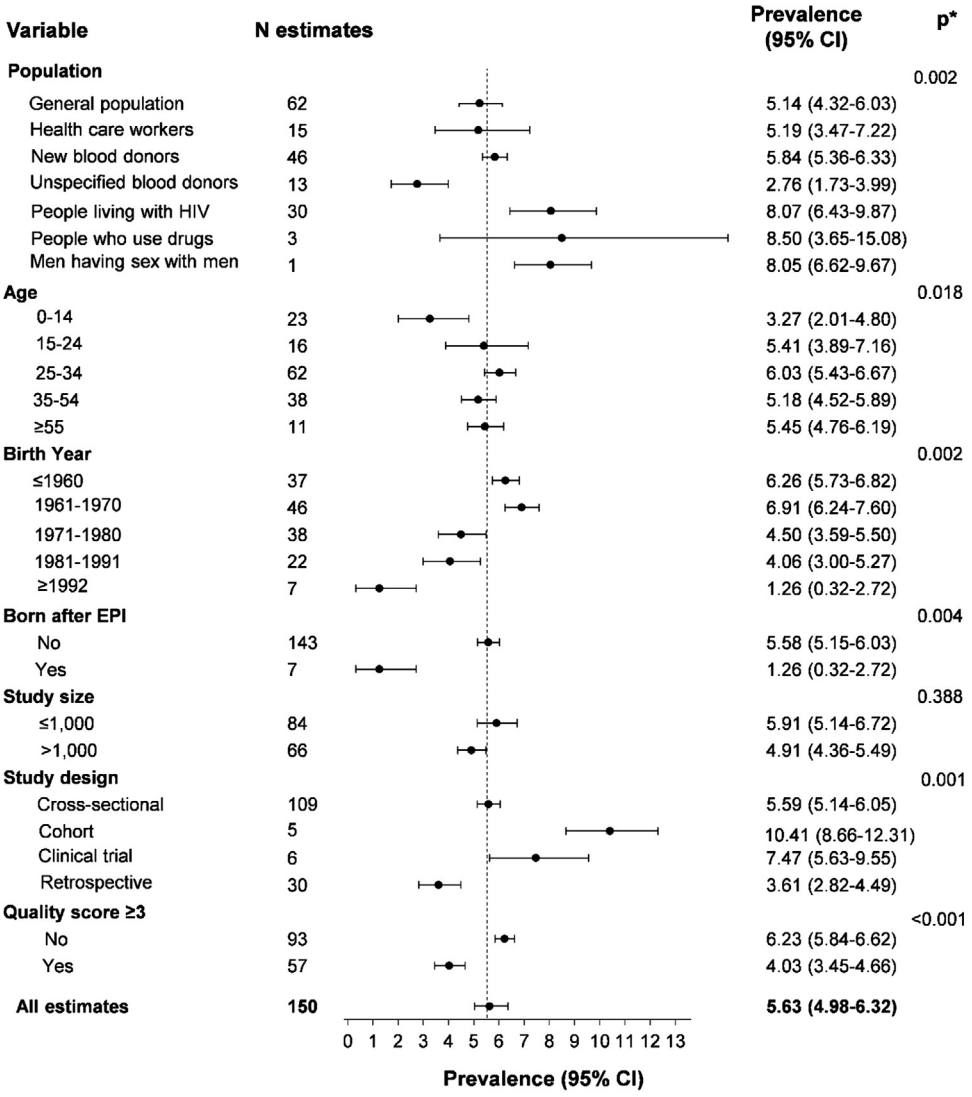

Figure 3. Pooled estimated hepatitis B surface antigen prevalence in Thailand, 1975–2015, estimated by meta-analysis, according to population, age, birth year, sample size, study design, and quality score. *p*-Values obtained by permutation in the univariable meta-regression. Abbreviations: CI, confidence interval; EPI, Expanded Program on Immunization.

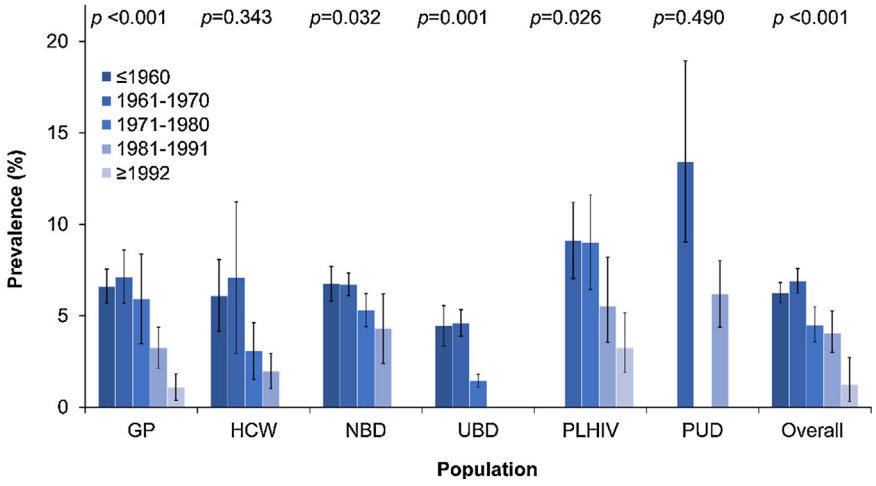

Figure 4. Estimated hepatitis B surface antigen prevalence according to birth year in six populations in Thailand, 1975–2015. Abbreviations: GP, general population; HCW, health care workers; NBD, new blood donors; PLHIV, people living with HIV; PUD, people who use drugs; UBD, unspecified blood donors.

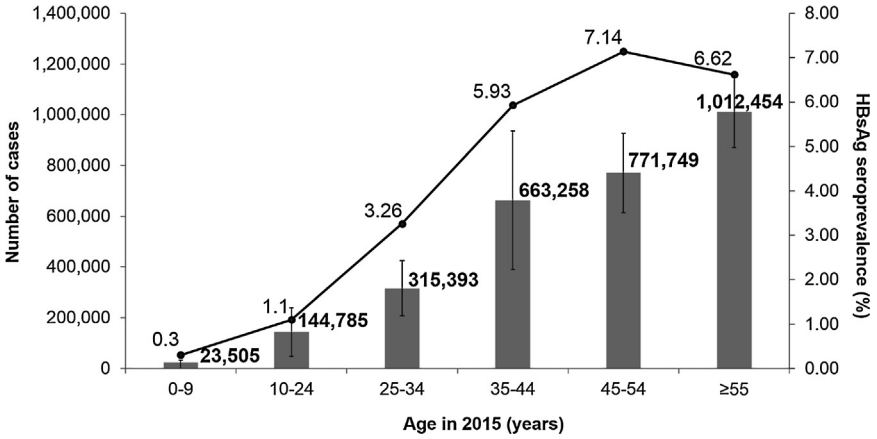

Figure 5. Estimated hepatitis B surface antigen prevalence and extrapolation of the number of people living with chronic hepatitis B in the general population in Thailand according to age in 2015, based on meta-analysis estimates and UN Population Division estimates.[17] Abbreviations: HBsAg, hepatitis B surface antigen.

groups born during the period 1961–1970 compared to the groups born before 1961, and the decrease became significant for the groups born during the next decades. In contrast, the multivariable analysis showed that age, quality criteria, and quality score were not significantly associated with the prevalence estimate. Detailed results are available in the **Supplementary Material**, Table S2. The adjustment of the model was satisfactory, as shown by a low I^2, the percentage of residual variation due to heterogeneity (0.0%), and R^2, the explained proportion of between-study variance (73.4%). The assumption of normal random-effects was supported by the probability plot of standardized shrunken residuals: the largest residual was >2 (**Supplementary Material**, Figure S2).

3.5. Prevalence according to birth year in the general population

When restricted to the general population group, the prevalence estimates ranged from 5.9% to 6.6% in groups born before 1980, then decreased to 3.3% in groups born between 1981 and 1991, and to 1.1% after 1992 (Figure 5). The extrapolation to the entire population led to an estimated total of 2 931 144 individuals (95% CI 2 146 079–3 732 527) living with HBsAg in Thailand in 2015 based on the age structure of the Thailand population provided by the UN[17] (Figure 5 and **Supplementary Material**, Table S3). The calculation assumed no deaths among individuals who participated in the studies, and made use of the prevalence estimate of 0.30% (95% CI 0.17–0.62) provided by a recent survey in individuals born after 2005 (aged 0–9 years in 2015).[7]

4. Discussion

According to this systematic review, approximately three million people in Thailand in 2015 would be HBsAg carriers, with significant differences across age groups. The prevalence estimates started to decrease in individuals born before 1992, the date on which the national HBV immunization program was implemented, but there was a much more pronounced decrease in individuals born later. The pre-universal immunization decrease may be related to modifications of life styles and the increasing use of disposable devices for all invasive procedures.

In terms of planning for hepatitis B care, estimates of prevalence by birth year are much more relevant because the risk of CHB complications is age-dependent, as is the need for treatment to prevent such complications. It was found that more than 60% of CHB cases, i.e. more than 1.8 million individuals, were people older than 45 years in 2015. Screening, evaluation, and treatment to prevent complications are needed for a huge number of individuals.

The 2013 WHO prevalence estimates were 6.4% for Thailand (i.e., about 4.3 million individuals), 4.1% for Cambodia, 3.4% for Myanmar, 8.7% for Laos, and 10.8% for Vietnam.[71] Several factors may have contributed to differences in estimates, as well as actual differences in prevalence: a smaller number of available studies estimating HBsAg prevalence in some neighboring countries and methodological differences in terms of the estimates, and the older age of the population in Thailand and time at which disposable devices became available for use for invasive procedures in terms of the actual differences. However, one would expect smaller differences and prevalence estimates closer to those from a recent study of migrants from neighboring countries to Thailand.[72]

The main limitation of this review is the heterogeneity between the studies. Indeed, studies were conducted in various geographical areas, using various methods, and targeting different populations. However, the stratification on several characteristics for the overall estimate minimized the effect of this heterogeneity. Conversely, the availability of studies on specific segments of the population, e.g. drug users, those with HIV, and blood donors, provides a more detailed account of the situation. Another limitation is that the birth year in several studies was estimated using indirect information. Finally, the mortality rate was not accounted for when calculating the number of cases in 2015; thus the estimate will be an overestimation in older populations, as the infection itself is associated with an increased risk of death compared with the general population.

In conclusion, a very effective program for universal immunization was implemented in Thailand more than two decades ago. However, a large number of individuals infected with HBV were born earlier. Interventions targeted at the older population have the potential to prevent significant morbidity and mortality. A national program would have to face various challenges, in particular the large numbers of individuals to be reached, tested, evaluated, and treated. Estimates similar to that presented for Thailand in this report could contribute to the preparation of national programs in other countries.

Specific author contributions

All authors contributed to the study. CL and GJ contributed to the concept and design, acquisition of data, analysis and interpretation of data, and drafting of the article. PA and SK contributed to the acquisition of data and analysis. WK and NN contributed to the acquisition of data. SO and SJ contributed to the concept and design of the study. All co-authors have reviewed the manuscript and approved the final submitted version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.08.017.

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