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Frontiers in Infectious Diseases and Microbiology

RESEARCH ARTICLE ISSN: 2771-1838

Antenatal hepatitis B surface antigen serological status and maternal asthma prevalence

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Abstract

The global prevalence of both chronic hepatitis B virus (HBV) infection and asthma vary greatly, and asthma tends to be less common in regions endemic with chronic HBV infection. This retrospective cohort study was conducted to explore the relationship between chronic HBV infection, determined by routine antenatal screening of hepatitis B surface antigen (HBsAg), with asthma history in 145644 gravidae managed in our hospital from 1997 to 2019. Asthma history was present in 1.73% (2528/145644) gravidae, who were slightly but significantly younger, taller, heavier, with more nulliparas, teenagers, and gravidae with medical history, but no difference in incidence of advanced age (≥35 years), short stature (<151 cm), and body mass index (BMI) ≥25 mg/m^2 (compatible with the categories of overweight and obesity by World Health Organization criteria), or Chinese ethnicity. Gravidae with asthma had lower prevalence of HBsAg seropositivity (5.8% versus 8.6%, p<0.001), and gravidae with HBV infection had reduced asthma prevalence overall (1.2% versus 1.8%, relative risk (RR) 0.657, 95% confidence intervals (CI) 0.556-0.775), and the association was significant for gravidae at ages 20-34.9 years, and BMI in the normal and overweight categories. Multiple logistic regression analysis confirmed the independent association between maternal HBsAg seropositivity with reduced asthma prevalence (aRR 0.677, 95% CI 0.572-0.801). This finding is in line with the reported reduction of asthma among subjects with childhood infections such as hepatitis A virus and is likely to have contributed to the variably lower prevalence of asthma in Asian countries and Asian immigrants in Western countries.

Keywords: *asthma; hepatitis B virus infection; pregnancy, antenatal screening*

Introduction

Asthma is considered the commonest chronic medical condition complicating pregnancy [1]. This may be due to the fact that the incidences are higher in females than in males after puberty, and after childhood, the incidence is highest at ages 36-40 years, while higher proportion of early-onset asthma relapsed and most of late-onset (onset >12 years of age) persisted or relapsed in adulthood [2]. Nevertheless, reported prevalence of asthma varies widely with differences of between 20- to 60-fold, being highest in western countries and lowest in some eastern European and Asian countries [3]. In the US, the prevalence of asthma among pregnant women estimated from several different data sources came up with figures from 3.7% to 8.4% between the years 1997 and 2001, but more important was the estimation that among adult women of childbearing age, asthma prevalence increased twofold from 2.9% to 5.8% between 1976-1980 and 1988-1994, with the increase being greater among women aged 18-24 which was from 1.8% to 6.0% [4]. Indeed, a marked increase in prevalence was found in the majority of the places surveyed, such as increasing from 1.3% to 7.0% in Taiwan from 1974 to 2005, and from 13.7% to 27.4% in Singapore from 1987 to 2001, yet the prevalence was unrelated to ambient air pollution despite its important role in morbidity of asthma patients [5]. In addition, there is substantial variations in asthma prevalence among Asian American immigrant subgroups in the US [6]. When considered together with differences in prevalence between affluent and developed versus less affluent and developing countries, other environmental factors, especially infections in childhood, have probably played important contributory roles [7].

Nevertheless, the literature on the role of infection in the development of asthma appears conflicting [7]. On the one hand, chronic asthma was associated with infection with Mycoplasma and Chlamydia species [8] and adult-onset asthma with respiratory infections within the past 12 months [9]. Neonatal urinary tract infection was associated with a higher risk of asthma in children; more so in boys than girls [10], while pertussis was associated with preadolescent incident asthma, and measles with adolescent incident asthma [11]. On the other hand, pertussis, chickenpox, and rubella infection have been reported to be protective against chronic asthma, an effect that persists to age 13 to 44 years [11]. Furthermore, repeated viral infections early in life, other than lower respiratory tract infections, reduces the risk of asthma up to school age [12]. These findings are in line with the observation that seropositivity for hepatitis A virus (HAV), T gondii, and herpes simplex virus 1, all reduced the probability of hay fever and asthma [13].

Asian countries, which tend to have the lowest prevalence of asthma [3], also happen to have much higher prevalence of chronic hepatitis B virus (HBV) infection which is endemic in many Asian populations as well as among Asian immigrants in western countries [14-16]. In children, chronic HBV infection has been associated with asthma, eczema, and atopy, compared with healthy controls and children with type 1 diabetes [17,18]. However, for full-term infants, the later development of childhood asthma was not associated with hepatitis B vaccination or age at the first dose of HBV vaccine, or with other types of childhood vaccination [19,20]. In adults, HBV infection has been associated with autoimmune conditions such as membranous glomerulonephritis, mesangial proliferative glomerulonephritis; polyarteritis nodosa; and possibly uveitis [21], but its prevalence was reduced in systemic lupus erythematosus, multiple sclerosis, type I diabetes, Sjögren's syndrome, and rheumatoid arthritis [22]. Yet no studies have examined the relationship between chronic HBV infection with asthma in adults. As perinatal transmission is the predominant route of chronic HBV infection in Asian countries, this would have antedated the onset of childhood asthma. If childhood infection is protective against asthma, it is possible that the lower prevalence of asthma in Asian populations could be related, at least in part, to the presence of endemic HBV infection. This study was therefore conducted to examine the relationship between asymptomatic HBV infections diagnosed at routine antenatal

screening with history of asthma in gravidae managed in our hospital in 1997-2019.

Materials and methods

A retrospective study was conducted on the obstetric population managed in our hospital between January 1997 and December 2019. Our department is one of the eight local public obstetric units providing free obstetric care to residents, and serves a population of 1.7 million, with an annual delivery rate of 7000 and a level III neonatal intensive care unit. Routine antenatal tests include the screening for hepatitis B surface antigen (HBsAg) status as an indicator of HBV infection, in order to identify the gravidae whose offspring require hepatitis B immunoglobulin in addition to the universal HBV vaccination that has been implemented for three decades [23]. A full course of vaccination consists of three doses given at the ages of zero, one and six months of life. Obstetric management is based on medical indications and protocols. In all cases, a medical history is taken at the booking antenatal visit, together with measurement of maternal height and weight to calculate the body mass index (BMI), which is recorded in the antenatal record. The results of antenatal investigations, past medical history, current obstetric complications and pregnancy outcome, as coded by the ICD coding, are captured in a computerised database set up by the Hong Kong Hospital Authority for the generation of annual statistics. The accuracy of the database was validated before [24] and was used as the basis of this study.

For this study, patient data was transferred from the hospital database to a research database without patient particulars that would allow identification of the individual patient in order to preserve anonymity. This study included all gravidae who were under our care from January 1997 to December 2019, regardless of pregnancy outcome or place of delivery, in order to avoid bias whereby gravidae with asthma or HBV infection could have been excluded due to unanticipated adverse pregnancy outcome that included miscarriage and therapeutic abortion for various reasons. More than 95% of our gravidae were ethnic Chinese mostly originating from Southern China. The study has been approved by the Institutional Review Board (Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, Reference Number CRE-2017.442).

The gravidae with asthma constituted the study group for comparison with the rest of the obstetric population. In addition to HBsAg seropositivity, we analysed maternal demographic and anthropometric parameters that included parity status (nulliparity or multiparity), teenage (<20 years), advanced maternal age (≥35 years) status, body mass index (BMI) categorised as overweight and above (≥25 kg/m^2) because in adult women, the risk asthma was reported to be significantly increased from BMI ≥25 kg/m^2 onwards [25], short stature (<151cm), presence of any medical history, and ethnic background as Chinese or non-Chinese owing to the different prevalence of asthma even among Asian immigrants of different racial/ethnic background in the US [6], comparing between gravidae with and without a history/diagnosis of asthma. Further analysis of the influence of HBsAg status on asthma diagnosis was performed according to maternal age categorised into six groups as follows: age <20, 20-24.9, 25-29.9, 30-34.9, 35-39.9, and ≥40 years; and according to the World Health Organization BMI categories in four groups as follows: underweight (<18.5), normal (≥18.5-24.99), overweight (≥25.0 to 29.9), and obese (≥30.0 kg/m^2). Further analysis by maternal age and BMI was performed because of the previous observations in our population that maternal HBsAg seropositivity was influenced by age, being highest for age 20-24.9 years in nulliparous and for age 25-29.9 years in multiparous gravidae [26]. As well, maternal BMI impacts rubella immunity status at antenatal screening, with BMI ≥25 kg/m^2 being associated with reduced rubella immunity [27], and obesity can impair the regulation of immune responses [28], while a relationship between rubella immunity and HBsAg seropositivity has also been demonstrated [24].

For statistical analysis, continuous variables were analysed with the t test, and categorical variable with the chi square test. A P value (two-tailed) of <0.05 was considered statistically significant. As this is a cohort study, differences in categorical variables are also expressed as relative risk (RR) and 95% confidence intervals (CI). Finally multiple logistic regression analysis was applied to determine the independent association between HBsAg seropositivity with asthma, adjusting for the possible confounding effects of all the aforementioned factors. For age, we used age 25-29.9 years as the referent group, and for BMI, we used BMI of 18.5-24.99 kg/m^2 as the referent group, as these groups are considered to be associated with the most optimal pregnancy outcome. The results are expressed by the adjusted relative risk (aRR) with 95% CI. Statistical analysis was performed using a commercially available statistical package (PASW Statistics 20.0, SPSS Inc., Chicago, Il).

Results

There were a total of 145644 cases in the database eligible for analysis. Excluded from analysis were 1829 cases in whom the HBsAg status was not entered, mostly as a result of emergency transfer / admission. A diagnosis of asthma was present in 2528 (1.74%) cases. Gravidae with asthma were slightly but significantly younger (p=0.002) with higher incidence of teenage mothers (RR 1.608, 95% CI 1.282-2.016), taller (p<0.001) but no difference in incidence of short stature, and heavier (p<0.001), but there was no difference in the booking BMI or incidence of overweight and obese (Table 1). They

	History of asthma		*P*	RR (95% CI)
	Positive (n=2528)	Negative (n=143117)		
Age (years)	30.3±5.7	30.6±5.5	0.002	-
Age ≥35 years (%)	23.2	23.8	0.437	0.972 (0.905-1.044)
Age <20 years (%)	3.0	1.8	<0.001	1.608 (1.282-2.016)
Height (cm)	158.7±5.9	158.0±5.5	<0.001	-
<151cm (%)	7.5	8.5	0.089	0.888 (0.774-1.019)
Weight (kg)	57.8±11.0	57.0±9.3	<0.001	-
Body mass index (kg/m^2)	23.0±4.1	22.8±3.5	0.147	-
>25 kg/m^2 (%)	24.0	23.2	0.334	1.035 (0.965-1.111)
Nulliparas (%)	58.1	51.9	<0.001	1.119 (1.082-1.157)
HBsAg seropositive (%)	5.8	8.6	<0.001	0.673 (0.574-0.788)
Any medical history (%)	21.7	10.9	<0.001	1.997 (1.852-2.154)
STD (%)	0.6	0.3	0.014	1.823 (1.124-2.958)
Autoimmune diseases (%)	0.6	0.8	0.222	0.715 (0.416-1.230)
Chinese race (%)	96.4	97.0	0.077	0.994 (0.986-1.001)

Table 1: Maternal characteristics between 145645 gravidae with and without history of asthma. Results expressed in mean ± SD or % as indicated and comparison with the t test or chi square test as appropriate; HBsAg: Hepatitis B Surface Antigen; RR: Relative Risk; CI: Confidence Intervals

also had more nulliparas (RR 1.119, 95% CI 1.082-1.157), and positive medical history overall (RR 1.997, 95% CI 1.852-2.154). There were many individual medical conditions in the history, and two specific categories were analysed further. These were sexually transmitted diseases (STDs, with the leading conditions being syphilis, gonorrhoea, and herpes simplex while other infections including that of human immunodeficiency virus were very rare), and autoimmune diseases (AIDs, with the leading conditions being immune thrombocytopenic purpura, systemic lupus erythematosus, and antiphospholipid syndrome, while other conditions were very rare) for which corticosteroid treatment, which could have caused reactivation of HBV infection, might have been prescribed before and/or during pregnancy. Gravidae with asthma had significantly increased STDs (RR 1.823, 95% CI 1.124-2,.958), but there was no significant difference in AIDs (RR 0.715, 95% CI 0.416-1.230). There was no difference in the incidence of Chinese ethnicity, and a significantly lower incidence of HBsAg seropositivity (RR 0.673, 95% CI 0.574-0.788).

The influence of HBsAg seropositivity on asthma diagnosis was further analysed according to maternal age and BMI (Table 2). The overall prevalence of asthma was significantly lower in gravidae seropositive for HBsAg (1.2% versus 1.8%, RR 0.657, 95% CI 0.556-0.775). When age was categorised, asthma diagnosis among HBsAg seropositive gravidae was reduced by the largest extent for age 20.0-24.9 years (RR 0.312, 95% CI 0.161-0.604), followed by age 25.0-29.9 years (RR 0.618, 95% CI 0.447-0.856), and least for age 30.0-34.9 years (RR 0.741, 95% CI 0.566-0.969). No difference was found for the other age groups. When BMI was categorised, asthma diagnosis among HBsAg seropositive gravidae was reduced by the largest extent for the overweight (RR 0.433, 95% CI 0.274-0.684) followed by the normal weight (RR 0.663, 95% CI 0.541-0.813) categories. There was no significant difference for the underweight and obese categories.

	HBsAg status		*P*	RR (95% CI)
Factor	Positive	Negative		
Overall (%)	1.2 (146/12432)	1.8 (2382/133213)	<0.001	0.657 (0.556-0.775)
Age <20 years (%) (n=2162)	3.3 (4/121)	3.0 (61/2041)	0.843	1.106 (0.409-2.991)
Age 20.0-24.9 years (%) (n=15812)	0.7 (9/1354)	2.1 (308/14458)	<0.001	0.312 (0.161-0.604)
Age 25.0-29.9 years (%) (n=39191)	1.1 (38/3488)	1.8 (629/35703)	0.003	0.618 (0.447-0.856)
Age 30.0-34.9 years (%) (n=53213)	1.3 (56/4458)	1.7 (827/48755)	0.028	0.741 (0.566-0.969)
Age 35.0-39.9 years (%) (n=29092)	1.4 (34/2463)	1.7 (456/26629)	0.221	0.806 (0.570-1.139)
≥40 years (%) (n=5620)	0.8 (4/500)	1.8 (92/5120)	0.101	0.445 (0.164-1.206)
BMI <18.5 kg/m^2 (%) (n=10217)	2.6 (18/694)	2.0 (194/9523)	0.321	1.273 (0.790-2.051)
BMI 18.5-24.99 kg/m^2 (%) (n=98744)	1.2 (97/8253)	1.8 (1604/90491)	<0.001	0.663 (0.541-0.813)
BMI 25.0-29.99 kg/m^2 (%) (n=28196)	0.7 (19/2628)	1.7 (427/25568)	<0.001	0.433 (0.274-0.684)
BMI ≥30 kg/m^2 (%) (n=5413)	2.6 (12/464)	2.9 (147/4949)	0.652	0.875(0.490-1.564)

Table 2: Influence of maternal HBsAg status on asthma prevalence by maternal age in and World Health Organization body mass index categories.
WHO: World Health Organization; BMI: Body Mass Index;
Data on age missing in 554 cases, BMI could not be calculated in 3074 cases due to missing data on height and/or weight at booking

Finally multiple logistic regression analysis was performed to determine the independent association between HBsAg seropositivity with asthma, adjusting for the confounding effects of nulliparity status, Chinese ethnicity, short stature, presence of medical history, age in 5-year groups with age 25.0-29.9 as the referent group, and the WHO BMI categories with BMI of 18.5-24.99 kg/m^2 as the referent group (Table 3). Both nulliparity status (aRR 1.230, 95% CI 1.130-1.338) and positive medical history (aRR 2.213, 95% CI 2.008-2.438) were found to be significantly associated with increased asthma diagnosis. For age groups, those <20 years (aRR 0.580, 95% CI 0.447-0.752) and at 20-24.9 years (aRR 0.861, 95% CI 0.752-0.987) were the only groups associated with reduced asthma diagnosis. For BMI, the obese group was also found to be associated with reduced asthma diagnosis (aRR 0.580, 95% CI 0.491-0.685). HBsAg seropositivity was found to be independently associated with reduced asthma diagnosis (aRR 0.677, 95% CI 0.572-0.801).

Factor	***P***	**RR (95% CI)**
Nulliparity status	<0.001	1.230 (1.130-1.338)
Chinese	0.082	0.827 (0.668-1.024)
Short stature	0.085	0.877 (0.755-1.019)
Medical history present	<0.001	2.213 (2.008-2.438)
Age - 25.0-29.9 years	Referent	
- <20 years	<20 years	0.580 (0.447-0.752)
- 20.0-24.9 years	20.0-24.9 years	0.861 (0.752-0.987)
- 30.0-34.9 years	30.0-34.9 years	1.026 (0.926-1.136)
- 35.0-39.9 years	35.0-39.9 years	1.019 (0.904-1.150)
- ≥40 years	≥40 years	1.003 (0.806-1.249)
WHO BMI categories – 18.5-24.99 kg/m^2	Referent	
<18.5 kg/m^2	0.081	0.879 (0.760-1.016)
25.0-29.99 kg/m^2	0.289	1.059 (0.953-1.177)
≥30.0 kg/m^2	<0.001	0.580 (0.491-0.685)
HbsAg seropositivity	<0.001	0.677 (0.572-0.801)

Table 3: *Regression analysis of the factors with P value of <0.1 and association with asthma history. WHO: World Health Organization; BMI: Body Mass Index; HBsAg: Hepatitis B Surface Antigen; aRR: Adjusted Relative Risk, CI: Confidence Intervals*

Discussion

It has been pointed out some years ago that different infections can either promote atopy (as in respiratory syncytial virus infection), or inhibit it (as in measles, hepatitis A, and tuberculosis), but the relationship between HBV carriers and atopic disorders has not been studied [29]. In this study based on a large obstetric population, we have demonstrated for the first time that antenatal seropositivity for HBsAg is significantly associated with reduced maternal prevalence of asthma by as much as one-third when compared with gravidae screened negative for HBsAg. Arguably any given obstetric population represents mostly healthy women in their prime reproductive age, and that asymptomatic HBsAg seropositivity is an irrefutable evidence of chronic HBV infection. The association between these two conditions would indicate that chronic HBV infection, which in our population is largely acquired through vertical transmission which can be prevented by means of combined active-passive immunization shortly after birth [23,30], represents a hitherto unknown factor which had probably contributed to the variably lower prevalence of asthma in Asian countries [3] and among the Asian immigrants in the US [6]. Our results also showed that both nulliparity status and presence of medical history are independently associated with increased asthma, while maternal age of <25 years and BMI of ≥30 kg/m^2 are independently

associated with reduced prevalence of asthma, findings which may appear contrary to some of the literature, probably due to the fact that other confounding factors such as the effects of chronic but asymptomatic infections have not been taken into account in previous studies. The interaction between age and BMI with environmental, medical (including infection), and nutritional factors on asthma diagnosis in the otherwise healthy women of reproductive age warrants further large-scale population studies for clarification.

Limited by the nature of the database, we do not have information on the age of onset and severity of, or the treatment received before and during pregnancy for, asthma in our gravidae. One valid concern has been whether the use of systemic and/or inhaled corticosteroid therapy for asthma could have increased the risk of HBV reactivation [31] and therefore positive HBsAg screening. However, in that study [31], the subjects included both males and females, their mean age was much older (55-57 years), and their respiratory conditions included both asthma and chronic obstructive pulmonary disease, the latter being of different aetiology and is extremely uncommon among pregnant women. Furthermore, if any form of corticosteroid treatment in our asthma group were to have activated occult HBV infection leading to HBsAg seropositivity, then we should have seen a positive, instead of negative, association between HBsAg seropositivity with asthma. We also could not determine the age of acquisition of the HBV infection, but in our locality, vertical and perinatal transmission is regarded as the major cause of HBV infection [23,30], thus the majority of our HBV carrier gravidae would have acquired the infection prior to the age of onset of childhood asthma. The strengths of this study are the large sample size with an almost homogenous ethnic group from one hugely populated region of one city, the universal screening for HBsAg serology and documentation of the results, together with available demographic and anthropometric data as well as medical history on almost all gravidae, so that the findings would be consistent and robust enough.

The scenario depicted by the findings of this study resembles the reported effect of HAV and other infections in reducing the probability of asthma and hay fever [13]. In this regard, urbanisation in Hong Kong has probably played an intermediary but vital role here, as urbanisation removes most of the natural microbial burden and predisposes a subject brought up in such an environment to a pattern of pro-allergic immune development from early life [32]. In the U.S., that the prevalence of asthma diagnosed at/before the age of 18 years had increased almost 15-fold from 0.4% to 5.8% in HAV-seronegative subjects born before 1920 compared with subjects born in the 1960s, while the corresponding figures remained constant around 2% in all cohorts of HAV-seropositive subjects [13], thus suggesting previous HAV infection to be powerful enough to abolish the effect of urbanisation. In addition to HAV, infections with measles and tuberculosis inhibit atopic response, while semi-sterile feeding, childhood vaccination, and use of antibiotics prevent Th1 stimulation thus allowing Th2 response to dominate [29]. The impact of chronic HBV infection on asthma prevalence in our gravidae are therefore in line with these observations and suggests that environmental factors maybe more powerful than ethnicity and genetic factors in the development of asthma and atopy, an idea which is in line with the concept of the hygiene hypothesis [7].

The underlying mechanism(s) for our observation remains to be elucidated. What has been reported is that tendency towards atopy is increased in chronic HBV infection because Th1 response is insufficient so that the higher Th2 response increases the tendency towards allergic and autoimmune diseases, while HBV vaccination activated antigen-presenting cells with increased Th1 response proportionately, and the presence of anti-HBs and absence of HBsAg reduced the risk of atopy [17,18,29,33]. Furthermore, response to HBV vaccination is not reduced by the presence of asthma or inhalation steroid therapy in children [34]. Thus, it would be expected that immunity against HBV, acquired through natural infection or vaccination, should have reduced the likelihood of atopy and asthma. Yet this view is contradicted by the results of this study which indicated that gravidae with HBV infection actually had significantly lower prevalence of asthma, and gravidae with asthma had significantly lower prevalence of HBV infection, and on this basis, we propose the following hypothesis. Asthma is known to be associated with increased Th1 immune response, which is also involved in clearance of HBV infection [35]. Adolescents with continuing asthma had increased production of Th1 cytokines IL-12, IFN-γ, and TNF-α in peripheral blood mononuclear cells compared with those who had resolved asthma [36], and the suppressive function of regulatory T cells (T_{reg}) is lower in asthmatic patients compared with controls [37]. On the other hand, chronic HBV infection induces T_{reg} in peripheral blood which suppress HBV-specific T helper cells and impair immune response against HBV [38], so that the immune response profile is inhibitory towards asthma, while subjects immune against HBV infection are likely to exhibit varying degrees of Th1 dominance and normal or reduced T_{reg} which predispose them towards of asthma, because childhood vaccination prevents infection-induced Th1 response and predisposes the subject towards atopy [29]. Although we cannot provide definitive proof, but given the introduction of HBV immunisation in our population from the late 1980s, it can be envisaged that many of our gravidae screened negative for HBsAg in fact had immunity against HBV infection, and that their heightened Th1 immune response would have predisposed them towards atopy and asthma. This hypothesis would be in line with the view that early life events are essential in shaping the immune response towards the Th1 or Th2 profile [39], so that the timing and sequence of different events probably determines the pattern of association of these conditions. Thus, HBV infection acquired in infancy and early childhood, which tends to evolve into the chronic carrier state, would have reduced tendency towards childhood asthma, while subjects uninfected in infancy who developed childhood asthma would have enhanced immunity against HBV infection, especially following routine neonatal HBV immunisation. In subjects with successful immunisation in infancy who subsequently became infected with HBV, these likely mechanisms are waning of immune protection in adolescence [40] and loss of anamnestic response [41].

In conclusion, our observation that among the general obstetric population, maternal chronic HBV infection identified through routine antenatal screening for HBsAg was associated with a one-third reduction of asthma compared with gravidae of similar ethnic background but screened negative for HBsAg, is in line with previous reports which have demonstrated a similar effect with other infections such as HAV [13,29]. Thus, chronic HBV infection, which was not looked for or diagnosed, could have contributed to the variably lower prevalence of asthma in both the non-pregnant and pregnant populations found previously, and improving hygiene together with effective childhood vaccination in many countries, could have been one of the reasons for the rising prevalence of asthma not only in the US [4], but especially in countries such as Taiwan and Singapore [5]. Future studies are warranted to explore the effects of timing and sequence of different infections and other early life events on the development of allergies and asthma.

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Received: 02 Dec 2021; **Accepted:** 04 Jan 2022; **Published:** 07 Jan 2022

Citation: Lao TT, Annie Hui SY, Sahota DS. Antenatal hepatitis B surface antigen serological status and maternal asthma prevalence. *Front Infect Diseases Microbiol.* 2022; 2: 106.