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The changing epidemiology of herpes zoster over a decade in South Korea, 2006–2015 ☆

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ABSTRACT

Background: In South Korea, the population is rapidly aging and the prevalence of comorbidities has increased. We investigated longitudinal changes in the herpes zoster (HZ) considering demographic changes and comorbidities in the era of universal single-dose varicella vaccination.
Methods: We used the population-based database of the National Health Insurance Service in South Korea, with approximately 50 million subscribers during 2006–2015. HZ cases were identified using ICD-10 codes and comorbid conditions were also collected. Incidence rates (IRs) and incidence rate ratios (IRRs) per year were calculated adjusting for age, sex, comorbidities and socioeconomic status, and the temporal trends were examined using segmented negative binomial regression analysis.
Results: Over a decade, the adjusted HZ IR increased significantly from 4.23 to 9.22 per 1000 person-years (adjusted IRR 1.05, 95% confidence interval [CI] 1.04–1.06). However, during 2012–2015, the increasing trends decelerated (adjusted IRR per year 1.01, 95% CI 0.98–1.04) and slope changes differed by age. There was a declining trend in children under 9 years, sustained increase in adults aged 30–39 years, and near-plateau in those aged 50–69 years. Nonetheless, the age distribution of HZ incidence did not change over a decade, with the peak in adults aged 60–79 years. HZ-associated hospitalization rates also increased, with a deceleration in the increasing trends during 2012–2015.
Conclusions: The HZ burden increased independently of demographic changes and prevalence of comorbidities. However, different trajectories by age group necessitate continuous HZ surveillance for better understanding of these changes, and to provide evidence for development of preventive strategies.
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1. Introduction

Varicella zoster virus (VZV) infection causes varicella and results in latent infection in the sensory ganglia. Herpes zoster (HZ) is caused by reactivation of the latent VZV when VZV-specific cell-mediated immunity (CMI) declines. HZ can lead to various complications, including post-herpetic neuralgia, and is associated with increased risk of cardiac and cerebrovascular events [1]. Risk factors for HZ are advancing age and comorbid conditions which can impair CMI [2]. In recent decades, temporal increases in HZ incidence have been reported globally [2]. Reasons for the increase in HZ incidence remain unclear, but widespread use of childhood varicella vaccine, which might decrease the boosting of exogenous immunity from exposure to circulating VZV [3], and an increase in the prevalence of comorbid conditions weakening CMI, as well as extended life expectancy, have been considered as responsible [4].

In South Korea, the disease burden of HZ increased over the years and with age. The prevalence of HZ increased from 7.9 to 12.5 per 1000 population between 2003 and 2007 in a previous study [5]. A recent longitudinal study also demonstrated the

Abbreviations: VZV, varicella zoster virus; HZ, herpes zoster; CMI, cell-mediated immunity; NHID, National Health Information Database; ICD-10, International Classification of Diseases, 10th Revision; SES, socioeconomic status; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; aIRR, adjusted incidence rate ratio.

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increasing trend in the overall incidence rates of HZ after accounting for age [6]. South Korea is a rapidly aging society and the population structure has changed dramatically over a decade, influenced by the rapidly falling fertility rate and decreasing mortality rate. Moreover, the prevalence of underlying diseases such as cancer and diabetes has gradually increased with the increasing survival rate and changing lifestyles [7,8].

The vaccination strategy could also affect the HZ epidemiology profoundly, as childhood varicella vaccination might increase the HZ incidence in the adult population by decreasing exogenous boosting [3], while the zoster vaccination decreases the HZ incidence [9]. In South Korea, a single-dose varicella vaccine was included in the National Immunization Program for children at 12–15 months in 2005, and varicella vaccine coverage was estimated at over 95% in children born after 2007 [10]. The live attenuated vaccine against HZ was introduced in 2012, and the zoster vaccine has been recommended for individuals aged 60 years or more unless contraindicated. In 2015 the recommendation was revised such that individuals aged 50–59 years may receive zoster vaccine on demand [11].

All these changes in demographics and vaccination policy could influence HZ incidence in South Korea. The impact of these changes could be different depending on age groups and presence of comorbidities. A better understanding of the current HZ epidemiology can help in development of an appropriate vaccination strategy to prevent HZ and reduce the disease burden.

In this study we aimed to investigate the temporal trend of HZ incidence using nationwide population-based data, in order to examine the longitudinal effect of age structure, presence of comorbidities, and vaccination strategy. This study was approved by the Institutional Review Board of the Catholic University of Korea, Daejeon St Mary's Hospital (DC19ZNSI0055).

2. Material and methods

2.1. Data source

In South Korea, the National Health Insurance (NHI) system was established in 1977 and achieved universal coverage in 1989. In 2000, the National Health Insurance Service (NHIS) was launched as a mandatory, single-payer insurance system. The NHIS provides the Korean population with comprehensive healthcare benefits, collects contributions, and reimburses providers. For universal health coverage, the entire Korean population is mandatorily enrolled in the NHI program. In addition, the Medical Aid program is operated by the government to secure the minimum livelihood of low-income households by providing medical services. Approximately 97% of the population is covered by the NHI program and the remaining 3% by Medical Aid program. The total number of beneficiaries has been approximately 50 million, which is more than 99% of the South Korean population, during the study period [12]. Since all medical institutions in South Korea are obliged to participate in the NHI system by law and operate based on a regulated fee-for-service system, all prescriptions, orders, and diagnosis codes are computerized and collected. In 2014, the NHIS established the National Health Information Database (NHID) based on the information collected in the existing database system. The NHID is maintained and provided by the NHIS to support health policy or medical research and it contains data starting from the year of 2002.

This study used the NHID from the period of January 1, 2002 to December 31, 2015. These data contain sociodemographic variables, principal diagnoses and comorbid conditions, prescribed medications, healthcare utilization (including hospital admissions and number of visits), insurance types, and medical expenses along with each patient's encrypted identification number [12]. Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10). In addition, serious diseases (e.g., malignancy) or rare incurable diseases (e.g., end-stage renal disease requiring dialysis, hematologic diseases, autoimmune diseases, and other immunocompromised conditions) are given special benefit codes for co-payment reduction [13]. Over the study period, there have been no changes in coding practices and billing system for HZ.

2.2. Case definitions and data collection

We defined HZ cases as patients with HZ-related ICD-10 codes (B02) in any diagnostic fields, who received either intravenous acyclovir $\geq$1 day or oral antiviral agents (e.g. famciclovir, valacyclovir) $\geq$5 days. As the NHID data are collected during the process of claiming healthcare services and reimbursement, accuracy of diagnosis has been an issue. In order to identify HZ cases more accurately, they were searched for using the previously validated operational definition comprising both diagnostic codes and medications, of which the positive predictive value for identifying HZ cases was 91.9% [14].

Comorbid conditions were collected from the database using the corresponding ICD-10 codes and special benefit codes for serious or rare incurable diseases. Comorbid conditions were diabetes mellitus, liver cirrhosis, chronic renal diseases, hematologic disorders, malignancies, transplantation, autoimmune diseases, and other immunocompromising conditions such as human immunodeficiency virus infection. A full list of the ICD-10 codes, codes for rare incurable diseases, and searching schemes used in this study is provided in Supplementary Table S1.

Socioeconomic status (SES) data were collected using data on income quintiles and coverage classification. Income quintiles of each insured individual represent their economic status and were based on the amount of health insurance payments [15]. SES was dichotomized as low or average: low SES was defined as individual income in the lowest 20% or being on Medical Aid program; otherwise, SES was defined as average.

An incident HZ case was defined as the first ever case identified during the study period. The years 2002–2005 were considered as the wash-out period, because the NHIS started to collect data electronically in 2002 and comorbid conditions have been collected more accurately since 2005.

2.3. Statistical analyses

We estimated the annual crude and age-specific incidence rates (IRs) per 1000 person-years for HZ. The annual IRs were calculated by dividing the number of incident HZ cases by person-years at risk. Person-years at risk were defined as the total population enrolled in the NHIS program in the given year, excluding the number of incident cases from the previous year. Age was grouped in 10-year intervals.

To account for temporal changes, we used negative binomial regression analysis to calculate the crude and adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) per year as a continuous variable, with the year 2006 as the reference year. Variables included in the model were age, sex, presence of comorbidities, and SES. To further analyze the trend, we performed a segmented regression analysis to explore the slope changes in the HZ IR over the study period. The study period was divided into two periods: period 1 (2006–2011) and period 2 (2012–2015). The age-specific IRs of HZ were calculated and analyzed in the same manner. We calculated the adjusted age-specific percentage changes in HZ IRs of year 2009–2011 and year 2012–2015 compared to year 2006–2008 as the reference.

HZ hospitalization rates were calculated per 1,000 person-years by dividing the number of hospitalized cases by person-years at risk. The trend analyses described above were also performed for hospitalized cases. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, United States of America (USA)) and Stata, version 13 (StataCorp, College Station, TX, USA).

3. Results

3.1. Trends in herpes zoster incidence

The number of HZ cases increased substantially from 192,448 in 2006 to 469,268 in 2015. HZ IRs increased significantly over the study period (crude IRR per year 1.09, 95% CI 1.06–1.12), and this increasing trend was significant even after adjustment for age, gender, presence of comorbidities, and SES (adjusted IRR [aIRR] per year 1.05, 95% CI 1.04–1.06) (Fig. 1A).

The segmented regression analysis also demonstrated increasing trends over the two periods; however, the increasing trend appeared to be decelerating over the years. During 2012–2015 the deceleration was statistically significant after adjusting for age, sex, presence of comorbidities and SES (aIRR 1.01 per year, 95% CI 0.98–1.04) (Table 1).

The risk of HZ generally increased with age, despite the slight decline in the elderly aged 80 years or more (Table 1). The increase in HZ IRs accelerated from 50 years of age and peaked at 60–79 years, and this age distribution of HZ incidence did not change over the periods (Supplementary Fig. 1).

The increasing trend in HZ incidence was similar in both sexes; however, females were at higher risk than males throughout the study period (aIRR 1.25, 95% CI 1.19–1.31) (Supplementary Fig. S2). The risk of HZ was significantly greater in individuals with comorbidities than those without (aIRR 2.12, 95% CI 2.02–2.22) (Table 1); however, individuals without comorbidities experienced more rapidly increasing trends over the study period (aIRR per year 1.08, 95% CI 1.07–1.09) than those with comorbidities (aIRR per year 1.04, 95% CI 1.03–1.05) (Supplementary Fig. S2). SES was not associated with overall HZ IRs.

3.2. Trends in age-specific herpes zoster incidence

The age-specific IRs were the greatest in individuals aged 60–79 years, followed by those aged 50–59 years and ≥80 years (Fig. 2A and 2B). However, the percentage change in HZ IRs was most prominent in individuals aged 30–39 years, and children aged <9 years, the adjusted percentage change was reduced in 2012–2015 compared to that in 2008–2011 (Fig. 2C).

The segmented regression analysis was consistent with the age-specific percentage change. In children under 9 years of age, the trend of HZ IRs began to decline during 2012–2015, whereas in adults aged 30–39 years, the increasing trend was sustained throughout the study period. The slope increase was the greatest in adults aged 30–39 years. In other age groups, the crude and adjusted age-specific HZ IRs generally followed the increasing trends, but the slope change tended to decelerate over time. In adults aged 50–69 years, in particular, the increasing trends significantly decelerated during 2012–2015 in both crude and adjusted analyses (Table 2, Supplementary Fig. S3).

The gender difference in HZ IRs changed with age. Female predominance was observed from the age of 20–29 to 70–79 years, with the peak in gender difference in the 50–59-year age group. These trends were similar over the study period (Supplementary Fig. S4).

3.3. Trends in herpes zoster-associated hospitalization rates

The number of hospitalized HZ cases increased from 19,103 to 39,227 between 2006 and 2015. The crude (IRR per year 1.09, 95%CI 1.06–1.12) and adjusted hospitalization rates (aIRR per year 1.03, 95% CI 1.01–1.05) increased over time as the overall HZ IRs increased (Fig. 1B). The segmented analysis showed that the increasing trends in crude hospitalization rates tended to decelerate during Period 2. However, the trends for both periods were similar after adjustment (Table 1).

The hospitalization rate increased with age, with the highest being in the elderly aged ≥80 years. Hospitalization rates were higher in individuals with comorbidities and in females (Table 1). However, in hospitalized cases, female predominance was observed from 40–49 years to 70–79 years; the gender difference

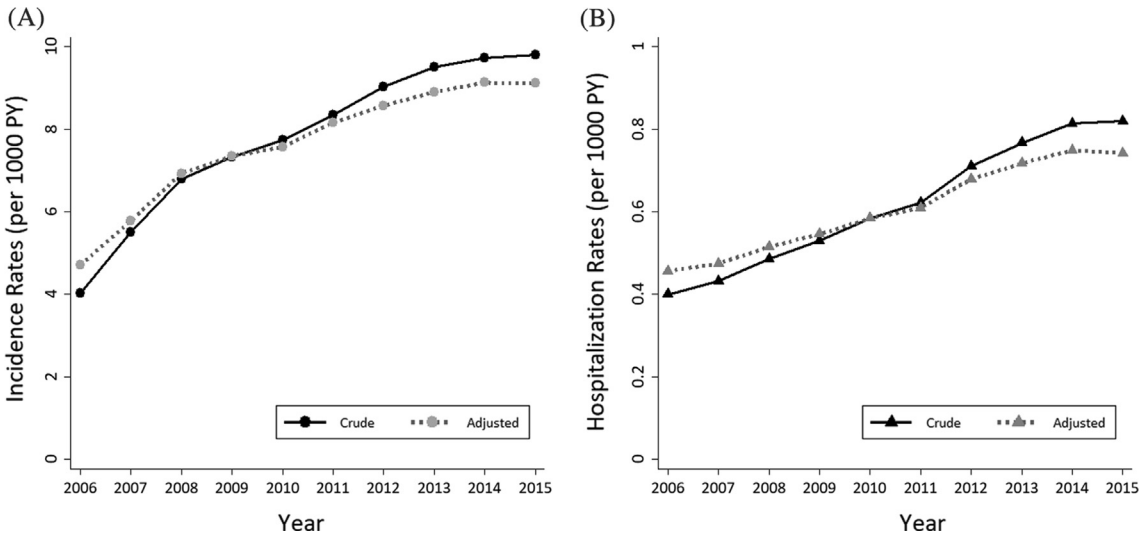

Fig. 1. The crude and adjusted annual incidence rates (A) and hospitalization rates (B) of herpes zoster from 2006 to 2015 in South Korea. Both rates were adjusted for age, age, gender, the presence of comorbidities and socioeconomic status. PY, person-years.

Table 1
Trend of incidence rate ratios of all herpes zoster cases and hospitalized cases per year for two periods (year 2006–2011 and year 2012–2015) in South Korea.

Variables	All herpes zoster		Hospitalized herpes zoster	
	Crude IRR	Adjusted IRR*	Crude IRR	Adjusted IRR*
Period 1 trend	1.14 (1.11–1.18)	1.09 (1.07–1.11)	1.10 (1.09–1.10)	1.02 (0.98–1.06)
Period 2 step change	0.88 (0.75–1.04)	0.91 (0.83–1.01)	1.04 (1.01–1.08)	1.06 (0.88–1.28)
Period 2 trend	1.03 (0.97–1.09)	1.01 (0.98–1.04)	1.05 (1.04–1.06)	1.02 (0.95–1.09)
Female		1.25 (1.19–1.31)		1.22 (1.11–1.34)
Comorbidities		2.12 (2.01–2.22)		6.76 (6.06–7.54)
Low SES		0.96 (0.92–1.01)		1.11 (1.01–1.22)
Age groups (years)				
<10		1.00		1.00
10–19		1.47 (1.31–1.65)		1.12 (0.90–1.39)
20–29		1.78 (1.60–1.99)		0.75 (0.61–0.93)
30–39		1.89 (1.69–2.11)		0.62 (0.50–0.77)
40–49		2.43 (2.18–2.71)		0.74 (0.60–0.92)
50–59		3.89 (3.48–4.34)		1.37 (1.10–1.70)
60–69		4.75 (4.25–5.30)		1.92 (1.54–2.40)
70–79		4.80 (4.30–5.36)		2.93 (2.35–3.65)
80+		4.01 (3.59–4.48)		3.94 (3.15–4.91)

Data are IRR (95% Confidence Interval) unless stated otherwise. Changes in trend are IRR per year during each period. IRR, incidence rate ratio; SES, socioeconomic status.
* Adjusted IRRs were adjusted for age, gender, the presence of comorbidities and socioeconomic status.

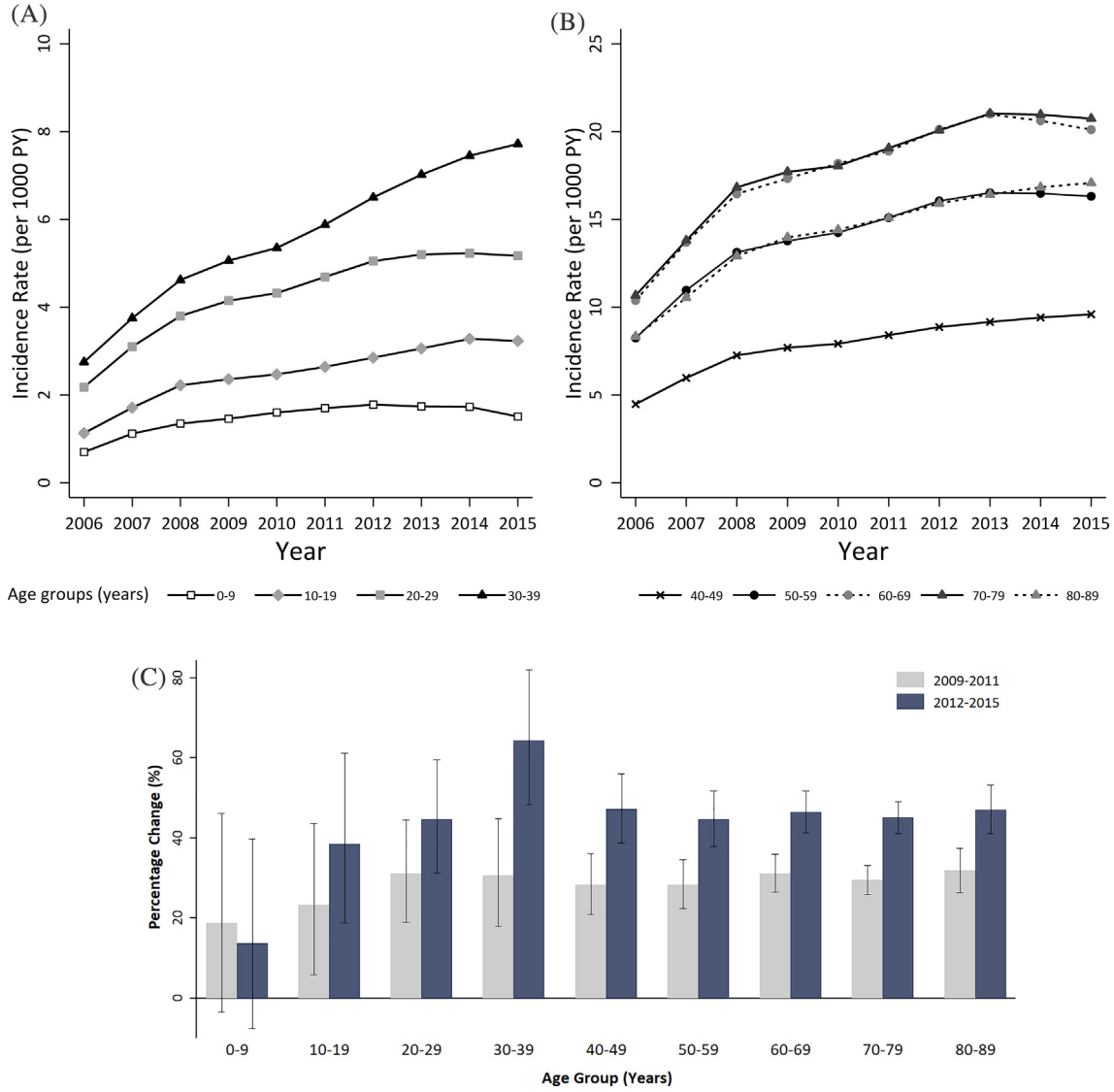

Fig. 2. Annual trends in age-specific incidence rates of herpes zoster (A and B) and sex-comorbidity adjusted percentage change in age-specific incidence rates of two periods (year 2009–2011 and year 2012–2015) compared to that of year 2006–2008 (C) in South Korea. PY, person-years.

Table 2
Trends of age-specific incidence rate ratios of herpes zoster per year during two periods (year 2006–2011 and year 2012–2015) in South Korea.

Age group (Years)	Crude			Adjusted*		
	Period 1 trend (2006–2011)	Period 2 step change	Period 2 trend (2012–2015)	Period 1 trend (2006–2011)	Period 2 step change	Period 2 trend (2012–2015)
<10	1.17 (1.12–1.22)	0.83 (0.65–1.04)	0.95 (0.88–1.03)	1.08 (1.04–1.13)	0.88 (0.72–1.08)	0.95 (0.89–1.01)
10–19	1.16 (1.11–1.22)	0.84 (0.66–1.07)	1.05 (0.96–1.14)	1.10 (1.07–1.14)	0.90 (0.77–1.05)	1.02 (0.97–1.08)
20–29	1.15 (1.11–1.19)	0.87 (0.72–1.05)	1.01 (0.94–1.08)	1.11 (1.09–1.13)	0.89 (0.80–1.00)	1.00 (0.96–1.04)
30–39	1.15 (1.12–1.19)	0.90 (0.77–1.06)	1.06 (1.00–1.12)	1.11 (1.09–1.13)	0.95 (0.85–1.06)	1.04 (1.00–1.08)
40–49	1.12 (1.09–1.16)	0.87 (0.74–1.03)	1.03 (0.97–1.09)	1.10 (1.09–1.12)	0.90 (0.84–0.98)	1.02 (0.99–1.05)
50–59	1.12 (1.08–1.15)	0.89 (0.76–1.05)	1.00 (0.95–1.06)	1.10 (1.09–1.12)	0.91 (0.85–0.98)	1.00 (0.98–1.03)
60–69	1.12 (1.08–1.15)	0.90 (0.76–1.05)	1.00 (0.94–1.06)	1.11 (1.10–1.12)	0.90 (0.84–0.95)	1.00 (0.98–1.02)
70–79	1.11 (1.08–1.15)	0.89 (0.76–1.05)	1.01 (0.95–1.07)	1.10 (1.09 1.12)	0.90 (0.84–0.95)	1.01 (0.99–1.03)
80+	1.12 (1.09–1.15)	0.87 (0.76–1.01)	1.02 (0.97–1.08)	1.11 (1.09 1.12)	0.88 (0.83–0.94)	1.02 (1.00–1.04)

Data are IRR (95% Confidence Interval) unless stated otherwise. Changes in trend are IRR per year during each period.
* Adjusted IRRs were adjusted for age, gender, the presence of comorbidities and socioeconomic status.

was less prominent compared to that for all HZ cases (Supplementary Fig. S4).

4. Discussion

This study showed a substantial increase in HZ IRs, even after adjustment for changes in age structure and comorbidities in the population over a decade. However, the increasing trends decelerated significantly during 2012–2015; this was observed in all age groups except for those of 30–39 years, where the increasing trend showed no significant deceleration. Notably, in children under 9 years the adjusted IR began to decline during 2012–2015. Despite such changes in the trend, the age distribution has not changed over the decade: the IR rose steeply after 50 years of age and peaked in those aged 60–79 years.

The increasing trend in HZ incidence is a global phenomenon, which has been reported in Europe, the USA, and Asia [2,16–18]. However, there have been no clear explanations for this trend. Several factors have been suggested as driving determinants: decline in exogenous boosting following universal varicella vaccination, the rapidly aging population and increase in comorbidities, possible environmental impact, or increased public awareness and improved accessibility to healthcare [19]. Among these, the impact of universal varicella vaccination on HZ incidence has been a focus of debate. Based on the Hope-Simpson hypothesis which postulated that immunity against VZV reactivation in adults could be exogenously boosted by exposure to circulating varicella [20], a decline in varicella through the universal varicella vaccination program in children could lead to an unintended increase in HZ incidence in adults. However, the evidence supporting this hypothesis is still mixed [21].

In South Korea, varicella vaccine was introduced in 1988 and has been more widely used since the mid-1990s. In 2005, a single-dose varicella vaccine targeting children aged 12–15 months was included in the National Immunization Program. As the varicella vaccination program matured, the varicella IR was reduced by 67.5%, most predominantly in children aged 1–4 years in South Korea [6], which could explain our finding of a decline in HZ incidence in children under 9 years of age in 2012–2015.

In this study, HZ incidence generally increased over a decade, and this might have been influenced by the decrease in exposure to varicella after universal vaccination. However, because there is only limited information on HZ incidence prior to implementing universal varicella vaccination, it is difficult to conclude that an overall increase in HZ is attributable to universal varicella vaccination. Furthermore, deceleration in the increasing trends was observed during 2012–2015, for which period the varicella incidence decreased substantially [6]. In particular, the HZ IRs virtually plateaued in adults aged 50–69 years during that period. Because zoster vaccine uptake was relatively low (estimated at 9.4% in 2015 in South Korea [22]), its impact would have been minimal. This finding therefore appeared to contradict the Hope-Simpson hypothesis.

Possible explanations for these changes could be suggested as follows. Firstly, the exogenous immunity boosting against HZ via contact with varicella patients might be temporary [23] or limited to subgroups such as parents of young children [21,23]. In our study, the sustained increase in individuals aged 30–39 years was notable. Considering that 30–39 years is the usual parenting age in South Korea [24], it can be postulated that a decline in household exposure to varicella in parents of young children can lead to a persistent increase in HZ incidence in this age group. Such trends in the parenting age group have recently been reported in Japan and the USA [25–27].

Secondly, given that VZV can be transmitted through contact with HZ cases, exposure to HZ might have a potential role in boosting immunity against HZ in adults. The Hope-Simpson hypothesis was formulated based on the observation of HZ cases where the risk of HZ was lowered by re-exposure to varicella in 1965 [20], when almost all children became infected with varicella whereas HZ incidence was relatively low [2]. Therefore, children with varicella were possibly the major contributor to circulating VZV in the past. However, the epidemiology of varicella and HZ has changed dramatically following the wide use of varicella vaccine. A marked reduction in varicella incidence has commonly been observed after implementing routine varicella vaccination for children in many countries, while the HZ incidence increased over time [28]. During this transition, the potential role of HZ in contributing to the circulating VZV might outweigh that of varicella [29]. It is well known that exposure to HZ can cause varicella in susceptible individuals, yet it is considered less contagious than varicella. Direct contact is the most common transmission route, but aerosol spread is possible from patients with disseminated zoster. Moreover, airborne transmission from localized HZ has been suggested. Without direct contact with index cases, exposure to localized HZ has led to transmission of varicella among healthcare workers or elderly patients in healthcare settings [30–32]. Even a seropositive healthcare worker contracted varicella after exposure to a localized HZ patient [30]. VZV DNA was detected in the air in the room where patients with localized HZ were hospitalized [33,34], and the environment could be rapidly contaminated from localized HZ [35]. In school or day-care center settings, 10% of secondary varicella cases were linked to HZ and environmental contamination from HZ cases was also detected [29]. Although detection of VZV DNA does not imply infectivity *per se*, these findings suggest the possibility that the transmission

potential from HZ might not be as low as expected. From this perspective, immunity could be boosted by exposure to HZ among adults, in the same manner as with varicella. Given that contacts are generally age-assortative [36], it can be presumed that older adults are more likely to have contact with older adults with HZ. Such repeated exposure to HZ might lead to exogenous immunity boosting in adults, which may partly explain recent deceleration in the increasing trend of HZ incidence among older adults. However, the supporting evidence is not yet sufficient and the magnitude of immunity boosting after exposure to HZ has not been measured although it was assumed to be similar for both HZ and varicella in one study [37]. Thus, further epidemiologic studies are required to validate the assumption.

Thirdly, endogenous boosting through asymptomatic reactivation of latent VZV can be one of explanations for the recent deceleration in the increasing trend of HZ epidemiology and divergence of age-specific trajectories [38,39]. Although its impact on the population-level epidemiology or the possible interplay with exogenous boosting remains unknown, endogenously boosted immunity against HZ may help maintain immunological control over HZ development. Lastly, temporal changes in public awareness and healthcare-seeking behavior for HZ could have influenced the trends in HZ incidence. Furthermore, the duration of observation was relatively short to demonstrate clearly that these changes were not a transient phenomenon. Therefore, HZ epidemiology should be continuously monitored for more robust and concrete trajectories of HZ incidences.

The presence of immunocompromising comorbidities is a well-known risk factor for development of HZ, which was also demonstrated in this study. However, in this study, a steeper increase in occurrence of HZ was identified in the population without comorbidities. This finding suggests that other factors, including the demographic changes, might play a more important role in driving the current changes in HZ epidemiology in South Korea. In terms of disease severity, however, the risk of HZ-associated hospitalizations was far greater in the population with comorbidities, and markedly increased in the elderly. These findings indicated the severity of disease and substantial impact of HZ on quality of life and economic burden in those with comorbidities and the elderly, which requires preventive strategies tailored for these populations. In particular, live attenuated HZ vaccines are contraindicated in severely immunocompromised individuals. Thus, the role of a recombinant subunit vaccine as a preventive measure should be further explored.

In our study, HZ IRs was higher than those from neighboring countries [17]. In 2015, crude HZ IR was 9.8/1000 person-years in South Korea versus 5.5/1000 person-years in Japan [25]. The difference in HZ IRs may have resulted from the differences in data sources and collecting methods and the differences in healthcare seeking behavior between countries.

In the Japanese study, the data were prospectively collected from 43 dermatology clinics in one prefecture in Japan which accounted for <1% of total Japanese population [40], whereas the NHID covering the entire South Korean population was used in our study. Although the Japanese study provided valuable information in terms of disease verification and prospective nature in data collection, it is possible that HZ incidence could have been underestimated or regional differences might exist in Japan. Like our study, the Taiwanese study used the National Health Insurance Research Database provided by the National Health Insurance Administration covering 99% of Taiwan's population. In that study, the HZ incidence rate was estimated to be 6.89/1000 person-years in 2008 [41], which was similar to that from our study in the same year (6.79/1000 person-years in 2008). German studies also showed a substantial difference in HZ IRs depending on the data source and collecting method: 6.9/1000 person-years using the German Pharmacoepidemiological Research Database versus [42] versus 2.71/1000 person-years using the German primary care sentinel surveillance data [43]. In South Korea, barriers to healthcare access are considered low because of universal healthcare coverage and low medical costs. Easy accessibility to healthcare allowed individuals to seek medical care, which could have led to high HZ incidence in South Korea.

Despite the recent deceleration in the increasing trend of HZ incidence, the incidence increased substantially over the decade. South Korea is a rapidly aging country, with the population over 65 years of age projected to rise 2.3 times in 2035 [44]. In this regard, the HZ burden is expected to grow in the future and could become a major public health issue. Following the introduction of HZ vaccine in 2012, the Korean Society of Infectious Diseases recommends that adults $\geq$60 years receive HZ vaccine, and that those of 50–59 years may receive HZ vaccine, depending on individual health conditions [11]. To prevent HZ and reduce the disease burden in the adult population, vaccination against HZ should be more actively recommended. In addition, changes in the epidemiology of HZ along with varicella need to be kept under continuous surveillance, to provide the evidence required to develop an effective prevention strategy in the future.

There are several limitations to be addressed in this study. First, this study was based on the insurance claims database, and thus may be susceptible to under-representation of patients with mild diseases, since patients who did not seek medical care would not be captured. However, improved access to healthcare and public awareness could have increased the utilization of healthcare services over the study period. Also, HZ cases may have been over-diagnosed. Given that identification of HZ cases using diagnostic codes alone was inaccurate [14,45], we used the previously validated operational definition comprising diagnostic codes and medications [14], which could have reduced over-estimation of HZ in this study. Second, recurrent HZ cases were not included in this study. The reported recurrence of HZ ranges from 1.18% to 5.3% in South Korea [46,47], hence HZ IRs might have been estimated higher if recurrent cases were included. Despite these limitations, given the extensiveness and completeness of the NHID, there are many strengths in utilizing the NHID for epidemiology research. The study included almost the entire Korean population for a decade; thus, the results can be generalizable to the Korean population. Also, it contains detailed information on healthcare utilization for each individual, which could possibly eliminate recall bias.

In conclusion, HZ IRs increased substantially over a decade, even after adjustment for changes in age structure and comorbidities in the population. However, trends in HZ incidence differed by age group during 2012–2015. These findings suggest that the impact of universal varicella vaccination on HZ epidemiology might be limited to subgroups such as parents of young children. However, the reason for the recent deceleration in increasing trends in older adults is still unknown. In the era of varicella vaccination where varicella incidence is markedly reduced, the potential role of HZ in contributing to exogenous immune boosting in adults should be explored. Despite the recent deceleration, HZ is a significant health burden that is expected to continue to increase. Therefore, the HZ incidence should be monitored continuously for better understanding of the recent changes in HZ epidemiology, and in order to provide the evidence to develop effective preventive strategies against HZ in the future.

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Authors contribution

All authors have read and approved the manuscript and have agreed to be accountable for all aspects of the work for appropriate portions of the content. JKC managed data and wrote the manuscript. SHP designed the study, performed statistical analysis, and wrote the manuscript. SP managed data and performed statistical analysis. SYC, HJL, SHK, SMC, DGL, JHC, and JHY provided critical reviews.

Declaration of Competing Interest

DGL has received research grants from GSK and MSD; has served as a consultant for MSD, Pfizer, and SK Chemical; and has received payment for lectures, including service on speakers' bureaus from MSD and Pfizer, outside the submitted work.

SYC has received research grants from GSK and MSD and has received payment for lectures, including service on speakers' bureaus from MSD, outside the submitted work.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.086.

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