

BMJ Open Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012

Emad A. Yanni,¹ Germano Ferreira,² Morgane Guennec,³ Yassine El Hahi,⁴ Amale El Ghachi,⁵ François Haguinet,⁶ Emmanuelle Espie,⁶ Veronique Bianco¹

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¹GSK, Rockville, Maryland, USA

²P-95 Epidemiology and Pharmacovigilance Services, Heverlee, Belgium

³Keyrus Biopharma c/o GSK, Wavre, Belgium

⁴Valesta c/o GSK, Wavre, Belgium

⁵AIXIAL c/o GSK, Boulogne-Billancourt, France

⁶GSK, Wavre, Belgium

Correspondence to

Dr Emad A. Yanni;
emad.a.yanni@gsk.com

ABSTRACT

Objectives Herpes zoster (HZ) is caused by reactivation of varicella-zoster virus which remains latent in individuals after a varicella infection. It is expected that HZ will be more frequent in immunocompromised (IC) individuals than in immunocompetent (IC-free). This study assessed the incidence rate (IR) of HZ in individuals with a wide set of IC conditions and in IC-free individuals.

Setting A retrospective cohort study was conducted in England using data (January 2000 to March 2012) from the Clinical Practice Research Datalink with linkage to the Hospital Episodes Statistics.

Participants A cohort of 621 588 individuals with 16 selected IC conditions and a gender/age-matched cohort of IC-free individuals were identified. The IC conditions included haematopoietic stem cell transplant (HSCT), solid organ transplant, malignancies, autoimmune diseases and users of immunosuppressive medications.

Outcomes IR of HZ per 1000 person-years (PY) was estimated. Proportions of postherpetic neuralgia (PHN) and other HZ complications within 90 days of HZ onset were also estimated among patients with HZ. Risk factors for PHN in IC individuals with HZ were assessed by a multivariate regression model.

Results The overall IR of HZ in the IC cohort was 7.8/1000 PY (95% CI 7.7 to 7.9), increasing with age from 3.5/1000 PY (3.4–3.7) in individuals aged 18–49 years to 12.6/1000 PY (12.2–13.0) in individuals aged ≥80 years. This IR in the IC-free cohort was 6.2/1000 PY (6.1–6.3). The overall IR of HZ varied across IC conditions, ranging from 5.3 (5.1–5.5) in psoriasis to 41.7/1000 PY (35.7–48.4) in HSCT. The proportions of PHN and other HZ complications were 10.7% (10.2–11.1) and 2.9% (2.7–3.2) in the IC cohort, but 9.1% (8.7–9.5) and 2.3% (2.1–2.6) in the IC-free cohort, respectively.

Conclusion IC population contributes to the public health burden of HZ in England. Vaccination might be the most preferable HZ preventive measure for the IC population.

INTRODUCTION

Herpes zoster (HZ) is usually a painful vesicular skin rash occurring more frequently in older adults and immunocompromised (IC) individuals. HZ is caused by reactivation of

Strengths and limitations of this study

- A retrospective cohort study based on the Clinical Practice Research Datalink (CPRD) to estimate the incidence of herpes zoster in individuals with the most common immunocompromised conditions in England.
- The CPRD includes continuous patients' records for about 7% of the UK population and is broadly representative of the characteristics of patients and general practitioner practices in the UK, with long follow-up and quality data.
- Sixty per cent of patients in the CPRD have data available in the Hospital Episode Statistics database and we used these linked data.
- A matched cohort of immunocompetent individuals was included, with 1:1 matching based on year of birth, gender and practice geographical location.
- The individuals with none of the selected immunocompromised conditions diagnosed are not necessarily immunocompetent.

the latent varicella-zoster virus (VZV) when VZV specific cell-mediated immunity (CMI) declines.^{1 2}

A variety of HZ risk factors including immunocompromising conditions (eg, solid organ and haematological malignancies, haematopoietic stem cell and solid organ transplant), immunosuppressive drugs, chronic medical conditions (eg, diabetes and chronic obstructive pulmonary disease (COPD)) and advancing age may negatively interfere with VZV-specific CMI.^{3–5}

Despite contributing a small fraction of overall HZ cases, individuals with IC conditions make a large contribution to the societal healthcare burden because of their higher risk for HZ and HZ complications, including HZ ophthalmicus and postherpetic neuralgia (PHN), that may require patient hospitalisation and/or changes of the treatment

regimen.^{3 4 6–9} IC patients with HZ are also more likely to develop recurrent HZ episodes.¹⁰

While there are few studies providing an estimate of the incidence of HZ in a set of selected IC conditions or patients with altered immune function,^{3 4} many studies have assessed the risk of developing HZ in specific individual IC conditions, such as cancers,^{5 11 12} rheumatoid arthritis (RA),¹³ psoriasis (PSOR)^{14–16} and inflammatory bowel diseases (IBD).¹⁷ Currently, there is no study evaluating the full burden of HZ in a wider IC population, including HZ complications, healthcare resource utilisation and associated costs.

This study therefore aimed to estimate the incidence of HZ in a selected IC population and in an IC-free (ie, immunocompetent) population aged ≥ 18 years. Among patients with HZ, the proportions of PHN and other HZ-related complications, recurrence and HZ-associated mortality rates were assessed. We also investigated risk factors for developing PHN among patients with HZ in the selected IC population.

METHODS

This was a retrospective observational cohort study using data from the UK Clinical Practice Research Data-link (CPRD). This is a primary care database of almost 12 million anonymised patient medical records including clinical events (medical diagnoses), referrals to specialists and secondary care, diagnostics tests, medical prescriptions, other routine medical services provided in general practices and some lifestyle factors (ie, smoking and alcohol consumption).¹⁸ The information in CPRD is coded with Read codes, which contain hundreds of thousands of clinical terms, synonyms and abbreviations covering all aspects of patient care including signs and symptoms, treatment and therapies, investigations, occupations, diagnoses and drugs.¹⁹

CPRD currently contains records for about 4.4 million individuals (7% of the UK population) registered with 674 general practitioner (GP) practices²⁰ and is considered to be broadly representative of the characteristics of patients and GP practices in the UK.^{18 20 21} Fifty-eight per cent of the CPRD practices (a subset of English practices) are linked to the Hospital Episode Statistics (HES) database storing International Classification of Diseases (ICD) codes from hospital attendances (admissions and outpatient visits) and to the Office for National Statistics mortality data including dates and causes of deaths.²⁰

Study cohorts

The study population consisted of active individuals aged ≥ 18 years recorded in CPRD with HES linkage any time between 1 January 2000 and 31 March 2012, and with at least 1 year of follow-up in CPRD before the study inclusion.

An IC cohort was selected including all eligible individuals with at least one of the following IC conditions or therapies: haematopoietic stem cell transplant (HSCT);

solid organ transplantation (SOT); solid organ malignancy (SOM); haematological malignancy (HM); HIV; end-stage renal disease (ESRD); corticosteroids exposure (CORTDS); other immunosuppressive therapy (OIT) exposures including biological treatments; other immunodeficiency conditions (OIC); and autoimmune diseases (AID). The AIDs comprised: RA, systemic lupus erythematosus (SLE), IBDs, PSOR, multiple sclerosis (MS), polymyalgia rheumatica and autoimmune thyroiditis (AT). Individuals could be included in more than one IC condition except in the event of CORTDS or OIT exposures, where no concurrent IC condition was permitted (see online supplementary material for further details on IC conditions case definition).

An index date for each IC individual was defined as the earliest date of diagnosis of the IC condition/medical procedure or the date of the earliest prescription of corticosteroids or OIT. The earliest index date possible was 1 January 2000.

An IC-free cohort was randomly selected from the study population of eligible individuals, who were not included in the IC cohort. IC-free individuals were matched 1:1 to IC individuals by year of birth, gender and geographical region of the GP practice. IC-free individuals were assigned the same index date as their matched IC individuals. The matched IC and IC-free cohorts were followed up from the index date until the earliest of the following events: transfer out of the practice date, the last GP practice collections date, death date or the end of the study (31 March 2012).

In order to ensure that HZ cases were new events, a period of at least 12 months of registration in CPRD was required before the inclusion of study population in the study. Individuals with a history of HZ or related complications identified within at least 12 months before the index date of IC condition (for the IC cohort) or the date of inclusion in the study (for the IC-free cohort) were excluded.

Endpoints related to HZ diagnoses

Incident HZ was identified as the first reported diagnosis of HZ by using ICD10 codes (B02, B02.0, B02.1, B02.3, B02.30–34, B02.39, B02.7, B02.8, B02.9) in HES or corresponding Read codes in CPRD (online supplementary table SM1). PHN was defined by using ICD10 codes (B02.2, B02.21–24, B02.29) in HES or Read codes (A531.11, A531200, A531300, A531500, A531511, F300.00) in CPRD, within 90 days of the incident HZ. HZ-related complications including neurological (other than PHN), ocular and disseminated were considered as HZ complications if they were coded as HZ complications (subhierarchy of ICD10 code B02 or corresponding Read codes) and if diagnosed within 90 days of the incident HZ (online supplementary table SM1). Potential associated vascular complications (such as stroke, transient ischaemic attack, optic neuritis and vascular retinitis, and myocardial infarction) were also identified (online supplementary table SM2).

A recurrent HZ episode was defined as any HZ episode occurring after a 180-day disease-free period of HZ or HZ complications (except PHN).

Statistical analyses

The incidence rate (IR, with 95% CI) of HZ per 1000 person-years (PY) was calculated as the total number of incident HZ cases divided by the sum of the number of PY at risk. The risk period for IC individuals was defined from the index date of the IC condition until the earliest of the following events: first reported HZ episode, end of IC drugs exposure (90 days for CORTDS and 180 days for OIT after the last prescription), date of death, transfer out of a GP practice contributing to CPRD, the last GP practice collections date or end of the study (31 March 2012). The IR was estimated by age strata, gender and by type of IC condition for the IC cohort.

The proportions of PHN and HZ complications other than PHN were calculated as the percentage of patients with HZ who developed PHN or at least one other HZ complication, respectively. The proportions were estimated overall and stratified by age group, gender and type of IC condition for the IC cohort.

The proportion of recurrent HZ was calculated as the proportion of patients with HZ with at least one recurrent HZ event within 24 months of the incident HZ. The mortality associated with HZ per 1 million PY was estimated as the total number of deaths attributable to HZ (ie, primary cause or contributory cause of death) divided by the number of PY at risk.

As PHN is the most frequently reported HZ complication, a logistic regression model was developed for IC individuals with HZ to identify the potential risk factors associated with the development of PHN. Factors such as age, gender, body mass index, smoking and alcohol consumption status and comorbidities (ie, COPD, depression, diabetes mellitus and asthma) were included in the model. A backward selection was conducted and the ORs with Wald 95% CIs were estimated.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

RESULTS

The study population included 3 698 346 individuals aged ≥ 18 years that met the inclusion criteria (online supplementary table SM3). Among them, 621 588 individuals were included in the IC cohort. The mean age of the IC individuals was 56.2 years, 56.1% were women, and the mean follow-up duration from the index date until the end of follow-up in the study was 5.1 years (table 1).

Incidence of HZ

The overall IR of HZ in the IC cohort was 7.77/1000 PY (95% CI 7.67 to 7.88) and in the IC-free cohort 6.21/1000 PY (95% CI 6.12 to 6.30). In the IC cohort, the overall

Table 1 Demographic characteristics of matched IC and IC-free cohorts, HES-CPRD, 2000–2012

Characteristics	Parameters or categories	IC cohort	IC-free cohort
		N=621 588	N=621 588
		Value or n (%)	Value or n (%)
Gender	Male	272 836 (43.89)	272 836 (43.89)
	Female	348 752 (56.11)	348 752 (56.11)
Age (years) at index date	Mean	56.2	56.2
	SD	18.83	18.83
	Median	58.0	58.0
	IQR	29.0	29.0
Age group (years) at index date	18–49	223 400 (35.94)	223 400 (35.94)
	50–59	107 003 (17.21)	107 003 (17.21)
	60–64	61 390 (9.88)	61 390 (9.88)
	65–69	58 401 (9.40)	58 401 (9.40)
	70–79	102 964 (16.56)	102 964 (16.56)
	≥ 80	68 430 (11.01)	68 430 (11.01)
Follow-up period from index date to the end of follow-up in the study (years)	Mean	5.1	4.9
	SD	3.9	3.8
	Median	4.3	4.1
	IQR	6.7	6.2

%, 100*n/N; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IC, immunocompromised; N, total number of individuals; n, number of individuals in the specified category.

IR of HZ increased with age from 3.55/1000 PY (95% CI 3.42 to 3.68) in persons aged 18–49 years to 12.22/1000 PY (95% CI 12.22 to 13.02) in persons aged \geq 80 years (table 2).

In this cohort, the age-specific IRs of HZ remained almost constant throughout the study period with no discernible trend for any age group (figure 1). The overall IR of HZ in IC women was 8.48/1000 PY (8.34–8.63), compared with 6.83/1000 PY (6.68–6.98) in IC men (figure 2).

For the selected IC conditions, the overall IRs of HZ ranged from 5.33/1000 PY (5.15–5.51) for PSOR to 41.70/1000 PY (35.72–48.40) for HSCT (table 2). For other IC conditions, the IRs of HZ were 15.19/1000 PY for HM, 12.25/1000 PY for ESRD, 12.13/1000 PY for SOT, 11.83/1000 PY for OIC, 11.78/1000 PY for HIV and 6.98/1000 PY for all AIDs combined. The IRs of HZ for most of IC conditions rose steadily with increasing age except for HSCT, HM, ESRD, SLE and MS (table 2).

Proportion of PHN

The proportion of PHN among patients with HZ in the IC cohort was 10.65% (10.24–11.08) within 90 days of the incident HZ (table 3). This proportion increased steeply with age from 3.21% (2.62–3.90) in patients aged 18–49 years to 15.05% (13.94–16.22) in patients aged \geq 80 years (online supplementary table SM4). The proportion of PHN was 9.09% (8.68–9.52) in the IC-free cohort. Across the IC conditions, the proportion of PHN ranged from 8.33% (3.67–15.76) in HIV-infected patients to 15.61% (10.54–21.89) in patients with HSCT (online supplementary table SM5).

Proportion of HZ-related complications other than PHN

Within 90 days of the incident HZ, 2.95% (2.72–3.18) of IC patients reported at least one HZ complication other than PHN, compared with 2.35% (2.13–2.57) of the IC-free patients (table 3). Ocular complications were the most frequently reported complications in both cohorts. Across the IC conditions, the proportion of patients with at least one HZ complication other than PHN ranged from 1.81% in patients with OIT to 6.94% in patients with HSCT (online supplementary table SM5). The proportions of IC patients with at least one HZ-associated vascular complication within 90 days of HZ onset were the following: 0.42% for stroke, 0.25% for transient ischaemic attack, 0.17% for myocardial infarction and 0.04% for optic neuritis/vascular retinitis (table 3).

Recurrence of HZ and HZ-associated mortality

HZ recurrence within 2 years of the incident HZ was 2.26% (2.01–2.52) in the IC cohort and 1.54% (1.33–1.77) in the IC-free cohort. The HZ-associated mortality rate was 7.42/1 000 000 PY (4.53–11.47) in the IC cohort and 3.72/1 000 000 PY (1.86–6.65) in the IC-free cohort.

Risk factors for developing PHN among IC patients with HZ

After adjusting for covariates, increasing age (eg, \geq 80 years vs 18–44 years, adjusted OR (AOR): 7.02; 5.22–9.43),

current (AOR: 1.35; 1.07–1.69) and ex-drinkers (AOR: 1.60; 1.02–2.49), depression (AOR: 1.31; 1.10–1.52) and COPD (AOR: 1.28; 1.12–1.46) were associated with increased risk of PHN (online supplementary table SM6).

DISCUSSION

To our knowledge, this study is the largest study to date investigating the incidence of HZ in \geq 18-year-old adults in the UK with a wide variety of IC conditions, including exposure to immunosuppressive therapies. It showed a high burden of HZ among individuals with the selected IC conditions, overall and across different age groups. With the exception of PSOR, MS and AT, the IRs of HZ for all the selected IC conditions were above the estimated overall IR in the IC-free cohort, with differences rising up to sevenfold as in patients with HSCT.

For some IC conditions, these findings are consistent with what was observed in other studies focusing on HSCT,³ RA,^{3 22–25} IBD⁴ and SLE.^{3 26 27} For other IC conditions, the estimated IRs were slightly lower than those reported in the literature: PSOR,^{3 14 15} IBD,^{3 17} MS,³ SOM^{5 11} and HM.^{5 11} However, this study showed the same ratio between HM and SOM as those previously reported, with incidence of HZ twofold higher in HM than in SOM.^{5 11} The observed differences between our findings and the other studies may be due to varying case definitions, study designs, age distributions of the study populations and use of different immunosuppressive treatments or regimens.

Regarding exposures to corticosteroids and immunosuppressive therapies, the study showed incidences of HZ similar to the overall incidence among IC individuals. As no study has evaluated the burden of HZ in a population only defined by the use of immunosuppressive drugs outside the context of a specific IC condition, these findings could not be put in perspective. However, they are similar to the findings of other studies such as a meta-analysis showing a higher risk of HZ for individuals using biologics, non-biological disease-modifying anti-rheumatic drugs or corticosteroids for AIDs²⁸ and studies describing an increased risk of HZ among patients with cancer who initiated treatment with immunosuppressants or chemotherapy.^{3 5 11}

Consistent with studies conducted in the UK and Germany, the IRs of HZ in the IC cohort increased steadily with age.^{4 29} However, regardless of the age group, the age-specific IRs of HZ in the IC cohort were almost constant throughout the study period 2000–2011.

The overall proportion of PHN in the IC cohort was 10.65% within 90 days of incident HZ; ranging from 8.43% in patients with OIT, AT, MS, HIV and SOT to 15.61% in patients with HSCT. These results are comparable to the findings of Forbes *et al*, except for the HSCT (PHN=29.4%).³⁰ On the other hand, a study conducted by Habel *et al* shows a lower proportion of PHN in patients with HM (5.7%) and SM (8.6%) within 90 days of HZ incident compared with their rates in this study.¹¹

Table 2 Incidence rates of HZ per IC status and IC conditions, overall and by age group, HES-CPRD, 2000–2012

IC status/condition	Incidence rate of HZ per 1000 PY (95% CI)						Overall
	18–49 years	50–59 years	60–64 years	65–69 years	70–79 years	≥80 years	
IC-free cohort (N=621 588)	2.12 (2.03 to 2.22)	4.90 (4.72 to 5.08)	6.92 (6.64 to 7.20)	8.62 (8.30 to 8.95)	11.04 (10.75 to 11.34)	11.02 (10.64 to 11.41)	6.21 (6.12 to 6.30)
IC cohort (N=621 588)	3.55 (3.42 to 3.68)	6.85 (6.62 to 7.08)	8.80 (8.46 to 9.14)	9.93 (9.56 to 10.30)	11.32 (11.03 to 11.63)	12.61 (12.22 to 13.02)	7.77 (7.67 to 7.88)
Haematopoietic stem cell transplant (HSCT) (n=1312)	34.14 (26.62 to 43.14)	50.46 (37.45 to 66.53)	60.32 (41.26 to 85.16)	46.98 (25.01 to 80.34)	34.97 (13.82 to 70.81)	10.35 (0.26 to 57.67)	41.70 (35.72 to 48.40)
Solid organ transplantation (SOT) (n=4759)	11.01 (8.91 to 13.46)	11.93 (9.08 to 15.39)	12.35 (8.39 to 17.53)	12.25 (8.00 to 17.94)	13.12 (9.29 to 18.01)	16.85 (10.90 to 24.87)	12.13 (10.74 to 13.66)
Haematological malignancies (HM) (n=26 959)	8.46 (7.29 to 9.77)	15.41 (13.61 to 17.37)	18.41 (16.09 to 20.97)	16.62 (14.41 to 19.07)	17.47 (15.81 to 19.26)	17.53 (15.47 to 19.79)	15.19 (14.45 to 15.97)
Solid organ malignancies (SOM) (n=21 025)	4.32 (3.96 to 4.70)	6.79 (6.36 to 7.25)	8.59 (8.01 to 9.20)	9.33 (8.75 to 9.94)	10.79 (10.34 to 11.25)	11.63 (11.08 to 12.20)	8.81 (8.61 to 9.02)
HIV (n=2522)	11.24 (8.81 to 14.13)	15.00 (8.74 to 24.02)	7.19 (0.87 to 25.99)	12.93 (1.57 to 46.71)	27.16 (3.29 to 98.10)	0.00 (0.00 to 207.06)	11.78 (9.54 to 14.38)
End-stage renal disease (ESRD) (n=38 134)	8.33 (6.84 to 10.06)	10.57 (8.66 to 12.77)	11.65 (9.37 to 14.32)	13.78 (11.58 to 16.28)	12.84 (11.58 to 14.21)	13.49 (12.25 to 14.83)	12.25 (11.58 to 12.95)
Polymyalgia rheumatica (PR) (n=26 868)	5.21 (2.92 to 8.59)	7.83 (6.08 to 9.92)	11.38 (9.40 to 13.66)	11.20 (9.57 to 13.03)	12.87 (11.85 to 13.96)	14.94 (13.85 to 16.10)	12.79 (12.18 to 13.42)
Systemic lupus erythematosus (SLE) (n=5041)	7.91 (6.34 to 9.76)	10.45 (8.16 to 13.18)	12.81 (9.11 to 17.52)	11.06 (7.22 to 16.21)	18.11 (13.72 to 23.46)	17.20 (10.90 to 25.81)	10.95 (9.75 to 12.26)
Rheumatoid arthritis (RA) (n=35 326)	4.74 (4.05 to 5.51)	8.79 (7.86 to 9.81)	11.00 (9.69 to 12.44)	12.61 (11.18 to 14.17)	14.02 (12.83 to 15.29)	14.47 (12.97 to 16.10)	10.58 (10.11 to 11.07)
Inflammatory bowel disease (IBD) (n=31 884)	3.99 (3.56 to 4.46)	6.82 (6.01 to 7.71)	7.98 (6.72 to 9.40)	12.22 (10.46 to 14.20)	11.50 (10.04 to 13.12)	13.86 (11.63 to 16.39)	7.02 (6.63 to 7.42)
Multiple sclerosis (MS) (n=9210)	3.71 (2.96 to 4.61)	5.99 (4.85 to 7.31)	6.94 (5.06 to 9.29)	10.18 (7.43 to 13.63)	7.00 (4.69 to 10.06)	10.17 (5.26 to 17.77)	5.69 (5.07 to 6.36)
Autoimmune thyroiditis (AT) (n=7140)	2.50 (1.82 to 3.35)	6.82 (5.19 to 8.80)	6.49 (4.11 to 9.73)	9.71 (6.22 to 14.45)	10.30 (7.04 to 14.54)	12.52 (7.54 to 19.55)	5.42 (4.70 to 6.22)
Psoriasis (PSOR) (n=117 760)	2.64 (2.47 to 2.82)	5.45 (5.06 to 5.87)	7.43 (6.76 to 8.14)	8.73 (7.93 to 9.60)	10.50 (9.75 to 11.30)	12.24 (11.04 to 13.54)	5.33 (5.15 to 5.51)
Other immunodeficiency conditions (OIC) (n=41 484)	6.16 (5.46 to 6.94)	11.45 (10.23 to 12.78)	13.46 (11.74 to 15.37)	15.00 (13.14 to 17.05)	15.22 (13.81 to 16.72)	16.06 (14.42 to 17.84)	11.83 (11.29 to 12.38)
Corticosteroids exposure (CORTDS) (n=183 646)	3.27 (3.02 to 3.54)	6.99 (6.50 to 7.51)	9.02 (8.30 to 9.78)	9.68 (8.92 to 10.49)	11.47 (10.80 to 12.18)	13.29 (12.22 to 14.43)	7.46 (7.23 to 7.69)
Other immunosuppressive therapies (OIT) (n=12 594)	5.24 (3.76 to 7.11)	7.44 (5.12 to 10.45)	8.46 (5.02 to 13.38)	17.48 (11.88 to 24.81)	14.60 (10.17 to 20.31)	8.09 (3.49 to 15.95)	8.49 (7.25 to 9.89)

CPRD, Clinical Practice Research DataLink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; N, total number of individuals; n, Number of individuals with that type of IC; PY, person-years.

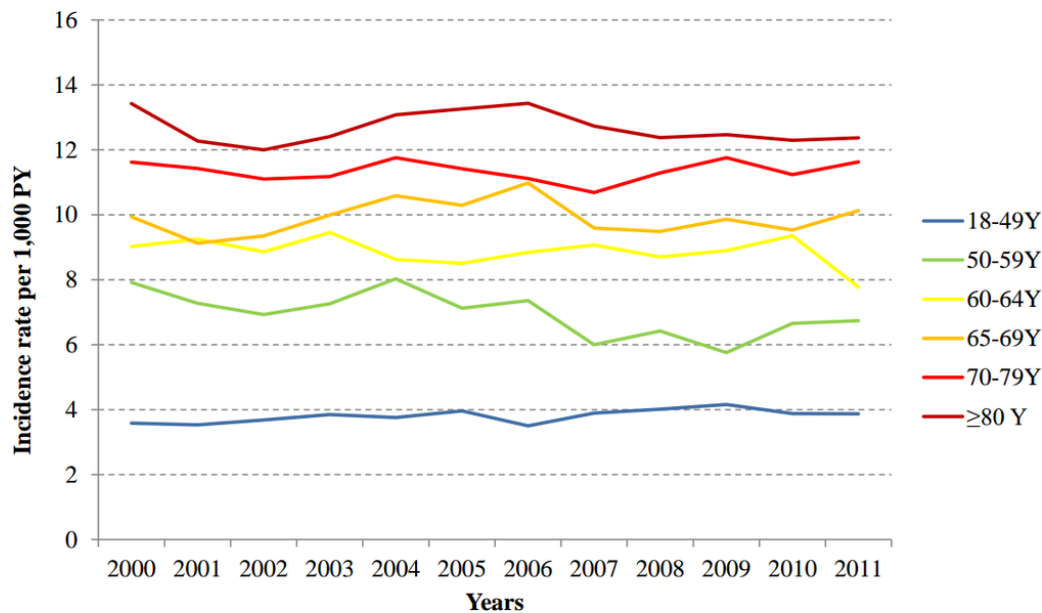


Figure 1 Age-specific yearly IRs of HZ in the IC cohort over the study period 2000–2012 (HES-CPRD). CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; IR, incidence rate; PY, person-years; Y, years old.

These differences may be explained by varying definitions of PHN used, different study designs and age distributions of the study populations.⁶ Here, PHN was identified based on diagnosis codes whereas other studies used algorithms combining PHN diagnosis codes and/or pain medication prescriptions.²⁹⁻³¹ The conservative approach used here may have led to an underestimation of PHN in certain IC populations. We used an equally conservative approach to identify HZ-related complications other than PHN. By using only the diagnosis codes mentioning HZ-related complications, the estimated overall proportion of around 3% (not including vascular complications) is probably an underestimate.

Furthermore, we estimated the proportion of patients with at least one of these non-PHN complications and not the frequency of each type separately, so patients with HZ with more than one complication were only counted once in the totals. Our results are nevertheless consistent with the literature and suggest that patients with HZ with IC conditions experience an age-related increase in the proportion developing non-PHN complications similar to what is observed in the general population.⁴

There is increasing evidence from general population studies establishing HZ as a risk factor for stroke and other vascular complications, particularly during the 3 months following HZ onset.³²⁻³⁴ No previous study has reported on the frequency of vascular complications in IC individuals with HZ infection. We estimated an overall proportion with at least one vascular complication of around 0.9% in the IC cohort of patients with HZ but this cannot be compared with the general population studies.

Additional analyses were performed to evaluate the proportions of HZ-related complications, including PHN, occurring within 365 days of incident HZ (data not shown). However, no difference was observed in the

proportion of HZ complications reported within 90 and 365 days of incident HZ. This confirms the findings of Yawn *et al* that the majority of HZ-related complications occur within a short time (3 months) of rash onset.³⁵

The proportion of patients with HZ experiencing HZ recurrence within 2 years of an HZ episode estimated in this study was lower than those reported in the literature,¹⁰ but higher than those observed in the IC-free cohort or in an immunocompetent US population.¹⁰ These differences might be explained by varying study population characteristics (ie, age distribution, underlying conditions and severity of immunosuppression).

There are few data available on HZ-related mortality and these are only for the general population.^{6, 36} The reported HZ-associated mortality incidence in the adult general population ranges from 0.94 to 2.86/1 000 000 PY,³⁷⁻³⁹ which is lower than what was observed in the IC-free cohort in this study.

Among the IC patients with HZ, we found that increasing age is strongly associated with increasing risk of PHN. Other risk factors including COPD, depression and alcohol consumption have lower effect as risk factors of PHN.³⁰ A previous study conducted in the general population of the UK has already established advancing age, severe immunosuppression and autoimmune conditions as PHN risk factors⁴⁰; confirming our findings. Other clinical features of acute HZ (such as prodromal pain and increased rash severity) have also been accepted as risk factors for PHN.⁴⁰⁻⁴² However, such data were not available in CPRD so these potential risk factors could not be assessed in this study.

The IC cohort in this study represented 16.8% of the study population; which was higher than their estimate in other studies.⁴³ This might be due to the large number of IC conditions that were followed up during the study

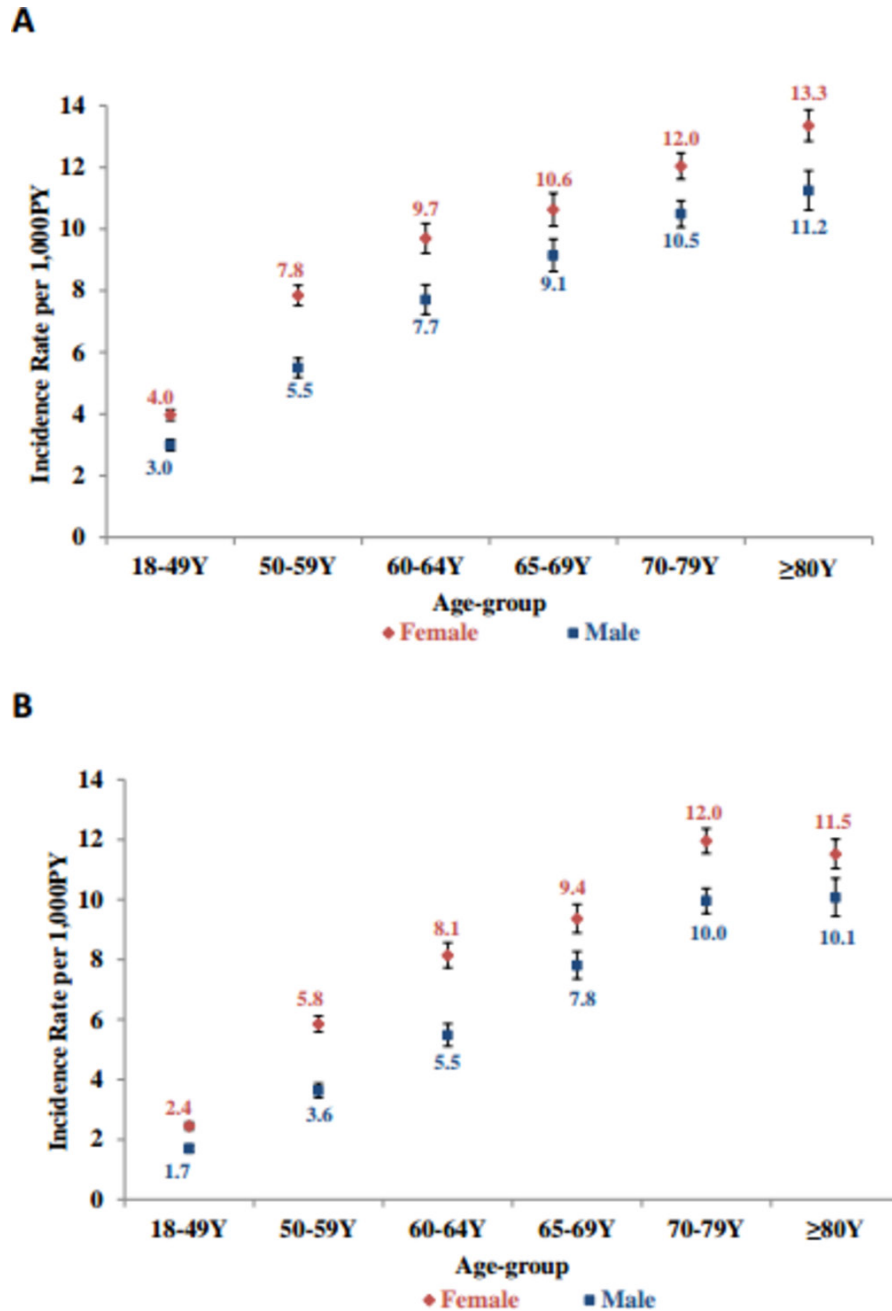


Figure 2 Incidence rates of HZ per 1000 PY in both IC (A) and IC-free cohorts (B) by age group and gender, HES-CPRD, 2000–2012. CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PY, person-years; Y, years old.

period. Our study results indicate that this IC population bears a disproportionate part of the burden of HZ and its complications in England.

The main strength of this study was the use of a large medical records database considered to be broadly representative of the UK population.²⁰ The linkage with HES data is only available for participants in England, but it has been reported that there are no substantial differences in participant characteristics between those that are linked to HES and those that are not.⁴⁴ Therefore, over a 12+ year study period, the use of CPRD with HES linkage allowed accurate and powerful estimation of HZ IRs.

In addition, the incidence of HZ in the IC-free cohort was slightly higher than the incidence of HZ observed in the UK general population (including both immunocompetent and IC people).^{31 45 46}

However, due to the varying quality and completeness over patients and time of this primary care database,²⁰ a misclassification of individuals into the IC or IC-free cohorts may have occurred, as the classification was based on the coding practices and depended on the reliability of the GPs' data entry.⁴⁷ Further research should explore the temporal relationship between the time of HZ incident and the level of severity of immunosuppression, in order

Table 3 Proportion of patients with HZ with PHN, at least one HZ complication other than PHN, or vascular complications as assessed within 90 days of HZ onset, HES-CPRD, 2000–2011

Type of complications	IC cohort (N=21 146)		IC-free cohort (N=18 583)	
	n (%)	95% CI	n (%)	95% CI
PHN	2253 (10.65)	10.24 to 11.08	1690 (9.09)	8.68 to 9.52
HZ complications other than PHN (overall)	623 (2.95)	2.72 to 3.18	436 (2.35)	2.13 to 2.57
Ocular	411 (1.94)	1.76 to 2.14	299 (1.61)	1.43 to 1.8
Neurological other than PHN	137 (0.65)	0.54 to 0.77	85 (0.46)	0.37 to 0.57
Disseminated	12 (0.06)	0.03 to 0.1	1 (0.01)	0 to 0.03
Other complications	69 (0.33)	0.25 to 0.41	54 (0.29)	0.22 to 0.38
Vascular complications				
Stroke	88 (0.42)	0.33 to 0.51	105 (0.57)	0.46 to 0.68
Transient ischaemic attack	52 (0.25)	0.18 to 0.32	30 (0.16)	0.11 to 0.23
Optic neuritis, vascular retinitis	9 (0.04)	0.02 to 0.08	5 (0.03)	0.01 to 0.06
Myocardial infarction	36 (0.17)	0.12 to 0.24	23 (0.12)	0.08 to 0.19

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; N, Number of patients with HZ; n (%), number (percentage) of the patients with HZ with this complication; PHN, postherpetic neuralgia.

to develop appropriate interventions to improve the quality of life of IC individuals. In addition, patients with chronic medical conditions might attend the GP practices more frequently than IC-free population. This may result in a potential information bias because of the increased likelihood that IC patients with any HZ-related symptoms will seek the GP medical advice more frequently than IC-free individuals.

The stable trend of age-specific IR of HZ in IC cohort throughout the study period (2000–2011) might show different pattern if we run the analysis in each IC condition. For instance, the development of new medical treatment regimens for certain IC conditions or the change of treatment guidelines might influence the course of IC disease and the risk of HZ.

Despite these limitations, the results of this study strengthen the evidence that immunodeficiency from any cause increases the risk of HZ. Individuals with IC conditions suffer a higher burden of HZ and related complications than IC-free or immunocompetent individuals. The existing treatments for HZ are not always effective, do not prevent the development of PHN and the outcomes are deemed unsatisfactory by the patients.⁴⁸ Therefore, new strategies to prevent HZ in patients with severe immunosuppression, such as vaccination, are an increasing priority.⁴⁹

CONCLUDING REMARKS

This study confirms that IC individuals contribute substantially and disproportionately to the public health burden of HZ in England because of their higher risk for HZ and HZ-related complications. Further research should explore HZ risk in relation to the severity of immunosuppression and other available clinical information, to develop appropriate interventions to improve the quality of life of IC individuals. The expected increase in lifespan of the general population including IC populations might

lead to an increase in the burden of HZ, unless appropriate preventive measures such as vaccination are in place.

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Competing interests VB, FH, EE and EAY are employees of the GSK group of companies. AEG, YEH and MG have nothing to disclose. GF was employed by the GSK group of companies between 2012 and February 2015, during which the study was designed and implemented. Later, as an employee of P-95 Epidemiology and Pharmacovigilance, GF provided contracted consultancy services to the GSK group of companies for this and other GSK-sponsored studies. P-95 provides contracted services to the GSK group of companies beyond the scope of this study.

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Ethics approval Approval was obtained from the Clinical Practice Research Datalink Independent Scientific Advisory Committee (14_222R).

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