ABSTRACT

Older adults, women and patients with immunocompromised (IC) or chronic medical conditions have a higher incidence of herpes zoster (HZ) and are at higher risk of developing HZ-associated complications such as postherpetic neuralgia. The incidence rates of HZ in various IC and chronic conditions have been previously reported in a retrospective cohort study using claims data from Japanese adults. Here, we report further analyses from this cohort using univariate and multivariable Cox regression to estimate crude and adjusted hazard ratios (HRs) associated with different IC and chronic conditions. After adjusting for multiple covariates (age, sex and other coexisting medical conditions), the risk of HZ was higher in women (HR, 1.14 [95% CI, 1.11–1.17]), irrespective of age and increased with increasing age, being substantially higher in patients aged 65 years or older (HR, 3.28 [95% CI, 3.07–3.49]) when compared with those aged 18–29 years. The highest HRs were observed for the following specific IC conditions: hematopoietic stem cell transplant recipients (HR, 9.85 [95% CI, 6.80–14.28]), hematological malignancy (HR, 3.22 [95% CI, 2.54–4.09]), systemic lupus erythematosus (HR, 2.46 [95% CI, 1.45–4.15]) and inflammatory bowel disease (HR, 1.59 [95% CI, 1.14–2.21]). For most other IC and chronic medical conditions, a higher risk was also apparent though of a smaller magnitude (HRs ranging from 1.2 to <1.5). These results corroborate our previous findings and demonstrate an increased risk of HZ associated with different IC and chronic conditions.

Key words: claims database, epidemiology, herpes zoster, immunocompromised, Japan.

INTRODUCTION

Herpes zoster (HZ), which is due to the reactivation of latent varicella zoster virus (VZV) within dorsal root/cranial nerve ganglia, presents a substantial clinical and health-care resource utilization burden, both globally and in Japan. HZ typically manifests as an acute blistering rash involving the affected dermatome(s), accompanied by pain, which may be substantial. The lifetime risk for developing HZ is estimated at 30%. Declining VZV-specific cell-mediated immunity, which predisposes an individual to VZV reactivation and clinical HZ, occurs as a result of age-related “immunosenesence”, which may explain the greater risk and higher incidence of HZ in individuals aged 50 years or more. Incidence and risk is greater in women and in individuals with immunocompromised (IC) medical conditions (e.g., patients with hematological or solid tumors or those receiving immunosuppressive therapies) and also in individuals with certain chronic medical conditions. Older adults and those with IC conditions (where complications may be more severe) and with chronic medical conditions are also at greater risk of HZ-associated complications, most commonly postherpetic neuralgia (PHN), but also other neurological complications, ocular complications, and disseminated HZ.

Previously, we reported on the HZ disease burden in the general adult Japanese population and in those patients with IC and chronic medical conditions, using data derived from the Japan Medical Data Center claims database (JMDC-CDB). The aim of that study was to estimate incidence rates (IRs) of HZ in adults aged 18–74 years, both in the general population and within subsets of patients with specific IC and chronic conditions. IRs of HZ were found to be higher in females (5.33/
METHODS

Study design and study population

The study design, data sources and study population have been previously reported.16 In brief, this was a retrospective, observational cohort study (GSK study identifier: 204513) using data derived from the JMDC-CDB,17 a nationwide electronic database of individual records from contracted health insurance associations (payers), which covers approximately 4 million registered individuals (representing ~3% of the total Japanese population <75 years of age in 2011). Medical claims data collected includes post-approved claims information for patient demographics, medication prescriptions, medical procedures, laboratory investigations and receipt of other medical services, with associated standardized International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes. Medication prescriptions are recorded using Anatomical Therapeutic Chemical (ATC) classification system codes.

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practices, and the principles of the Declaration of Helsinki, and also national ethical guidelines.18 The JMDC-CDB is comprised of anonymized, unlinked secondary data, so the study protocol and other relevant study information were filed with the local institutional review board, and access to medical records granted by the ethics committee of external healthcare providers (Kitamachi Clinic Ethics Committee, Tokyo, Japan) who granted a waiver of informed consent.

The overall study cohort was comprised of those individuals registered in the JMDC-CDB aged 18 years or older at any time between 1 January 2005 and 31 December 2014 with data available for at least 1 year during this period. Individuals were also categorized on the basis of coexisting specific IC or chronic medical conditions (as determined using ICD-10 codes, procedure codes and/or ATC codes). Those subjects with an IC condition were also included in an overall IC cohort. Patient disposition is shown in Figure 1.

Specific IC conditions included autoimmune thyroiditis (AT), chronic kidney disease accompanied by the requirement for dialysis or renal transplant for the treatment of end-stage renal disease (ESRD), congenital immune immunodeficiency (CID), hematological malignancies (HM), hematopoietic stem cell transplant (HSCT), inflammatory bowel disease (IBD), multiple sclerosis (MS), polymyalgia rheumatica (PR), psoriasis (PSOR), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), solid organ malignancies (SOM), solid organ transplantation (SOT), type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM2), viral hepatitis.

For these conditions, incidence rates and hazard ratios were not computed as these groups either had fewer than 100 subjects and/or fewer than 10 incident HZ episodes.

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artery disease including angina or myocardial infarction) (IHD), osteoarthritis (OA), osteoporosis (OST_PO), renal failure (RF), stroke (ST), type 2 diabetes mellitus (DM2), and viral hepatitis (VH).

An individual could have more than one condition and so could be included in more than one condition category. To ensure that follow-up was started at the actual time of diagnosis, subjects were considered as having an IC or chronic disorder provided that the date of the first claim related to this IC or chronic disorder occurred at least 12 months (365 days) after the individual's entry into the JMDC-CDB.

All subjects from the previously reported overall study population were included in the analysis. Index date definitions (or start of follow up) were as previously reported. In brief, the index date for any given subject was set as follows: for an individual with an IC/chronic condition, the index date was set to the earliest of such index dates; for all other subjects, the index date was set to 12 months after entry index date for any given subject was set as follows: for an individual with multiple IC/chronic conditions, the index date was set to the earliest of such index dates; for all other subjects, the index date was set to 12 months after entry into the database or, if younger than 18 years at this date, to 1 January of the year they turned 19 years (if <18 years at such date); note that these dates relate to the date of diagnosis and so the index date is not necessarily the date of disease onset. For an individual with multiple IC/chronic conditions, the index date was set to the earliest of such index dates; for all other subjects, the index date was set to 12 months after entry into the database or, if younger than 18 years at this date, to 1 January of the year they turned 19 years.

Study assessments
Case definition of HZ episodes were as previously described. In brief, a HZ episode was defined as individuals reporting at least one medical claim related to HZ (ICD-10 codes B02, B02.0, B02.1, B02.2, B02.3, B02.7, B02.8 and B02.9) associated with a prescription claim for an appropriate antiviral drug (e.g., acyclovir) within 1 month of the date of the HZ diagnosis. The incident HZ episode was defined as the first recorded HZ episode occurring after the index date in the overall study cohort.

Statistical analyses
Incidence rates of HZ
Incidence rates of HZ per 1000 person-years (PY) with exact Poisson 95% confidence intervals (CIs) were calculated for the overall study cohort, the overall IC cohort and for each separate IC and chronic condition, and were also stratified by age and sex. In brief, the IR was calculated as the total number of incident HZ cases divided by the period at risk (in PY) in the corresponding cohort or condition category and strata. In this, the period at risk was calculated from the index date until the earliest of the following dates: first recorded HZ episode; end of follow up within the JMDC-CDB; or end of study (31 December 2014). IRs were not computed for any medical condition category with fewer than 100 individuals or fewer than 10 incident HZ episodes overall.

Risk of HZ
Univariate and multivariable Cox regression analyses were conducted in the overall study population to evaluate risk factors for developing HZ and to estimate the risk of HZ (HR with 95% CI) associated with specific IC or chronic conditions.

The dependent variable was the time from the index date in the overall study cohort (T0) to the first recorded HZ episode (“incident HZ”). Subjects without any HZ events were censored at the end of follow up or end of study (31 December 2014). The following potential risk factors were included in the analysis as covariates: occurrence of each IC/chronic condition (each modeled as a time-varying covariate); age at index date; and sex. IC and chronic conditions included as risk factors in the Cox regression models were those occurring in at least 100 subjects with the condition and with at least 10 HZ cases.

Hazard ratios for the risk of HZ in the overall IC cohort and for each individual IC and chronic condition were generated using the remainder of the total study cohort as the comparator (i.e., for the overall IC cohort the comparator was all subjects not belonging to the overall IC cohort, while for the individual IC and chronic medical condition categories the comparator was all subjects not belonging to the relevant individual IC and chronic condition categories); depending on the condition category being evaluated, this might have included subjects with other IC or chronic medical conditions.

As a first step, univariate Cox models were computed separately for each risk factor (i.e., age, sex and each condition), without adjustment for the other covariates. This analysis generated unadjusted HR with 95% CI for any IC condition (constituting the overall IC cohort) and for each separate IC or chronic medical condition.

For the preliminary multivariable analysis, Cox models were performed separately, in the overall IC cohort (any IC condition) and for each individual IC and chronic condition, while adjusting for both age and sex. Interactions between the condition and age or sex were also assessed. Interactions were included in the final model if this changed the HR by threefold or higher and if the P-value associated with the interaction was lower than 0.01. Each of these preliminary models provided age and sex adjusted HRs for each condition and its 95% CI, IC and chronic medical conditions of $P < 0.1$ in these preliminary models were retained in the final multivariable model to generate adjusted HR (with 95% CI) for each condition adjusted for age, sex and for other IC or chronic medical conditions. All statistical analyses were performed using the Statistical Analysis System version 9.3 (SAS Institute, Cary, NC, USA) and the Drug and Development web portal.

RESULTS
The overall study cohort comprised of 2 778 476 subjects; 45.2% were women and 76.1% were less than 50 years of age; only 2.8% were 65 years or older. In total, 51 818 subjects (1.86%) had at least one incident IC condition. A total of 27 795 HZ episodes were reported for the overall study cohort, with 877 HZ episodes in subjects within the IC cohort (Fig. 1).

Incidence rates of HZ
Incidence rates of HZ in the overall study cohort, the overall IC cohort and for the individual IC and chronic conditions...
**Table 1. HZ incidence rates per 1000 patient-years (with 95% CI) in the overall study cohort, the total IC cohort and in each IC and chronic conditions by age and sex**

| Condition category | Overall | Age strata (years) | Sex | Female | Male |
|--------------------|---------|--------------------|-----|--------|------|
|                    |         | 18-49             | 50-64 | ≥65    |      |
| Overall study cohort | 4.92 (4.86-4.98) | 4.02 (3.96-4.08) | 7.21 (7.04-7.39) | 9.71 (9.31-10.11) | 12.63 (11.99-13.30) |
| Total IC cohort     | 8.87 (8.29-9.48) | 6.50 (5.86-7.20) | 10.50 (9.32-11.79) | 14.59 (12.12-17.42) | 16.94 (13.37-20.90) |
| IC conditions       |         |                   |      |        |      |
| Autoimmune thyroiditis (AT) | 8.34 (6.64-10.34) | 5.91 (4.20-8.07) | 10.81 (7.08-15.84) | 17.12 (8.21-31.48) | 20.76 (8.34-42.76) |
| Congenital immune deficiency (CID) | 6.28 (5.06-7.70) | 5.82 (4.53-7.36) | 6.87 (3.84-11.33) | 17.80 (7.16-36.17) | 5.44 (0.14-30.28) |
| Hematological malignancies (HM) | 28.18 (22.75-34.52) | 20.21 (14.23-27.86) | 31.94 (21.85-45.09) | 53.87 (30.15-88.85) | 50.44 (23.06-95.75) |
| Hematopoietic stem cell transplant (HSCT) | 151.68 (111.45-201.71) | 115.34 (71.40-176.31) | 215.79 (129.92-336.99) | 180.28 (98.54-320.72) | – |
| Inflammatory bowel disease (IBD) | 7.35 (5.15-10.17) | 6.76 (4.49-9.76) | 8.33 (7.04-19.43) | 10.76 (0.27-59.95) | 19.52 (0.49-108.75) |
| Psoriasis (PsOR) | 5.55 (4.26-7.09) | 3.49 (2.28-5.11) | 8.28 (5.31-12.33) | 12.64 (5.78-24.00) | 10.64 (2.19-31.08) |
| Rheumatoid arthritis (RA) | 9.18 (6.95-11.86) | 6.17 (3.82-9.44) | 10.27 (6.44-15.55) | 13.30 (4.88-28.95) | 39.75 (17.16-78.33) |
| Systemic lupus erythematosus (SLE) | 15.91 (8.91-26.25) | 16.71 (8.34-29.89) | 13.71 (2.83-40.08) | – | – |
| Solid organ malignancies (SOM) | 9.41 (5.10-13.82) | 6.73 (3.59-8.03) | 9.81 (8.28-11.53) | 13.42 (10.55-16.82) | 14.94 (11.29-19.40) |
| Vascular (autoimmune) (VAs) | 6.06 (3.23-10.36) | 4.76 (1.91-9.81) | 4.42 (0.54-15.98) | 21.58 (4.45-63.08) | 12.77 (0.32-71.14) |
| Other autoimmune/collagen- connective tissue disease (OAC) | 9.93 (6.84-13.95) | 8.54 (5.06-13.49) | 12.73 (6.53-22.77) | 9.18 (1.11-33.18) | 16.96 (2.05-61.26) |
| Chronic conditions |         |                   |      |        |      |
| Asthma (AST) | 5.40 (4.57-6.34) | 4.92 (4.04-5.95) | 6.76 (4.53-9.71) | 8.36 (3.61-16.47) | 7.42 (2.02-19.01) |
| Chronic hepatitis, cirrhosis (CHC) | 5.91 (5.34-6.52) | 4.86 (4.26-5.52) | 8.02 (6.62-9.63) | 11.18 (7.78-15.54) | 8.07 (4.17-14.10) |
| Chronic obstructive pulmonary disease (COPD) | 7.25 (6.06-8.60) | 5.97 (4.63-7.59) | 9.71 (7.03-13.08) | 6.92 (3.32-12.73) | 11.66 (5.82-20.87) |
| Depression (Dep) | 5.98 (5.46-6.51) | 5.26 (4.74-5.82) | 7.80 (6.36-9.47) | 15.63 (10.12-23.08) | 15.97 (9.30-25.56) |
| Heart failure (HF) | 6.57 (5.07-7.29) | 5.15 (4.42-5.95) | 8.63 (7.10-10.38) | 8.99 (6.26-12.50) | 12.72 (8.45-18.38) |
| Ischemic heart disease (IHD) | 8.64 (7.49-9.92) | 5.81 (4.38-7.51) | 9.16 (7.25-11.41) | 10.45 (7.19-14.67) | 15.17 (10.44-21.30) |
| Osteoarthritis (OA) | 8.08 (7.06-8.57) | 5.00 (4.44-5.62) | 8.85 (6.06-9.71) | 12.20 (10.50-14.10) | 15.83 (13.18-18.60) |
| Osteoporosis (OST_P0) | 12.90 (10.83-15.26) | 9.11 (5.57-14.08) | 11.26 (6.22-15.07) | 14.72 (8.96-21.14) | 17.98 (12.96-24.30) |
| Stroke (ST) | 9.26 (6.37-13.00) | 9.24 (4.23-17.55) | 8.38 (4.18-15.00) | 8.13 (2.64-18.97) | 12.23 (5.28-24.10) |
| Renal failure (RF) | 5.68 (3.82-10.84) | 3.58 (0.98-9.17) | 14.73 (7.61-25.72) | – | – |
| Type 2 diabetes mellitus (DM2) | 6.79 (6.05-7.59) | 4.85 (3.93-5.90) | 6.97 (4.79-8.32) | 10.14 (7.60-13.27) | 12.93 (9.00-17.98) |
| Viral hepatitis (VH) | 7.89 (6.63-9.33) | 6.28 (4.83-8.03) | 9.16 (6.71-22.22) | 10.47 (5.88-17.27) | 14.30 (7.39-24.98) |

95% CIs calculated using the exact Poisson test. Only condition categories with at least 100 subjects and at least 10 HZ cases overall are reported (see also Fig. 1). For each condition, IR and associated CI are not reported within strata with less than 10 cases or less than 100 subjects (annotated as "-"). A person can have more than one IC or chronic condition and can be included in several condition categories. CI, confidence interval; HZ, herpes zoster, IC, immunocompromised.
Table 2. Hazard ratios for the risk of HZ (univariate and multivariable analyses)

| Category/Condition | n/N | Univariate analysis | Multivariable analysis (preliminary step) | Multivariable analysis (final model) |
|--------------------|-----|---------------------|------------------------------------------|-------------------------------------|
|                    |     | HR (95% CI)         | P                                        | HR (95% CI)                         | P                                        |
| Any IC condition   | 877/51 818 | 1.83 (1.71–1.96) | <0.001 | 1.52 (1.42–1.63) | <0.001 |
| IC conditions      |     |                     |                                            |                                    |
| Autoimmune thyroiditis (AT) | 83/5495 | 1.72 (1.39–2.14) | <0.001 | 1.48 (1.19–1.84) | <0.001 | 1.41 (1.13–1.75) | 0.002 |
| Congenital immune deficiency (CID) | 92/712 | 1.29 (1.05–1.59) | 0.017  | 1.32 (1.07–1.62) | 0.010 | 1.21 (0.98–1.49) | 0.078 |
| Hematological malignancies (HM) | 93/1896 | 5.94 (4.85–7.29) | <0.001 | 4.94 (4.03–6.66) | <0.001 | 3.22 (2.54–4.09) | <0.001 |
| Hematopoietic stem cell transplant (HSCT) | 47/281 | 27.32 (19.91–37.49) | <0.001 | 23.37 (17.00–32.13) | <0.001 | 9.85 (6.80–14.28) | <0.001 |
| Inflammatory bowel disease (IBD) | 36/2254 | 1.53 (1.10–2.13) | 0.012  | 1.63 (1.17–2.27) | 0.004 | 1.59 (1.14–2.11) | 0.006 |
| Other autoimmune/collagen-/connective tissue disease (OAI) | 33/1517 | 2.05 (1.45–2.90) | <0.001 | 1.73 (1.23–2.45) | 0.002 | 1.54 (1.09–2.19) | 0.015 |
| Psoriasis (PSOR) | 63/5316 | 1.11 (0.86–1.43) | 0.437  | 1.00 (0.78–1.29) | >0.99 |
| Rheumatoid arthritis (RA) | 57/2711 | 1.89 (1.45–2.46) | <0.001 | 1.53 (1.17–1.98) | 0.002 | 1.42 (1.09–1.85) | 0.01 |
| Systemic lupus erythematosus (SLE) | 15/452 | 3.17 (1.88–5.35) | <0.001 | 2.84 (1.68–4.80) | <0.001 | 2.46 (1.45–4.15) | <0.001 |
| Solid organ malignancies (SOM) | 401/24 495 | 1.94 (1.75–2.14) | <0.001 | 1.42 (1.28–1.57) | <0.001 | 1.36 (1.23–1.51) | <0.001 |
| Vacculitis (autoimmune) (VAS) | 13/1100 | 1.21 (0.69–2.11) | 0.515  | 1.07 (0.61–1.89) | >0.805 |
| Chronic conditions  |     |                     |                                            |                                    |
| Asthma (AST)       | 150/12 930 | 1.12 (0.95–1.31) | 0.185  | 1.11 (0.95–1.31) | 0.196 |
| Chronic hepatitis, cirrhosis (CHC) | 400/32 222 | 1.18 (1.07–1.31) | 0.001  | 1.13 (1.02–1.25) | 0.017  | 1.10 (0.99–1.21) | 0.078 |
| Chronic obstructive pulmonary disease (COPD) | 151/9374 | 1.49 (1.25–1.77) | <0.001 | 1.28 (1.08–1.53) | 0.005  | 1.24 (1.04–1.47) | 0.018 |
| Depression (DEP)   | 527/40 498 | 1.20 (1.10–1.31) | <0.001 | 1.26 (1.15–1.38) | <0.001 | 1.23 (1.13–1.34) | <0.001 |
| Heart failure (HF) | 357/26 661 | 1.33 (1.20–1.48) | <0.001 | 1.19 (1.07–1.32) | 0.002  | 1.15 (1.03–1.28) | 0.012 |
| Ischemic heart disease (IHD) | 203/12 374 | 1.72 (1.49–1.98) | <0.001 | 1.28 (1.11–1.47) | <0.001 | 1.22 (1.06–1.41) | 0.006 |
| Osteoarthritis (OA) | 107/77 334 | 1.65 (1.55–1.75) | <0.001 | 1.22 (1.14–1.30) | <0.001 | 1.19 (1.12–1.27) | <0.001 |
| Osteoporosis (OST_PO) | 136/6284 | 2.60 (2.19–3.09) | <0.001 | 1.50 (1.26–1.78) | <0.001 | 1.41 (1.19–1.68) | <0.001 |
| Stroke (ST)        | 33/2080 | 1.84 (1.30–2.62) | <0.001 | 1.20 (0.85–1.71) | 0.305  |
| Renal failure (RF) | 16/1438 | 1.27 (0.76–2.10) | 0.363  | 0.98 (0.59–1.63) | 0.947  |
| Type 2 diabetes mellitus (DM2) | 308/22 336 | 1.29 (1.15–1.45) | <0.001 | 1.00 (0.89–1.13) | 0.985  |
| Viral hepatitis (VH) | 137/8522 | 1.59 (1.34–1.89) | <0.001 | 1.34 (1.13–1.60) | <0.001 | 1.18 (1.00–1.41) | 0.058 |

1Unadjusted HR. 2HR for each condition adjusted for age at index date and Sex. Conditions of P < 0.1 in this model entered the final multivariable model. 3HR for each condition adjusted for age at index date and Sex and for other IC or chronic conditions. 495% CI are Wald-type 95% CI obtained from Cox regression. P-values calculated using Wald test. *Denotes overall P-value. n value is the number of HZ cases in any category; N value is the number of subjects in each category. Only condition categories counting at least 100 subjects and at least 10 HZ cases overall were included as risk factors in the Cox regression analysis (see also Fig. 1). For each category, HRs were generated using the remainder of the total study cohort as the comparator (see statistical analysis section). CI, confidence interval; HR, hazard ratio; HZ, herpes zoster, IC, immunocompromised.

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(stratified by age and sex) are presented in Table 1. IRs were higher in women and increased with age, both for the overall study cohort and for the subset of subjects from the total IC cohort. A similar trend was observed for most individual IC and chronic conditions. The highest IRs were observed in subjects with HSCT: 201.09/1000 PY (95% CI, 127.47–301.73) in females and 122.77/1000 PY (95% CI, 78.66–182.68) in males (Table 1).

Risk of HZ
The risk of HZ associated with IC and chronic conditions was assessed in the overall study cohort using univariate and multivariable Cox regression to calculate unadjusted and adjusted HR with 95% CI (Table 2). On univariate analysis, the risk hazard of HZ was 15% higher in women than in men (HR, 1.15 [95% CI, 1.13–1.18]), and it increased with increasing age; with a threefold greater risk in subjects aged 65 years or older compared with those aged 18–29 years (HR, 3.51 [95% CI, 3.30–3.74]).

Unadjusted risk in the IC cohort was significantly higher than in the rest of the overall study cohort (HR, 1.83 [95% CI, 1.71–1.96]). Of the specific IC conditions, the highest risk was seen in subjects with HSCT (HR, 27.32 [95% CI, 19.91–37.49]) and in those with HM (HR, 5.94 [95% CI, 4.85–7.29]). Of the autoimmune conditions, the highest risk was observed for individuals with SLE (HR, 3.17 [95% CI, 1.88–5.35]) (Table 2).

The final multivariable model provided the risk of HZ associated with each IC or chronic condition after adjustment for age, sex and other IC or chronic conditions (Table 2, Fig. 2). IC conditions associated with the highest risk (HR, >2.0) were HSCT (HR, 9.85 [95% CI, 6.80–14.28]), HM (HR, 3.22 [95% CI, 2.54–4.09]) and SLE (HR, 2.46 [95% CI, 1.45–4.15]). Other IC conditions associated with a moderately higher risk of HZ (1.5 to <2.0) were IBD and OAI. A few chronic medical conditions (AT, CID, RA, SOM, COPD, DEP, IHD, OA and OST_POU were also associated with a small magnitude of increased risk (1.2 to <1.5). In this final model, the slightly greater risk in females (HR, 1.14 [95% CI, 1.11–1.17]) and substantially higher risk in subjects aged 65 years or more (HR, 3.28 [95% CI, 3.07–3.49]) compared with those aged 18–29 years remained, as did the marked trend for increasing risk with increasing age (Table 2).

**DISCUSSION**
In this retrospective observational cohort study, we used claims data to evaluate the risk of HZ associated with different IC and chronic medical conditions.

Previously, for this same study population we found that IRs for HZ were higher in females compared with males and increased with greater age, and were highest in patients with IC conditions (and in particular those undergoing HSCT, subjects with HM and those with SLE), and somewhat lower in subjects with chronic medical conditions. Those findings are consistent with those from other epidemiological studies which report an increasing incidence of HZ with older age, and also a higher incidence in patients with malignancy, and other IC conditions such as SLE. In the further data we...
present here, we show that the influence of age and sex is also apparent in patients with different IC and chronic medical conditions.

When evaluating the risk of HZ in the current study analysis, HRs obtained through Cox regression in univariate analyses demonstrated a similar pattern to that of IRs, with an increased risk of HZ in females, an increasing risk of HZ with increasing age, and the highest risk of HZ observed for subjects undergoing HSCT, and in subjects with HM or SLE. Adjustment for age and sex in the preliminary multivariable analyses had some impact; with the resultant adjusted HR being generally lower across nearly all IC and chronic conditions (although remaining highest in the HSCT, HM or SLE categories). However, in the final multivariate model, which also accounted for the presence of coexisting IC or chronic medical conditions, we found that for most conditions the HRs were relatively unchanged. In contrast, the risk in patients with HSCT and with HM decreased substantially. Although IC conditions are the main drivers of increased risk of HZ in this population, age and sex remain important considerations when determining the overall risk for each individual patient.

The increased incidence and greater risk of HZ in older subjects and in particular in those subjects with specific IC and chronic conditions reported here indicates that these patient populations may benefit most from preventive strategies including vaccination. At present, a number of effective vaccines to prevent episodes of primary or recurrent HZ episodes are available. These include a live attenuated HZ vaccine (ZVL, Zostavax [Merck Sharp & Dohme, Kenilworth, NJ, USA]) which is globally available, and an alternative live vaccine in Japan, Varicella Vaccine Live [VVL], which contains a similar varicella titer to that used in ZVL. More recently, an adjuvanted recombinant zoster vaccine (RZV, Shingrix [GSK, Rixensart, Belgium]) has been approved for use in older adults in Japan (≥50 years), and elsewhere including the USA and Canada (≥50 years), and Germany (≥60 years).

The efficacy of RZV has been demonstrated in two large, global phase III trials (both of which included Japanese subjects) where vaccine efficacy of over 90% for HZ and for PHN was observed. Recent cost-effectiveness analyses for the use of RZV in Japan have estimated that RZV could prevent a substantially greater number of HZ cases and reduce

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**Plain Language Summary**

**What is the context?**
- Three out of 10 adults are at risk of developing herpes zoster (shingles). Symptoms include a painful skin rash while pain lasting for months or for even longer periods is a common complication.
- Herpes zoster primarily affects adults over 50 years of age and individuals with weaker immune defences.
- The risk of Japanese patients who are immunocompromised or have a chronic disease such as an autoimmune disease, diabetes or a chronic respiratory disease developing herpes zoster is not fully understood.

**What is new?**
- We studied the link between 16 immunocompromising conditions and 12 chronic disease conditions and herpes zoster development in Japanese patients.
- The results show an increased risk of developing herpes zoster for patients with pre-existing immunocompromising conditions or some chronic disease conditions.
- Age and gender remain important risk factors in these patients.

**What is the impact?**
- Specific medical conditions that weaken immune defences increase the risk of developing herpes zoster.
- Preventive strategies in these patients are important.

**Figure 3.** Plain-language summary.
resource utilization in older adults compared with VVL and would be a cost-effective strategy.\textsuperscript{20,21} Furthermore, in the context of our findings, as a recombinant vaccine, RZV has the potential for use in immunocompromised subjects in which live attenuated vaccines are contraindicated.\textsuperscript{27} The safety and immunogenicity of RZV immunization in immunocompromised subjects has been evaluated in a number of randomized studies (in patients undergoing HSCT, in patients with hemato- logical or solid cancers, and in patients following renal transplantation) with no safety concerns.\textsuperscript{28–32} Although RZV is not approved for use in immunocompromised individuals aged less than 50 years, it is possible that future use in these patients could provide additional benefits to reduce the disease burden in those at greatest risk of HZ.

The present study has some limitations. As a retrospective study, HZ episodes were identified using claims-based data and were not clinically validated. The HZ episode definition required prescription of an antiviral agent as well as the associated ICD-10 code, so HZ cases where antiviral therapy was not prescribed would not have been included, which might have led to the underestimation of incidence rates. Another limitation is that the index date for IC and chronic conditions was the first date of diagnosis and as for some diseases the first symptoms can appear a long time before the first diagnosis, the index date may not necessarily represent the date of disease onset. In addition, our study population was relatively young, with more than 75% aged under 50 years; this might have influenced the HZ incidence and also the prevalence of medical conditions within our cohort. In our regression analyses, while we adjusted for important covariates, we did not account for the effects of exposure to specific immunosuppressive or immunomodulatory agents (including corticosteroids, chemotherapy, immunosuppressants such as methotrexate and biologic therapies). As it is recognized that these agents are associated with increased risk of HZ,\textsuperscript{8,12,14,33–36} they might have had an impact on the HRs reported in this study.

Nevertheless, our general findings that the risk of HZ is greater in subjects with IC conditions are consistent with those reported in previous studies.\textsuperscript{8,12,14,33–36} While our findings should be interpreted in light of such limitations, the main strength of this study was the use of a large insurance claims database which allowed for the analysis of a large and broadly representative portion of the Japanese population. Figure 3 presents a plain-language summary of the context, outcomes and potential impact of this study for health-care providers.

ACKNOWLEDGMENTS: GlaxoSmithKline Biologicals was the funding source and was involved in all study activities and overall data management (collection, analysis and interpretation) of this study (GSK identifier: 204513). GlaxoSmithKline Biologicals also funded all costs associated with the development and publishing of the present manuscript. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. The authors are grateful to Arnaud Didierlaurent, Jing Chen, Masayuki Ogawa, Toshihiko Kaise and Jennifer Han (all at GSK) for their valuable comments during manuscript draft development and to Rebecca Crawford (GSK) for supporting publication development. The authors would like to thank Business & Decision Life Sciences platform for editorial assistance and manuscript coordination, on behalf of GSK. Matthieu Depuydt coordinated manuscript development and editorial support. Iain O’Neill (freelance medical writer, on behalf of GSK) provided medical writing assistance. Shingrix is a trademark owned by or licensed to the GSK group of companies. Zostavax is a trademark of Merck Sharp & Dohme.

CONFLICT OF INTEREST: S. I. has received consulting fees and honoraria from the GSK group of companies. T. M. is an employee of the GSK group of companies, Y. G. has received consulting fees from the GSK group of companies. G. D. and C. J. report consulting fees to their organization, Business & Decision Life Sciences, from the GSK group of companies as a part of their function in Statistical Programming. D. R. is an employee of the GSK group of companies and holds shares in the GSK group of companies.

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