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TITLE PAGE

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

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ABSTRACT

[[298/300 words]]

Objective

Individuals with immunocompromised (IC) conditions are at a higher risk of developing herpes zoster (HZ) than IC-free individuals. This study assessed the healthcare resource utilization (HCRU) burden and costs, of HZ in IC and IC-free individuals ≥18 years of age (YOA).

Methods

We conducted an observational retrospective study in a cohort of IC (N=621,588) and IC-free (N=621,588) individuals, matched by age, gender and GP practice region, contributing to the Clinical Practice Research Datalink database from 2000 to 2012 and linked to the Hospital Episode Statistics inpatient data. HCRU (i.e. primary and secondary care consultations, hospital inpatient stays, and treatment prescriptions) was analyzed from 7 days before to: (1) 30, (2) 365 days after the HZ diagnosis date for individuals with (1) HZ only (no postherpetic neuralgia [PHN]) and (2) individuals with HZ and PHN only. Healthcare costs were computed by multiplying the number of units of resources utilized by the unit costs, summed across all HCRU categories to obtain a total cost per subject. Values were expressed in 2014 UK pound sterling (£) and presented for HZ cases overall, stratified by age (i.e. 18-49, 50-59, 60-69, 70-79 and ≥80 YOA) and IC status.

Results

The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC

and IC-free individuals aged ≥80 YOA, respectively). Similarly, HZ-related mean treatment costs per subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged ≥80 YOA, respectively). Costs varied considerably by IC condition.

Conclusions

Individuals with IC conditions, not only have a higher risk of HZ than IC-free individuals, but also incur higher HZ-related healthcare costs.

Keywords

Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study is an observational retrospective descriptive study presenting the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations aged ≥18 years of age (YOA) in England.
- The IC population included 621,588 individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions and matched to the Hospital Episode Statistics (HES) database by age, gender and practice location to extract the IC-free population (N=621,588).
- The particularity of this study is that the design allowed calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s).
- This key study will provide data to be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in IC populations.
- A limitation of the study is that the diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts.

LIST OF ABBREVIATIONS

£, 2014 UK pound sterling

A&E, Accident and Emergency

AID, autoimmune diseases

ARDI, age-related decline in immunity

AT, Autoimmune Thyroiditis

BNF, British National Formulary

CPRD, Clinical Practice Research Datalink

GP, General Practitioner

HCRU, healthcare resource utilization

HES, Hospital Episode Statistics

HIV, human immunodeficiency virus

HM, hematological malignancies

HSCT, hematopoietic stem cell transplantation

HZ, herpes zoster

HZ-Comp, HZ and complications with no PHN

IC, immunocompromized

ICD-10, International Classification of Diseases-10th revision

ISAC, Independent Scientific Advisory Committee

PHN, postherpetic neuralgia

PSSRU, Personal Social Services Research Unit

PY, person-years

RA, rheumatoid arthritis

SLE, systemic lupus erythematosus

SOT, solid organ transplantations

UK, United Kingdom

US, United States

VZV-CMI, varicella zoster virus cell-mediated immunity

YOA, years of age

ZVL, zoster vaccine live

INTRODUCTION

[[2,819/4,000 words; 6/5 tables+figures but journal allow flexibility]]

Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes zoster (HZ)[1]. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not optimal in individuals with immunocompromized (IC) conditions and the age-specific incidence and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune disease, malignancy, or organ transplantation[2].

The incidence and severity of HZ is marked with an increase in people ≥50 years of age (YOA) due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among individuals aged ≥85 YOA[3]. Further to the impact of ARDI, a study by Forbes et al. in 2014 investigated the increased risk for HZ in the UK population, associated with autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and asthma[2]. In addition to the increased risk of HZ in the various IC conditions these populations also experience increased severity of disease. In a study in Canada, Drolet et al. reported that individuals with an impaired immune status had HZ severity of illness scores, as measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with normal immune function[4 5]. In a study in the United States (US), Yawn et al. reported that although 8% of HZ cases were in individuals who were immunocompromised, these individuals represented 23.8% of the total HZ-related costs[6]. The increase in healthcare costs was associated

with higher rates of postherpetic neuralgia (PHN) and non-pain complications in this group of individuals[6].

This study aims to estimate the healthcare resource utilization of HZ in selected IC populations and in an IC-free (i.e., immunocompetent) population aged ≥18 YOA in England. The clinical burden of disease epidemiological results of the study are reported elsewhere[7]. The prevalence of IC conditions increased from 7.6% in individuals aged 18-44 YOA to 42.2% in individuals aged ≥80 YOA. The incidence rate of HZ in the IC cohort was 3.5/1000 PY in individuals aged 18-49 YOA increasing to 12.6/1000 PY in individuals aged ≥80 YOA. In this manuscript, we focus on the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations.

METHODS

The study was conducted as an observational retrospective descriptive study (e-track number: 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥18 YOA). The IC population included individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions (See Supplemental Text). The CPRD IC population cohort linked to the Hospital Episode Statistics (HES) database was matched to a cohort of HES linked IC-free population (N=621,588), by age, gender and practice location. Individuals with a missing date of IC diagnosis were excluded from the study population. Clinical diagnoses were based on READ codes used in CPRD and with the International Classifications of Diseases-10th revision (ICD-10) codes in the HES database.

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency database research (ISAC protocol number 14_222R). The study was conducted in accordance with all applicable regulatory requirements, with the Guidelines for Good Pharmacoepidemiology Practices[8], all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

Healthcare resource data were extracted for IC and Matched IC-free HES-linked individuals who were incident HZ cases during the study follow-up. Only reported records (resource utilization) with available event dates during the individuals' eligibility period and those that occurred 7 days before the initial HZ onset date, up to 365 days after the initial HZ onset date, were extracted. Individuals who recorded the first PHN event date after 365 days post HZ event date were excluded.

Data sources

Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation, Clinical, Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI dataset; (3) HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource utilization was defined as: HZ-treatment related prescribed medications (CPRD tbl:therapy); Consultations and care provided by General Practitioners (GPs) or others in the GP practice (CPRD tbl:consultations); HES secondary care outpatient visits (HES outpatient events); and HES inpatient hospitalizations (HES inpatient events).

For each subject, healthcare costs stratified by subcategory of interest (HES Inpatient Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by

their unit costs. These were then summed over all resource use categories to obtain a total cost for each subject. Values were expressed in 2014 UK pound sterling (£).

Healthcare resource costs

For each subject, the cost of each prescription was calculated by merging the product code, package type and prescribed quantity (prodcode-packtype-quantity) with the associated standard package size and unit cost. The unit cost of a product in a prescription instance (i.e. one distinct record in the CPRD therapy) was calculated using the cost described in the British National Formulary (BNF), 2015 (as listed price if included or indicative price based on price in BNF).

Ambulatory visits included consultations with GPs and nurses in primary or community care. Visits included consultations at the practice or at the home of the patient, during working hours and out of hours. Consultations for which no clinical intervention was recorded were not included in the cost estimate for GP practice related healthcare utilization, for example: information technology data migration, administrative recording of received information. Administrative resource use in primary care was considered, including time on the phone, writing reports, referrals, etc. A referral to secondary care noted in a patient's record, *per se*, was not allocated the cost of the secondary care appointment. The most conservative option for the cost per unit as included in the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care, 2014 were applied e.g. GP consultation costs excluded qualification, direct staff care and travel costs[9]. Where specific costs for 2013/14 were not available, 2012/13 costs, were adjusted by applying the Hospital and Community Health Services inflation index[9]. Administration costs were based on unit costs as stated in the PSSRU, 2014.

Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient resource utilization concerned HZ related referrals for non-inpatient hospital consultations, derived from the HES Outpatient data. Additionally, visits to the Accident and Emergency (A&E) department in hospitals were also recorded and costed. Inpatient hospitalization costs were based on the average cost per episode using HES data for 2013/14 (calculated from the total average payment by result spell cost and the average number of episodes per spell). Hospital outpatient costs were sourced from National Tariff costs (2014) for specific consultant led outpatient consultations; conservative costs were allocated i.e. wherever applicable costs for first attendance by a single professional appointment were used[10]. Costs allocated to A&E visits were based on the cost of a category 3 investigation with category 1-3 treatment[10]. Only events related to HZ were costed out. Resources related to HZ complications were considered using ICD-10 Code B020.

No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in CPRD. Further details are provided in the Supplementary Text.

RESULTS

The HES-linked matched IC and IC-free population cohorts (n=621,588 each) included approximately 44% males and 56% females with a mean age of approximately 56 years. The age distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥80 YOA (11.01%).

The proportion of inpatient hospital admissions by age group for the HES-linked Matched IC and IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel A) or 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 1. Hospital

admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset (Panel B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and IC-free individuals aged ≥80 YOA, respectively). Multiple HZ-related hospital visits were reported for some individuals. As such, Table 1 presents the mean number of healthcare resources utilized by IC Status, Age Group and Analysis period. The mean number of hospitalizations per HZ case for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free individuals aged 18-49 YOA, respectively and 0.173 and 0.115 in IC and IC-free individuals aged ≥80 YOA, respectively. A similar pattern of higher healthcare resource utilization with increasing age and in IC individuals was observed for all resources for which costs were assigned. A similar mean number of sick leave certificates were observed between the IC and the IC-free cohorts with the mean decreasing with age. Nursing home care / admissions were only recorded for individuals aged ≥70 YOA in CPRD.

Figure 2 and Table 2 present the overall healthcare costs by HES-linked matched IC cohort and age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs increase with age and are consistently higher in the IC cohort compared with the IC-free cohort. Although the absolute cost difference between IC and IC-free individuals increases with age from £85.5 in individuals aged 18-49 YOA to £156.1 in individuals aged ≥80 YOA the relative difference is higher in younger individuals (i.e. 75.8%-99.2% in <70 YOA) compared with older individuals (i.e. 38.9%-57.6% in ≥70 YOA).

Figure 3 presents the overall healthcare costs by each IC condition in the HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ

onset. For all IC conditions, the costs were higher than those for the IC-free group, in particular for the hematopoietic stem cell transplantation (HSCT), hematological malignancies (HM) and solid organ transplantations (SOT) conditions. In general, there was a similar trend of increasing costs with increasing age-groups. A few outliers were observed due to small sample sizes. For example, only 3 and 8 individuals aged ≥70 YOA were included in the HIV and HSCT groups, respectively. Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis (AT) and SOT were included, respectively.

Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean healthcare costs were approximately 2 to 4 times higher for individuals with HZ complications compared to individuals with HZ only.

DISCUSSION

In this study, we presented the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations. An important feature of this study was that the design enabled the calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s).

Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the mean healthcare costs per HZ subject, from an National Health Services perspective, of £85.6 and £400.9 in individuals aged <65 YOA and ≥65 YOA, respectively[11]. A later UK study that used the HES and the health improvement network databases, estimated the mean cost of treating a HZ patient to be £65.5 in the first month of diagnosis, with patients aged ≥70 YOA having a mean

cost of £83 in the first month and £15.80 in months 2 and 3[12]. The costs of treating individuals with PHN were much higher, i.e. mean cost per subject was estimated to be £921 in all individuals and £909.60 in individuals aged ≥70 YOA[12]. Another study evaluated mean healthcare costs (excluding hospitalization costs) to be £75.63 per HZ patient with mean direct costs for treating PHN episodes (PHN pain occurring or persisting for 3 months) of £340.04[13]. These values augmented with hospitalization costs were used as inputs in a cost-effectiveness model evaluating a HZ vaccine using the population of England and Wales[3]. The costs estimated by van Hoek et al. are consistent with the values estimated in our study for IC-free individuals by age group[3].

In a previous study, mean prescription costs per HZ subject were reported to be £40.52[13]. In our study, the mean prescription costs per HZ subject ranged from £19.7 to £40.8 depending on the age group, IC status and analysis period included. Our study aimed to include only medications considered to be directly related to HZ; i.e. excluded medications that may be linked to IC conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from other conditions). This restriction and the introduction of generic versions of medications such as acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed to the reduced overall medication costs reported in this study.

In this analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days post HZ onset, although it is recognized that HZ episodes can last for longer. The costs of PHN were analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days prior to 365 days post HZ onset. The rationale for the time periods studied was that using analysis period 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2 only could overestimate these costs. The most frequently used definition of PHN is: pain

persisting or appearing at least 90 days following rash onset. The median duration of PHN has been reported to be 10.3 and 12.9 months in individuals aged ≤69 and ≥70 YOA respectively[14], and is likely to be longer in individuals who are immunocompromised[5].

The healthcare costs associated with PHN and complications were higher than those for individuals with HZ only. However, as reported elsewhere, when considering the overall cost of disease at a population level, the overall healthcare-associated cost is higher for HZ only[15]. This is primarily a result of the higher incidence rates of HZ only.

Few studies have investigated healthcare resource utilization and costs in IC individuals. Schroder et al. carried out a study using the German Pharmacoepidemiological Research Database , which consists of claims data from four statutory health insurances[16]. They reported that during the quarter of the HZ diagnosis or during the two following quarters, 10% of all HZ patients with an IC condition were hospitalized (with a HZ diagnosis), whereas among IC-free HZ patients, 4.2% were hospitalized. White et al. reported that in their study using the US Market Scan Research Database, direct medical costs were nearly twice as high in IC patients compared with IC-free patients[17]. Li et al. carried out a study using the US Truven Health MarketScan Commercial and Medicare Supplemental Insurance databases[18]. They concluded that patients with the studied IC conditions (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer) had significantly higher healthcare utilization and cost when developing HZ than their comparable matches without HZ.

This study has several limitations. Diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts. Increasing healthcare resource utilization and cost is likely to be related to increased

severity of IC conditions. In a study, Schroder et al. categorized individuals as low IC and high IC[16]. However, insufficient details are recorded in the CPRD and HES databases to allow adequate definition of patients' severity of immunosuppression e.g. laboratory parameters, immunosuppressive medication details such as chemotherapy. In addition, many IC individuals had prescriptions that included more than one immunosuppressing medicine.

CONCLUSION

In conclusion, individuals with IC conditions incurred higher healthcare utilization and costs than IC-free individuals. The current HZ vaccine which is licensed in the UK is a live vaccine (zoster vaccine live [ZVL]), and is contraindicated for use in immunosuppressed or immunodeficient individuals in whom administration of ZVL may result in disseminated disease[2]. New HZ vaccines which may be used in IC populations are currently under development[19 20]. The results from this study could be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in these populations.

AUTHOR CONTRIBUTIONS

VB, AEG, YEH, GF, MH and DC participated in the conception and design of the study. VB, AEG, YEH, GF and MH participated in the collection or generation of the study data. VB, AEG and YEH performed the study. AEG, YEH, MH and DC contributed to the material. VB, AEG, YEH, GF, MH and DC were involved in the analysis or interpretation of the data. All named authors provided substantial intellectual and scientific input during the manuscript development, critically reviewing the content, revising the manuscript and giving final approval before submission. The work described was carried out in accordance with the ICMJE recommendations for conducting, reporting, editing and publishing scholarly work in medical journals. All authors had full access to the data and gave final approval before submission.

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CONFLICTS OF INTEREST

VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the GSK group of companies between 2012 and Feb 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.

DATA SHARING STATEMENT

All data used in this study are presented in the manuscript, references to the original material are provided. Please contact the corresponding author shall you require any additional information

ETHICAL APPROVAL

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

FUNDING

GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK study identifier: e-track number: 201615) activities and overall data management (collection, analysis and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and the corresponding author was responsible for submission of the publication.

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TABLES

Table 1 : Mean number of healthcare resources by IC status, age group and analysis period

	IC cohort		IC-Free cohort	
	90 Day	365 Day	90 Day	365 Day
HES Hospital admission				
18-49	0.035	0.035	0.005	0.005
50-59	0.042	0.046	0.006	0.007
60-64	0.053	0.055	0.009	0.010
65-69	0.049	0.050	0.014	0.014
70-79	0.072	0.076	0.029	0.030
≥80	0.163	0.173	0.108	0.115
HES Outpatient consultation				
18-49	0.095	0.116	0.041	0.045
50-59	0.086	0.122	0.062	0.086
60-64	0.136	0.180	0.065	0.078
65-69	0.146	0.217	0.085	0.108
70-79	0.165	0.267	0.113	0.181
≥80	0.173	0.313	0.149	0.231
CPRD Ambulatory visits				
18-49	2.816	3.168	2.186	2.360
50-59	3.334	4.175	2.466	2.907
60-64	3.733	5.081	2.598	3.115
65-69	4.089	6.009	2.774	3.610
70-79	4.534	6.959	3.413	4.767
≥80	4.881	7.422	3.811	5.367
CPRD Other ambulatory visits				

18-49	0.319	0.411	0.155	0.170
50-59	0.433	0.623	0.218	0.277
60-64	0.545	0.885	0.251	0.360
65-69	0.607	1.064	0.330	0.454
70-79	0.686	1.251	0.417	0.722
≥80	0.860	1.616	0.668	1.183
CPRD Prescriptions (All treatments)				
18-49	1.247	1.363	0.890	0.931
50-59	1.670	1.994	1.143	1.227
60-64	1.969	2.602	1.379	1.489
65-69	2.129	2.894	1.473	1.717
70-79	2.310	3.295	1.814	2.347
≥80	2.405	3.743	1.844	2.575
CPRD Referrals*				
18-49	0.018	0.020	0.011	0.012
50-59	0.021	0.026	0.018	0.022
60-64	0.031	0.040	0.020	0.024
65-69	0.031	0.044	0.015	0.023
70-79	0.033	0.054	0.031	0.047
≥80	0.040	0.065	0.029	0.048
CPRD Sick leave*				
18-49	0.162	0.175	0.155	0.161
50-59	0.156	0.178	0.173	0.182
60-64	0.060	0.069	0.080	0.087
65-69	0.017	0.017	0.008	0.008
70-79	0.001	0.001	0.002	0.003
≥80	0.000	0.000	0.000	0.000
CPRD Nursing home care/admission*				

18-69	0.000	0.000	0.000	0.000
70-79	0.001	0.001	0.001	0.001
≥80	0.004	0.004	0.003	0.003

* No costs were assigned for CPRD Referrals, CPRD Sick leave, CPRD Nursing home care / admission

Abbreviations: IC, immunocompromized; HES, Hospital Episode Statistics; CPRD, Clinical Practice Research Datalink; Costs were assigned for HES Hospital admission, HES Outpatient consultation, CPRD Ambulatory Visits, CPRD Other Ambulatory Visits, CPRD Prescriptions.

Table 2 : Mean cost (£) of healthcare resource utilization by IC status, age group and analysis period*

Age groups (YOA)	Mean cost (£)			
	IC cohort		IC-free cohort	
	90 Day	365 Day	90 Day	365 Day
18-49	173.3	189.3	98.2	103.8
50-59	199.0	237.8	118.9	135.3
60-64	236.2	294.2	126.8	147.7
65-69	241.6	317.4	145.5	174.4
70-79	289.6	391.7	189.8	248.6
≥80	427.0	557.1	319.7	401.0

* post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; HZ: herpes zoster; IC, immunocompromized; YOA: years of age

Table 3 : Mean cost (£) of healthcare resource utilization by IC status, age group, analysis period and HZ complication status

Age groups (YOA)	Mean cost (£), IC			
	HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	156.6	302.4	746.6	573.3
50-59	168.1	468.0	998.9	562.6
60-64	190.8	538.7	1135.5	780.5
65-69	195.6	489.3	1064.3	551.8
70-79	228.9	540.4	1200.2	847.5
≥80	307.6	779.5	1536	1396.4
	Mean cost (£), IC-free			
	HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	91.6	216.1	391.9	246.4
50-59	106.8	262.8	540.8	275.1
60-64	114.1	270.5	556.1	192.7
65-69	123.7	287.7	595.5	592.6
70-79	149.2	388.2	813.7	511.5
≥80	242.0	607.4	1,182.8	1,046.5

* Individuals with HZ only (i.e. without PHN and complications): includes only costs 7 days prior to 30 days post initial HZ onset

Individuals with HZ and PHN: includes only costs 7 days prior to 90 days post initial HZ onset

! Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset

§ Individuals with HZ and complications but no PHN: includes only costs 7 days prior to 30 days post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ: ,herpes zoster; PHN, postherpetic neuralgia; HZ-Comp, HZ and complications with no PHN; YOA: years of age

FIGURE

Figure 1 : Inpatient Hospital Admission by HES-linked Matched IC or IC-free cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to 365 days post initial HZ onset (Panel B)

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A) and 365 days (Panel B)

Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, postherpetic neuralgia

Figure 2 : Healthcare Costs for by HES-linked Matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset

Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits;HES, Hospital Episode Statistics; HES-Out, HES Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN, postherpetic neuralgia;

Figure 3 : Healthcare Costs for each IC condition in the HES-linked Matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.

Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM, hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, postherpetic neuralgia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID, other immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica;

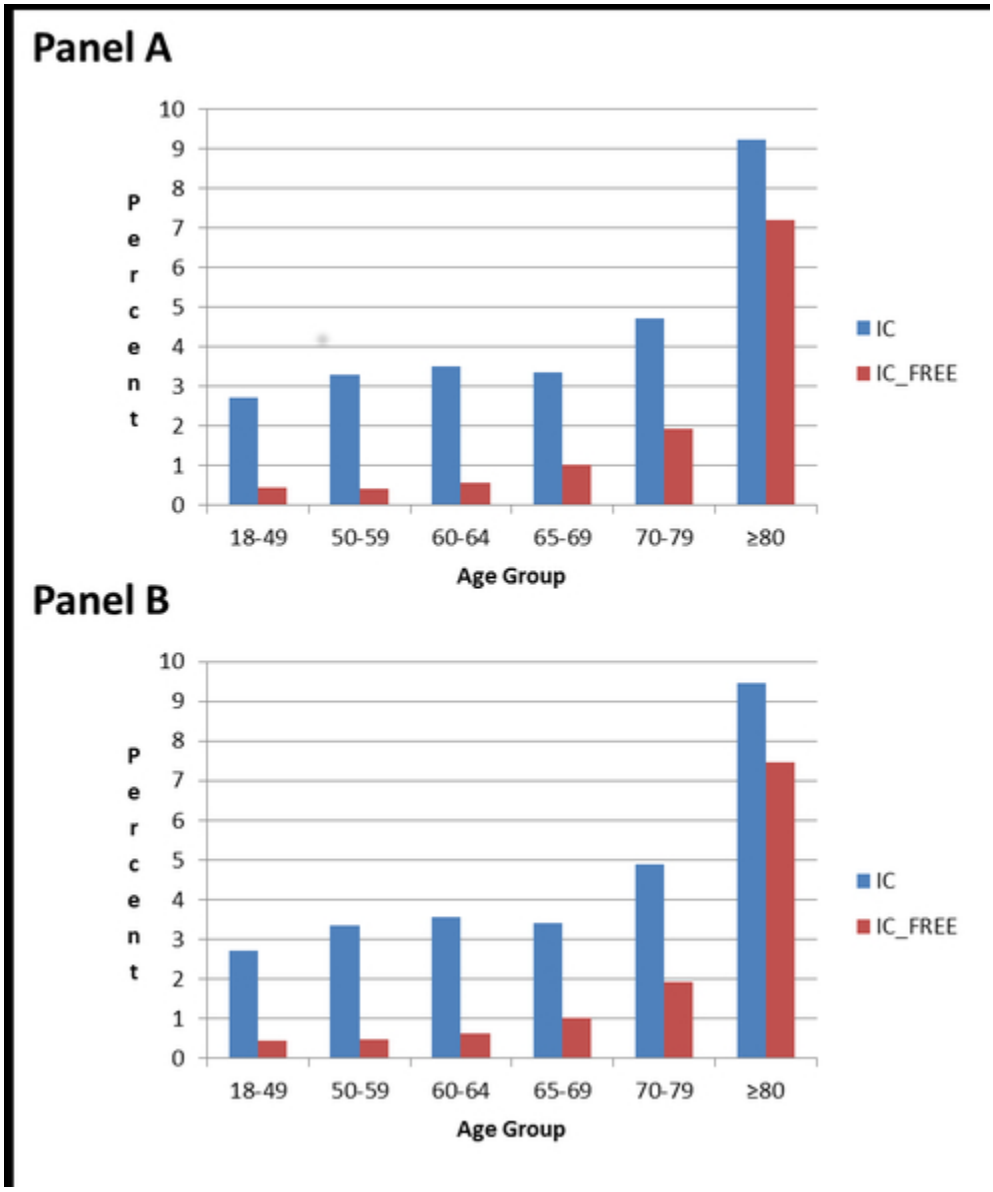

Figure 1

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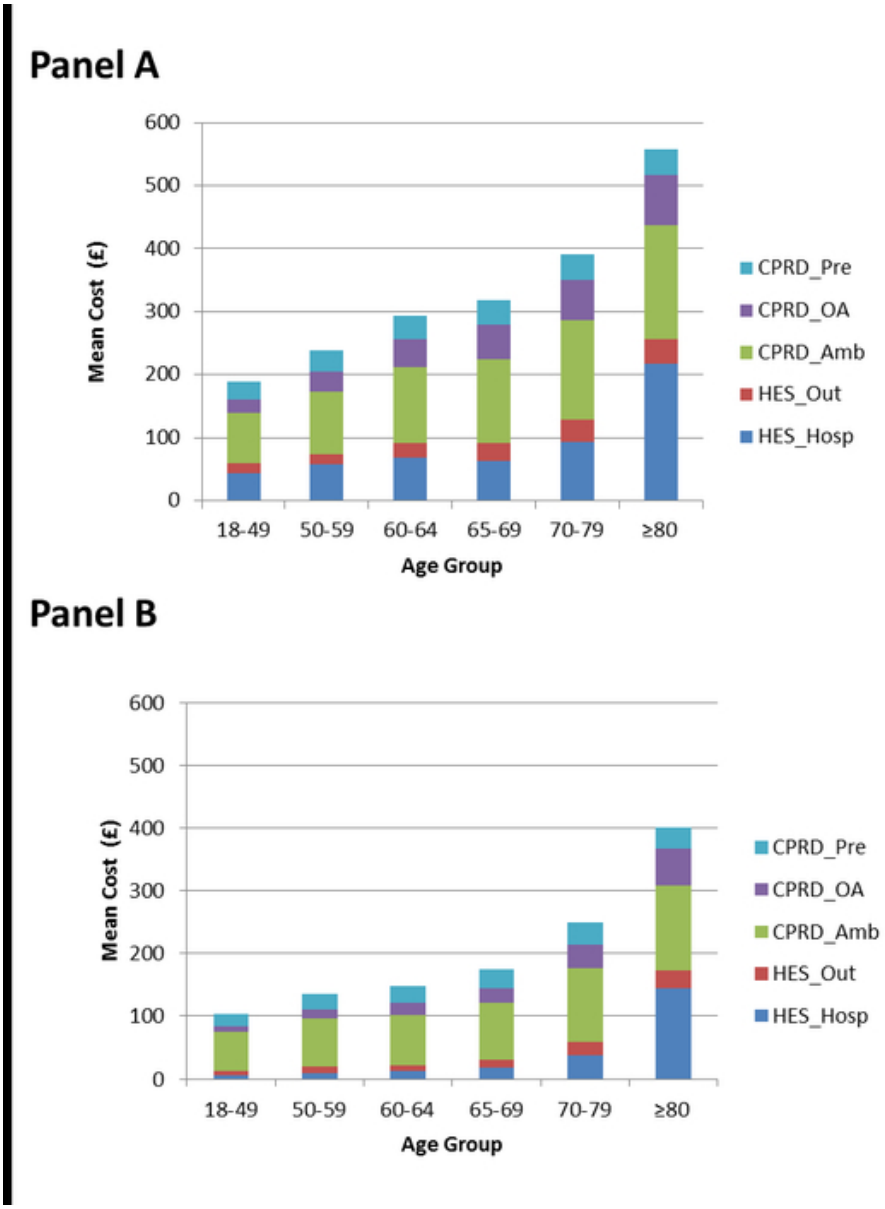

Figure 2

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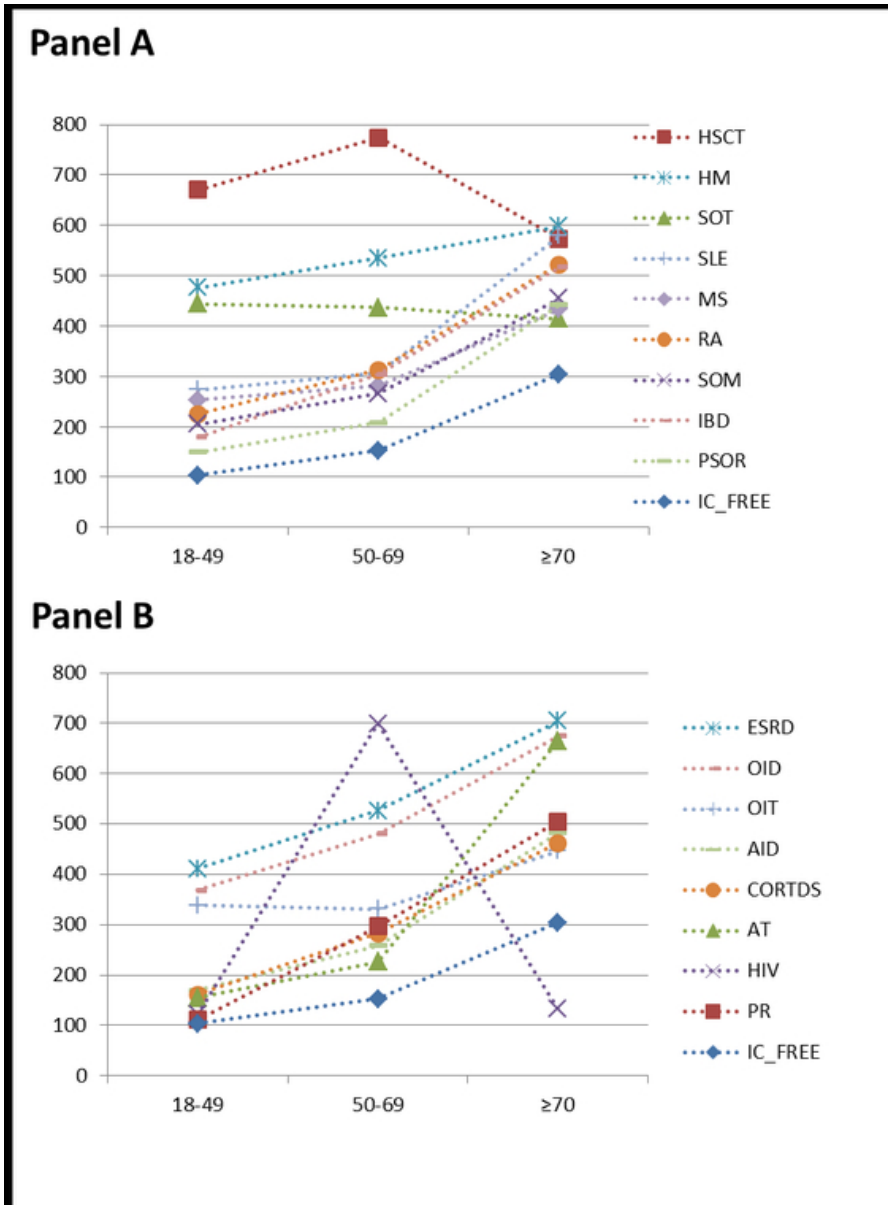

Figure 3

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Supplementary Material

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

Desmond Curran, Manjit Hunjan, Amale El Ghachi, Yassine El Hahi, Veronique Bianco, Germano Ferreira

BMJ Open

IC Population

The immunocompromised (IC) population, referred to as the IC cohort hereafter, included eligible subjects reporting at least one of the following conditions or therapies at any time before 31st March 2012:

- Hematopoietic stem cell transplant (HSCT);
- Solid organ transplantation (SOT);
- Solid organ malignancies (SOM);
- Hematological malignancies (HM): Leukemia, Lymphoma, Myeloma;
- Autoimmune diseases (AID):
    - Rheumatoid Arthritis (RA);
    - Systemic *Lupus erythematosus* (SLE);
    - Inflammatory Bowel Disease (IBD);
    - Psoriasis (PSOR);
    - Multiple sclerosis (MS);
    - Polymyalgia rheumatica (PR) and;
    - Autoimmune thyroiditis (AT).
- Human immunodeficiency virus (HIV);
- End-stage renal disease (ESRD);
- Corticosteroid exposure (CORTDS);
- Other immunosuppressive therapy (OIT) exposure;
- Other immunodeficiency (OID) conditions.

For autoimmune diseases, each disease was considered as a separate IC condition. Any subject with a code for any IC condition listed above at any time in their record was excluded from the IC-free cohort. Only subjects that were part of IC conditions based on treatment administration ("Corticosteroid exposure" and/or the "Other immunosuppressive therapy exposure" IC conditions) had an end of follow-up based on prescriptions and could present a gap of exposure in the IC cohort between the end of exposure in that IC condition and the beginning of the next one, if any, during which they could not be considered as IC.

IC Matching

The IC-free matched population included a random sample of the IC-free population described above matched to the subjects of the IC population with a ratio of 1:1 (IC: IC-free subjects) when possible. The matching factors were:

- Hospital Episode Statistics (HES) linkage eligibility;
- The year of birth of the subject;
- The gender of the subject, and;
- The practice geographical region.

In addition, the IC-free subjects were included in the study at their corresponding matched IC subject's index date and should not have reported any history of HZ before the matched IC index date.

Herpes Zoster (HZ) Diagnosis

HZ cases identified in the Clinical Practice Research Datalink (CPRD) database were defined as subjects reporting at least one HZ-related READ code. Incident cases were subjects with at least 12 months of active registration in CPRD and no past record of HZ diagnosis during at least 12 months prior to inclusion or even before in their available medical records. HZ cases were identified in HES using the International Classification of Diseases-10th revision (ICD-10) codes that appeared in the diagnosis fields. If HZ diagnosis codes were recorded in both HES and the CPRD, the earliest event date was considered as the onset date.

Supplementary Table 1: Post-herpetic neuralgia

Source: CPRD or HES	READ code/ICD-10 code	Complication
CPRD	A531.11	Post-herpetic neuralgia
CPRD	A531200	Post-herpetic trigeminal neuralgia
CPRD	A531300	Post-herpetic polyneuropathy
CPRD	A531500	Post-zoster neuralgia
CPRD	A531511	Post-herpetic neuralgia
CPRD	F300.00	Post-herpetic trigeminal neuralgia
HES	B02.2	Zoster with other nervous system involvement

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ICD-10, International Classifications of Diseases-10th revision;

Complications (other than post-herpetic neuralgia [PHN]) were grouped into four main categories for the analyses:

- Neurological (other than PHN): i.e. HZ meningitis, HZ encephalitis, Ramsay - Hunt syndrome;
- Ocular HZ (i.e. HZ eyelid; HZ iridocyclitis, etc);
- Disseminated HZ;
- Other HZ complications (i.e. HZ otitis externa and unspecified complications).

Healthcare costing

- HZ subjects without PHN:

- Period = the HZ case onset date -7 prior to the case onset date + 30 days (a);

- HZ subjects reporting a PHN event within 365 days from the HZ case onset date, two analyses periods were used:
  - Period 1 = the HZ case onset date -7 prior to the case onset date + 90 days (b);
  - Period 2 = the HZ case onset date -7 prior to the case onset date + 365 days (c);

The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days after HZ event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).

Additionally, main categories of resource utilization and cost tables were presented for the following sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days and 365 days post-initial HZ onset date:

- HZ only (i.e. no PHN and no HZ-related complication);
- HZ and PHN within 1 year of HZ event;
- HZ and other HZ-related complications but no PHN (overall and by complications sub-categories:
  - Neurological;
  - Ocular;
  - Cutaneous;
  - Other complications.

A detailed mapping linking the exact event definition variables and criteria to the reference unit cost was used. The unit costs for each type of resource were obtained from the following reference sources:

- General practitioner (GP) prescribed medication costs: British National Formulary (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the prescription costs for each drug (prodcode) of interest. A detailed mapping was used to link the exact cost of prodcode quantity and packtype for each drug;

- Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014);
- HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs (National Schedule of Reference Costs, 2013/2014).

Supplementary Table 2: List of medications

Treatment Groups	Description
Antiviral	Aciclovir
	Famciclovir
	Valacyclovir
NSAIDs	Aspirin
	Ibuprofen
COX-2	Paracetamol
Topical Agents	Lidocaine
	Capsaicin
Anticonvulsants	Gabapentin
	Pregabalin
Tricyclic antidepressants	Amitriptyline
	Nortriptyline
	Desipramine
Corticosteroids	Prednisolone
Opioid analgesics	Tramadol
	Morphine
	Oxycodone
	Methadone

Supplementary Table 3: Ambulatory and Outpatient Costs

	Consultation type	Details	Tariff Code	Cost
AMBULATORY AND OTHER AMBULATORY VISITS	GP Surgery Consultation	Per patient contact lasting 11.7 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£35
	GP Clinic Consultation	Per patient contact lasting 17.2 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£50
	GP Telephone Consultation	Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP Home visit	Per out of surgery visit lasting 23.4 minutes (including 12 minutes travel) without qualification costs, excluding direct care staff costs[2] Inflated to 2014 prices using the HCHS annual price inflation[1]	N/A	£87
	GP Home visit out of hours	Ratio of direct to indirect time; Out of surgery visits (home visits and clinics; includes travel time) - 1:0.99[2]	N/A	£86

	Consultation type	Details	Tariff Code	Cost
	GP Practice Nurse Consultation	Per 15.5 minute surgery consultation @ £44/hour (excluding qualification costs)[1]	N/A	£11
	GP Results by Phone	Assume same as GP Telephone Consultation Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP Time spent on phone/writing letter	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£23
	GP Time on administration	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£8
AMBULATORY AND OTHER AMBULATORY VISITS	District Nurse Visit	Mean average cost for a face-to-face contact in district nursing services (based on NHS reference costs) was £39 in 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£40

	Consultation type	Details	Tariff Code	Cost
	Health visitor Visit	Mean average cost for a face-to-face contact in health visiting services (based on NHS reference costs) was £51 in for 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£52
OUTPATIENT HOSPITAL ATTENDANCE	Anaesthetics, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	190	£125
	Dermatology, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	330	£104
	General Medicine, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	300	£178
	Ophthalmology, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	130	£119

	Consultation type	Details	Tariff Code	Cost
	A&E Attendance	Category 3 investigation with category 1-3 treatment[3]	VB03Z	£163
	Pain Management, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	191	£138

	Consultation type	Details	Tariff Code	Cost
OUTPATIENT HOSPITAL ATTENDANCE	Neurosurgery, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	150	£182
	Palliative Medicine, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	315	£167
	Neurology, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	400	£174

GP, General Practitioner; N/A, not available; NHS, National Health Service; HCHS, community health services; A&E, accident and emergency;

Source:

1. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014.
2. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2013. University of Kent, 2013
3. 2014/5 National Tariff Payment System. Annex 5A National Prices, 17 December 2013 https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015
4. National Schedule of Reference costs 2013-14 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls

Supplementary Table 4: Hospital Inpatient costs

Diagnosis Code	Detail	Average tariff per admission
B020	Zoster encephalitis	£5,038.39
B021	Zoster meningitis	£2,065.47
B022	Zoster other nervous system involvement	£1,440.48
B023	Zoster with ocular diseases	£2,226.36
B027	Disseminated Zoster	£2,255.30
B028	Zoster with other complications	£2,060.70
B029	Zoster without complications	£1,790.57

Source: Hospital Episode Statistics (HES) Admission data IMS, 2013/14

HZ treatment prescriptions

All HZ treatment prescriptions, defined according to British National Formulary (BNF) indication and clinical expert input, were identified by product codes from the HZ TREATMENT CPRD Prodcodes List, and were extracted from the CPRD Therapy dataset.

Analysis datasets used

HZ treatments prescriptions (CPRD Therapy dataset);
CPRD Ambulatory Visits (CPRD Consultation dataset);
Specialists Referrals by GP (CPRD Referral dataset);
Hospitalizations (HES Inpatient: HES_DIAGNOSIS_EPI dataset);
Outpatient Visits (HESOP Clinical dataset);
Nursing home visits and Time off sick (CPRD Clinical dataset);

Supplementary Table 5: Costs by Category, IC Status, Time period of Analysis and Age Groups

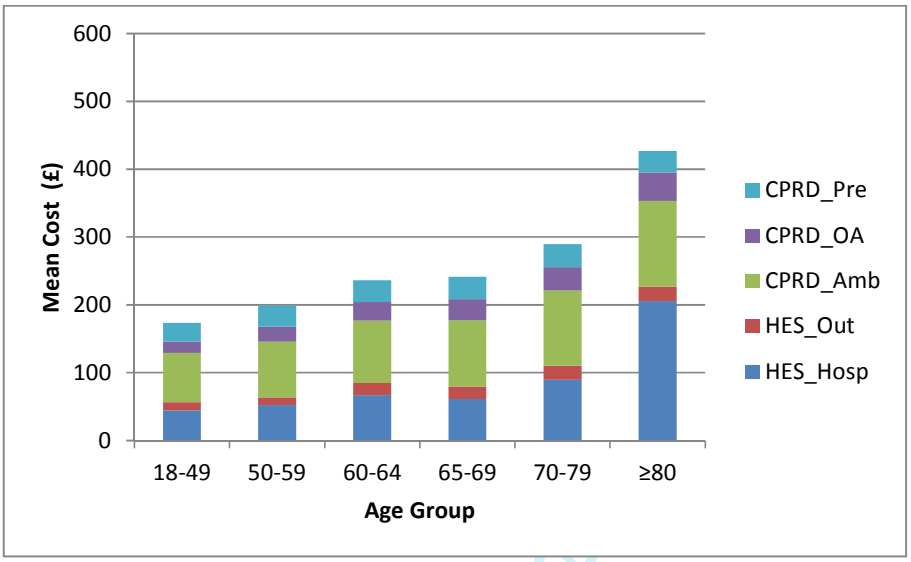
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
IC Population (≤90 days)						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES Outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD Ambulatory Visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD Other Ambulatory Visits	16.1	22	27.7	31	34.6	41.8
CPRD Prescriptions	27.6	31.1	31.9	33.3	33.9	31.9
Total	**173.2**	**199.0**	**236.2**	**241.6**	**289.6**	**427.0**
IC Population (≤365 days)						
Hospitalizations	44.2	56.7	68	62.4	93.8	216.5
HES Outpatient consultations/visits	15.1	16.1	23.9	28.1	34.4	40.1
CPRD Ambulatory Visits	80.6	100.1	120.2	134.5	158.1	180.8
CPRD Other Ambulatory Visits	20.7	31.6	44.9	54.4	63.2	78.8

CPRD Prescriptions	28.7	33.3	37.3	38.1	42.2	40.8
Total	**189.3**	**237.8**	**294.2**	**317.4**	**391.7**	**557.0**
IC-Free Population (≤90 days)						
Hospitalizations	6.3	8.5	11.5	17.5	36.4	136.5
HES Outpatient consultations/visits	5.2	7.8	8.2	10.4	13.9	18.2
CPRD Ambulatory Visits	59	66.7	69.6	72.7	88.8	102.8
CPRD Other Ambulatory Visits	8	11.2	12.9	16.9	21.2	32.8
CPRD Prescriptions	19.7	24.7	24.6	28	29.4	29.4
Total	**98.2**	**118.9**	**126.8**	**145.5**	**189.7**	**319.7**
IC-Free Population (≤365 days)						
Hospitalizations	6.3	8.9	12	17.9	37	144
HES Outpatient consultations/visits	5.7	10.8	10	13.4	22.7	28.4
CPRD Ambulatory Visits	63	75.8	80.4	90	117.3	135.9
CPRD Other Ambulatory Visits	8.8	14.2	18.6	23.2	36.8	58.7
CPRD Prescriptions	20	25.6	26.8	29.9	34.9	34.1
Total	**103.8**	**135.3**	**147.7**	**174.4**	**248.6**	**401.0**

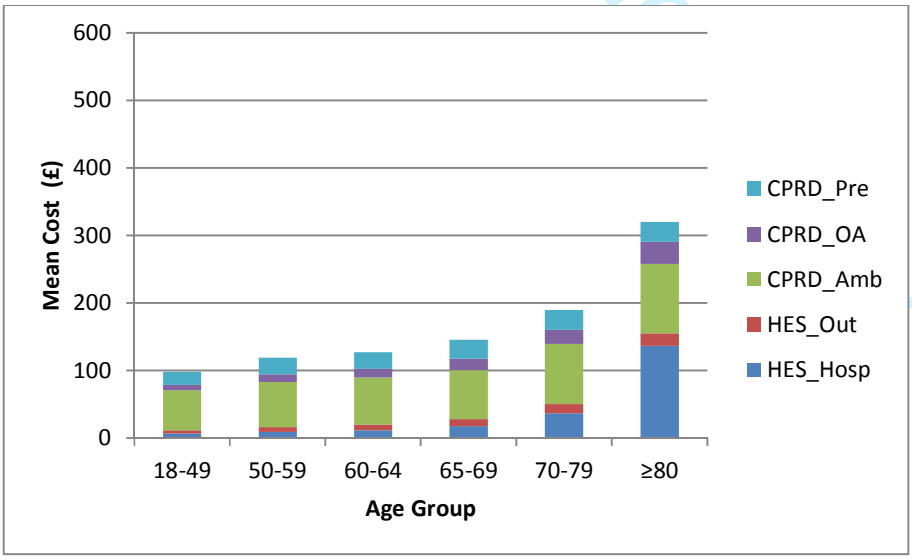
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

Supplementary Figure 1: Healthcare costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



Panel B



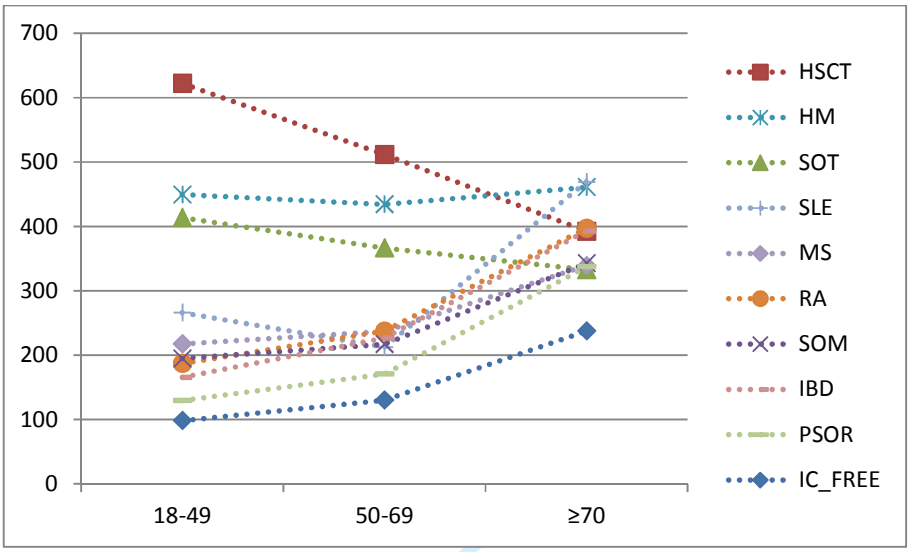
For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-OA, CPRD Other Ambulatory

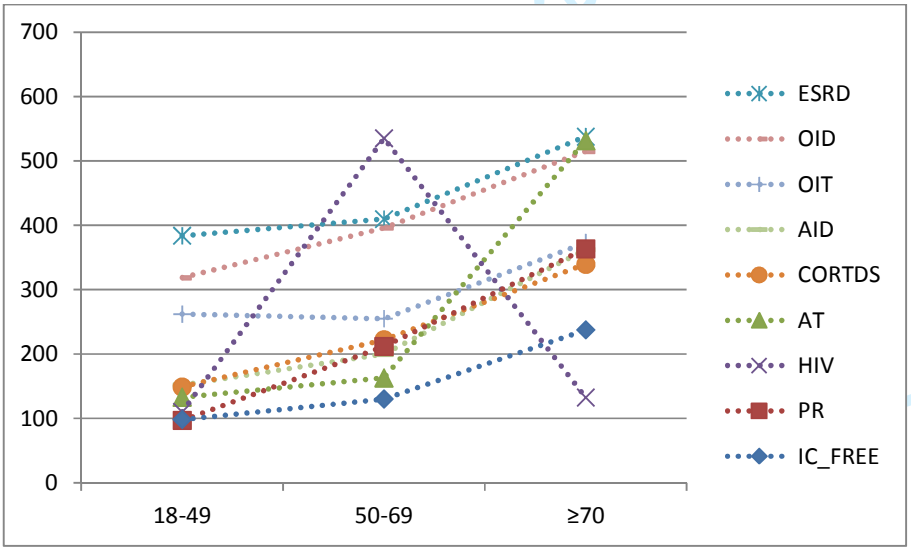
Visits; CPRD-Amb, CPRD Ambulatory Visits; HES-Out, HES Outpatient consultation; HES-Hosp, HES Hospital admission;

Supplementary Figure 2: Healthcare Costs for each IC condition by age group for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



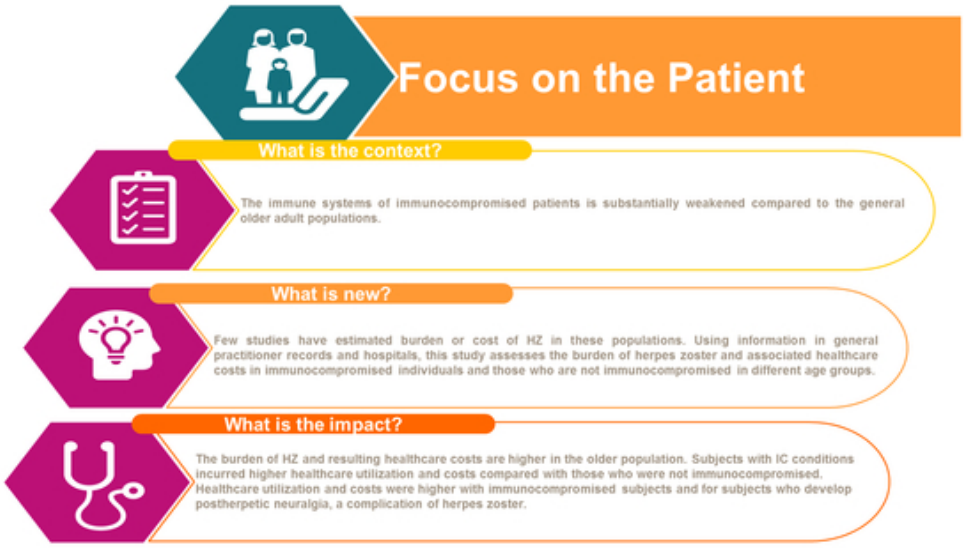
Panel B



For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; HSCT, hematopoietic stem cell transplantation; HM, haematological malignancies; SOT, solid organ transplantations; SLE, systemic lupus erythematosus; MS, multiple sclerosis; RA, rheumatoid arthritis; SOM, solid organ malignancies; IBD, inflammatory bowel syndrome; PSOR, psoriasis; ESRD, end-stage renal disease; OID, other immunodeficiency; OIT, other

immunosuppressive therapy; AID, autoimmune diseases; CORTDS, corticosteroid exposure; AT, autoimmune thyroiditis; HIV, human immunodeficiency virus; PR, polymyalgia rheumatica



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pages 1 and 2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8,9
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Pages 9,10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 9,10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

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TITLE PAGE

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

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ABSTRACT

[[298/300 words]]

Objective

Individuals with immunocompromised (IC) conditions are at a higher risk of developing herpes zoster (HZ) than IC-free individuals. This study assessed the healthcare resource utilization (HCRU) burden and costs, of HZ in IC and IC-free individuals ≥18 years of age (YOA).

Methods

We conducted an observational retrospective study in a cohort of IC (N=621,588) and IC-free (N=621,588) individuals, matched by age, gender and GP practice region, contributing to the Clinical Practice Research Datalink database from 2000 to 2012 and linked to the Hospital Episode Statistics inpatient data. HCRU (i.e. primary and secondary care consultations, hospital inpatient stays, and treatment prescriptions) was analyzed from 7 days before to: (1) 30, (2) 365 days after the HZ diagnosis date for individuals with (1) HZ only (no post-herpetic neuralgia [PHN]) and (2) individuals with HZ and PHN only. Healthcare costs were computed by multiplying the number of units of resources utilized by the unit costs, summed across all HCRU categories to obtain a total cost per subject. Values were expressed in 2014 UK pound sterling (£) and presented for HZ cases overall, stratified by age (i.e. 18-49, 50-59, 60-69, 70-79 and ≥80 YOA) and IC status.

Results

The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and IC-free individuals aged ≥80 YOA, respectively). Similarly, HZ-related mean treatment costs per

subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged ≥80 YOA, respectively). Costs varied considerably by IC condition.

Conclusions

Individuals with IC conditions, not only have a higher risk of HZ than IC-free individuals, but also incur higher HZ-related healthcare costs.

Keywords

Herpes zoster, post-herpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study is an observational retrospective descriptive study presenting the healthcare resource utilization and costs associated with herpes zoster (HZ) in both immunocompromised (IC) and IC-free populations aged ≥18 years of age in England.
- The IC population included 621,588 individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions and matched to the Hospital Episode Statistics (HES) database by age, gender and practice location to extract the IC-free population (N=621,588).
- The particularity of this study is that the design allowed calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s).
- This key study will provide data to be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in IC populations.
- A limitation of the study is that the diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts.

LIST OF ABBREVIATIONS

£, 2014 UK pound sterling

A&E, Accident and Emergency

AID, autoimmune diseases

ARDI, age-related decline in immunity

AT, Autoimmune Thyroiditis

BNF, British National Formulary

CPRD, Clinical Practice Research Datalink

GP, General Practitioner

HCRU, healthcare resource utilization

HES, Hospital Episode Statistics

HIV, human immunodeficiency virus

HM, hematological malignancies

HSCT, hematopoietic stem cell transplantation

HZ, herpes zoster

HZ-Comp, HZ and complications with no PHN

IC, immunocompromized

ICD-10, International Classification of Diseases-10th revision

ISAC, Independent Scientific Advisory Committee

PHN, post-herpetic neuralgia

PSSRU, Personal Social Services Research Unit

PY, person-years

RA, rheumatoid arthritis

SLE, systemic lupus erythematosus

SOT, solid organ transplantations

UK, United Kingdom

US, United States

VZV-CMI, varicella zoster virus cell-mediated immunity

YOA, years of age

ZVL, zoster vaccine live

INTRODUCTION

[[2,819/4,000 words; 6/5 tables+figures but journal allows flexibility]]

Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes zoster (HZ)[1]. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not optimal in individuals with immunocompromized (IC) conditions and the age-specific incidence and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune disease, malignancy, or organ transplantation[2].

The incidence and severity of HZ is marked with an increase in people ≥50 years of age (YOA) due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among individuals aged ≥85 YOA[3]. Further to the impact of ARDI, a study by Forbes et al. in 2014 investigated the increased risk for HZ in the UK population, associated with autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and asthma[2]. In addition to the increased risk of HZ in the various IC conditions these populations also experience increased severity of disease. In a study in Canada, Drolet et al. reported that individuals with an impaired immune status had HZ severity of illness scores, as measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with normal immune function[4 5]. In a study in the United States (US), Yawn et al. reported that although 8% of HZ cases were in individuals who were immunocompromised, these individuals represented 23.8%

of the total HZ-related costs[6]. The increase in healthcare costs was associated with higher rates of post-herpetic neuralgia (PHN) and non-pain complications in this group of individuals[6].

This study aims to estimate the healthcare resource utilization of HZ in selected IC populations and in an IC-free (i.e., immunocompetent) population aged ≥18 YOA in England. The clinical burden of disease epidemiological results of the study are reported elsewhere[7], and may be summarized as follows: the prevalence of IC conditions increased from 7.6% in individuals aged 18-44 YOA to 42.2% in individuals aged ≥80 YOA; the incidence rate of HZ in the IC cohort was 3.5/1000 PY in individuals aged 18-49 YOA increasing to 12.6/1000 PY in individuals aged ≥80 YOA. In this manuscript, we focus on the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations.

METHODS

The study was conducted as an observational retrospective descriptive study (e-track number: 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥18 YOA). The IC population included individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions (See Supplemental Material). The CPRD IC population cohort linked to the Hospital Episode Statistics (HES) database was matched to a cohort of HES linked IC-free population (N=621,588), by age, gender and practice location. Individuals with a missing date of IC diagnosis were excluded from the study population. Clinical diagnoses were based on READ codes used in CPRD and with the International Classifications of Diseases-10th revision (ICD-10) codes in the HES database.

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency database research (ISAC protocol number 14_222R). The study was conducted in accordance with all applicable regulatory requirements, with the Guidelines for Good Pharmacoepidemiology Practices[8], all applicable patient privacy requirements and the guiding principles of the Declaration of Helsinki.

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[7]. Healthcare resource data associated with an incident HZ episode during the study follow-up were extracted for IC and Matched IC-free HES-linked individuals. Only reported records (resource utilization) with available event dates during the individuals' eligibility period and those that occurred 7 days before the initial HZ onset date, up to 365 days after the initial HZ onset date, were extracted. Consequently, individuals who recorded the first PHN event date after 365 days post HZ event date were classified as not having PHN.

Patient and Public Involvement

This is a retrospective database analysis carried out following ethical committee approval. No patient or the public was involved in the study design or in the recruitment or the conduct of this study. No specific dissemination of study results to participants was done. However, we provided a lay language summary contextualizing the results and potential clinical research relevance and impact in Figure 1.

Data sources

Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation, Clinical, Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI dataset; (3)

HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource utilization was defined as: HZ-treatment related prescribed medications (CPRD tbl:therapy); Consultations and care provided by General Practitioners (GPs) or others in the GP practice (CPRD tbl:consultations); HES secondary care outpatient visits (HES outpatient events); and HES inpatient hospitalizations (HES inpatient events).

For each patient, healthcare costs stratified by subcategory of interest (HES Inpatient Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by their unit costs. These were then summed over all resource use categories to obtain a total cost for each patient. Values were expressed in 2014 UK pound sterling (£).

Healthcare resource costs

For each patient, the cost of each prescription was calculated by merging the product code, package type and prescribed quantity (prodcode-packtype-quantity) with the associated standard package size and unit cost. The unit cost of a product in a prescription instance (i.e. one distinct record in the CPRD therapy) was calculated using the cost described in the British National Formulary (BNF), 2015 (as listed price if included or indicative price based on price in BNF).

Ambulatory visits included consultations with GPs and nurses in primary or community care. Visits included consultations at the practice or at the home of the patient, during working hours and out of hours. Consultations for which no clinical intervention was recorded were not included in the cost estimate for GP practice related healthcare utilization, for example: information technology data migration, administrative recording of received information. Administrative resource use in primary care was considered, including time on the phone, writing reports, referrals, etc. A referral

to secondary care noted in a patient's record, *per se*, was not allocated the cost of the secondary care appointment. The most conservative option for the cost per unit as included in the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care, 2014 were applied e.g. GP consultation costs excluded qualification, direct staff care and travel costs[9]. Where specific costs for 2013/14 were not available, 2012/13 costs, were adjusted by applying the Hospital and Community Health Services inflation index[9]. Administration costs were based on unit costs as stated in the PSSRU, 2014.

Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient resource utilization concerned HZ related referrals for non-inpatient hospital consultations, derived from the HES Outpatient data. Additionally, visits to the Accident and Emergency (A&E) department in hospitals were also recorded and costed. Inpatient hospitalization costs were based on the average cost per episode using HES data for 2013/14 (calculated from the total average payment by result spell cost and the average number of episodes per spell). Hospital outpatient costs were sourced from National Tariff costs (2014) for specific consultant led outpatient consultations; conservative costs were allocated i.e. wherever applicable costs for first attendance by a single professional appointment were used[10]. Costs allocated to A&E visits were based on the cost of a category 3 investigation with category 1-3 treatment[10]. Only events related to HZ were costed out. Resources related to HZ complications were considered using ICD-10 Code B020.

No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in CPRD. Further details, including information on the IC populations included, ICD-10 codes for HZ and PHN, and unit healthcare costs are provided in the Supplementary Material, specifically in Supplementary Tables 1 to 4.

RESULTS

The HES-linked matched IC and IC-free population cohorts (n=621,588 each) included approximately 44% males and 56% females with a mean age of approximately 56 years. The age distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥80 YOA (11.01%).

The proportion of inpatient hospital admissions by age group for the HES-linked Matched IC and IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel A) or 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 2. Hospital admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset (Panel B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and IC-free individuals aged ≥80 YOA, respectively). Multiple HZ-related hospital visits were reported for some individuals. As such, Table 1 presents the mean number of healthcare resources utilized by IC Status, Age Group and Analysis period. The mean number of hospitalizations per HZ case for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free individuals aged 18-49 YOA, respectively and 0.173 and 0.115 in IC and IC-free individuals aged ≥80 YOA, respectively. A similar pattern of higher healthcare resource utilization with increasing age and in IC individuals was observed for all resources for which costs were assigned. A similar mean number of sick leave certificates were observed between the IC and the IC-free cohorts with the mean decreasing with age. Nursing home care / admissions were only recorded for individuals aged ≥70 YOA in CPRD.

Figure 3 and Table 2 present the overall healthcare costs by HES-linked matched IC cohort and age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs increase

with age and are consistently higher in the IC cohort compared with the IC-free cohort. Although the absolute cost difference between IC and IC-free individuals increases with age from £85.5 in individuals aged 18-49 YOA to £156.1 in individuals aged ≥80 YOA the relative difference is higher in younger individuals (i.e. 75.8%-99.2% in <70 YOA) compared with older individuals (i.e. 38.9%-57.6% in ≥70 YOA). It is also noteworthy that the means are consistently higher than medians, and as is common for healthcare cost data, the distribution is skewed to the right. Supplementary Table 5 and Supplementary Figures 1 and 2 provide additional data on healthcare Costs for the analysis period 7 days prior to 90 days post initial HZ onset.

Figure 4 presents the overall healthcare costs by each IC condition in the HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset. For all IC conditions, the costs were higher than those for the IC-free group, in particular for the hematopoietic stem cell transplantation (HSCT), hematological malignancies (HM) and solid organ transplantations (SOT) conditions. In general, there was a similar trend of increasing costs with increasing age-groups. A few outliers were observed due to small sample sizes. For example, only 3 and 8 individuals aged ≥70 YOA were included in the HIV and HSCT groups, respectively. Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis (AT) and SOT were included, respectively.

Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean healthcare costs were approximately 2 to 4 times higher for individuals with HZ complications compared to individuals with HZ only.

Supplementary Table 6 presents the non-HZ related hospital inpatient stay for the period 7 days to 365 days post initial-HZ onset. The mean number of non-HZ related hospitalizations were consistently higher in IC patients compared to and IC-free patients and increased with age.

DISCUSSION

In this study, we presented the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations using large electronic health record databases in the UK. An important feature of this study was that the design enabled the calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s), see Yanni et. al. for further detail on epidemiological outcomes[7]. In this study, every effort was made to include only resources directly related to HZ. For example, only hospitalized patients were included who had an ICD-10 HZ diagnosis identified in the HES database. Similarly, only medications potentially related to HZ treatment were included (see Supplementary Material Tables 2 and 4). HZ-related mean treatment costs per patient were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA, respectively increasing to £557 *versus* £401 in IC and IC-free individuals aged ≥80 YOA, respectively).

Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the mean healthcare costs per HZ patient, from an National Health Services perspective, of £85.6 and £400.9 in individuals aged <65 YOA and ≥65 YOA, respectively[11]. A later UK study that used the HES and the health improvement network databases, estimated the mean cost of treating a HZ patient to be £65.5 in the first month of diagnosis, with patients aged ≥70 YOA having a mean cost

of £83 in the first month and £15.80 in months 2 and 3[12]. The costs of treating individuals with PHN were much higher, i.e. mean cost per patient was estimated to be £921 in all individuals and £909.60 in individuals aged ≥70 YOA[12]. Another study evaluated mean healthcare costs (excluding hospitalization costs) to be £75.63 per HZ patient with mean direct costs for treating PHN episodes (PHN pain occurring or persisting for 3 months) of £340.04[13]. These values augmented with hospitalization costs were used as inputs in a cost-effectiveness model evaluating a HZ vaccine using the population of England and Wales[3]. The costs estimated by van Hoek et al. are consistent with the values estimated in our study for IC-free individuals by age group[3].

In a previous study, mean prescription costs per HZ patient were reported to be £40.52[13]. In our study, the mean prescription costs per HZ patient ranged from £19.7 to £40.8 depending on the age group, IC status and analysis period included. Our study aimed to include only medications considered to be directly related to HZ; i.e. excluded medications that may be linked to IC conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from other conditions). This restriction and the introduction of generic versions of medications such as acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed to the reduced overall medication costs reported in this study.

Many studies on HCRU and costs include a number of days prior to diagnosis, e.g. 14 or 21 days, as there may be a delay in diagnosis and HCRU may be utilized prior to diagnosis[6,14]. In this analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days post HZ onset, although it is recognized that HZ episodes can last for longer. The costs of PHN were analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days prior to 365 days post HZ onset. The rationale for the time periods studied was that using analysis period 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2 only could

overestimate these costs. The most frequently used definition of PHN is: pain persisting or appearing at least 90 days following rash onset. The median duration of PHN has been reported to be 10.3 and 12.9 months in individuals aged ≤69 and ≥70 YOA respectively[15], and is likely to be longer in individuals who are immunocompromised[5].

The healthcare costs associated with PHN and complications were higher than those for individuals with HZ only. However, as reported elsewhere, when considering the overall cost of disease at a population level, the overall healthcare-associated cost is higher for HZ only[16]. This is primarily a result of the higher incidence rates of HZ only.

Few studies have investigated healthcare resource utilization and costs in IC individuals. Schroder et al. carried out a study using the German Pharmacoepidemiological Research Database, which consists of claims data from four statutory health insurances[17]. They reported that during the quarter of the HZ diagnosis or during the two following quarters, 10% of all HZ patients with an IC condition were hospitalized (with a HZ diagnosis), whereas among IC-free HZ patients, 4.2% were hospitalized. White et al. reported that in their study using the US Market Scan Research Database, direct medical costs were nearly twice as high in IC patients compared with IC-free patients[18]. Li et al. carried out a study using the US Truven Health MarketScan Commercial and Medicare Supplemental Insurance databases[19]. They concluded that patients with the studied IC conditions (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer) had significantly higher healthcare utilization and cost when developing HZ than their comparable matches without HZ. Insurance databases include not only the healthcare resource utilization but also costs. In the CPRD and HES Databases only the resource utilization is captured. As such the overall costs need to be calculated by assigning unit costs to the resource utilization. There are advantages however of using the CPRD and HES in that the databases offer more diversity than might be observed using

insurance databases, the latter of which may be somewhat limited by bias associated with factors such as age, race, and income.

This study has several limitations. Diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts. Increasing healthcare resource utilization and cost is likely to be related to increased severity of IC conditions. In a study, Schroder et al. categorized individuals as low IC and high IC[17]. However, insufficient details are recorded in the CPRD and HES databases to allow adequate definition of patients' severity of immunosuppression e.g. laboratory parameters, immunosuppressive medication details such as chemotherapy. In addition, many IC individuals had prescriptions that included more than one immunosuppressing medicine.

CONCLUSION

In conclusion, individuals with IC conditions, seeking healthcare in the UK, incurred higher healthcare utilization and costs than IC-free individuals[6,7,14]. The results from this study could be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in these populations.

AUTHOR CONTRIBUTIONS

VB, AEG, YEH, GF, MH and DC participated in the conception and design of the study. VB, AEG, YEH, GF and MH participated in the collection or generation of the study data. VB, AEG and YEH performed the study. AEG, YEH, MH and DC contributed to the material. VB, AEG, YEH, GF, MH and DC were involved in the analysis or interpretation of the data. All named authors provided substantial intellectual and scientific input during the manuscript development, critically reviewing the content, revising the manuscript and giving final approval before submission. The work described was carried out in accordance with the ICMJE recommendations for conducting, reporting, editing and publishing scholarly work in medical journals. All authors had full access to the data and gave final approval before submission.

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CONFLICTS OF INTEREST

VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the GSK group of companies between 2012 and Feb 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.

DATA SHARING STATEMENT

All data used in this study are presented in the manuscript, references to the original material are provided. Please contact the corresponding author shall you require any additional information

ETHICAL APPROVAL

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

FUNDING

GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK study identifier: e-track number: 201615) activities and overall data management (collection, analysis and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and the corresponding author was responsible for submission of the publication.

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TABLES

Table 1: Mean number of healthcare resources by IC status, age group and analysis period

	IC cohort		IC-Free cohort	
	90 Day	365 Day	90 Day	365 Day
HES Hospital admission				
18-49	0.035	0.035	0.005	0.005
50-59	0.042	0.046	0.006	0.007
60-64	0.053	0.055	0.009	0.010
65-69	0.049	0.050	0.014	0.014
70-79	0.072	0.076	0.029	0.030
≥80	0.163	0.173	0.108	0.115
HES Outpatient consultation				
18-49	0.095	0.116	0.041	0.045
50-59	0.086	0.122	0.062	0.086
60-64	0.136	0.180	0.065	0.078
65-69	0.146	0.217	0.085	0.108
70-79	0.165	0.267	0.113	0.181
≥80	0.173	0.313	0.149	0.231
CPRD Ambulatory visits				
18-49	2.816	3.168	2.186	2.360
50-59	3.334	4.175	2.466	2.907
60-64	3.733	5.081	2.598	3.115
65-69	4.089	6.009	2.774	3.610
70-79	4.534	6.959	3.413	4.767
≥80	4.881	7.422	3.811	5.367
CPRD Other ambulatory visits				
18-49	0.319	0.411	0.155	0.170
50-59	0.433	0.623	0.218	0.277

60-64	0.545	0.885	0.251	0.360
65-69	0.607	1.064	0.330	0.454
70-79	0.686	1.251	0.417	0.722
≥80	0.860	1.616	0.668	1.183
CPRD Prescriptions (All treatments)				
18-49	1.247	1.363	0.890	0.931
50-59	1.670	1.994	1.143	1.227
60-64	1.969	2.602	1.379	1.489
65-69	2.129	2.894	1.473	1.717
70-79	2.310	3.295	1.814	2.347
≥80	2.405	3.743	1.844	2.575
CPRD Referrals*				
18-49	0.018	0.020	0.011	0.012
50-59	0.021	0.026	0.018	0.022
60-64	0.031	0.040	0.020	0.024
65-69	0.031	0.044	0.015	0.023
70-79	0.033	0.054	0.031	0.047
≥80	0.040	0.065	0.029	0.048
CPRD Sick leave*				
18-49	0.162	0.175	0.155	0.161
50-59	0.156	0.178	0.173	0.182
60-64	0.060	0.069	0.080	0.087
65-69	0.017	0.017	0.008	0.008
70-79	0.001	0.001	0.002	0.003
≥80	0.000	0.000	0.000	0.000
CPRD Nursing home care/admission*				
18-69	0.000	0.000	0.000	0.000
70-79	0.001	0.001	0.001	0.001

≥80	0.004	0.004	0.003	0.003

* No costs were assigned for CPRD Referrals, CPRD Sick leave, CPRD Nursing home care / admission

Abbreviations: IC, immunocompromized; HES, Hospital Episode Statistics; CPRD, Clinical Practice Research Datalink; Costs were assigned for HES Hospital admission, HES Outpatient consultation, CPRD Ambulatory Visits, CPRD Other Ambulatory Visits, CPRD Prescriptions.

Table 2: Mean cost (£) of healthcare resource utilization by IC status, age group and analysis period*

Age groups (YOA)	Statistic	Mean cost (£)			
		IC cohort		IC-free cohort	
		90 Day	365 Day	90 Day	365 Day
18-49	Mean	173.3	189.3	98.2	103.8
	Median, SD	86.1, 332.54	86.9, 375.31	59.6, 139.37	62.0, 152.82
50-59	Mean	199.0	237.8	118.9	135.3
	Median, SD	106.6, 372.15	108.8, 528.36	74.6, 197.77	74.8, 249.02
60-64	Mean	236.2	294.2	126.8	147.7
	Median, SD	120.2, 473.92	124.1, 606.36	78.9, 215.45	80.9, 279.29
65-69	Mean	241.6	317.4	145.5	174.4
	Median, SD	132.2, 447.25	140.0, 590.29	87.9, 239.31	90.7, 307.75
70-79	Mean	289.6	391.7	189.8	248.6
	Median, SD	154.2, 531.25	163.9, 744.81	108.8, 366.74	113.6, 508.42
≥80	Mean	427.0	557.1	319.7	401.0
	Median, SD	176.2, 815.38	188.6, 1059.68	143.0, 630.70	154.0, 767.72

* post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; HZ: herpes zoster; IC, immunocompromized; YOA: years of age, SD:Standard Deviation

Table 3: Mean cost (£) of healthcare resource utilization by IC status, age group, analysis period and HZ complication status

Age groups (YOA)		Mean cost (£), IC			
		HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	Mean	156.6	302.4	746.6	573.3
	Median, SD	81.8, 298.78	194.7, 354.78	465.7, 813.67	176.5, 799.00
50-59	Mean	168.1	468.0	998.9	562.6
	Median, SD	93.9, 280.38	262.8, 779.39	588.8, 1410.97	226.0, 788.06
60-64	Mean	190.8	538.7	1135.5	780.5
	Median, SD	108.8, 360.09	297.7, 812.63	688.2, 1204.79	226.4, 1240.23
65-69	Mean	195.6	489.3	1064.3	551.8
	Median, SD	109.6, 388.27	305.4, 605.84	738.9, 960.15	204.9, 778.37
70-79	Mean	228.9	540.4	1200.2	847.5
	Median, SD	129.0, 413.49	324.5, 783.04	808.4, 1294.77	337.4, 1166.29
≥80	Mean	307.6	779.5	1536.0	1396.4
	Median, SD	148.6, 614.83	384.3, 1051.87	937.3, 1663.11	516.5, 1769.26
		Mean cost (£), IC-free			
		HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	Mean	91.6	216.1	391.9	246.4
	Median, SD	54.9, 118.74	137.7, 318.86	261.9, 393.31	106.6, 347.45
50-59	Mean	106.8	262.8	540.8	275.1
	Median, SD	72.0, 141.43	208.2, 332.40	391.3, 589.56	118.1, 864.14
60-64	Mean	114.1	270.5	556.1	192.7
	Median, SD	74.6, 199.18	191.9, 308.00	409.4, 608.19	78.1, 331.63
65-69	Mean	123.7	287.7	595.5	592.6
	Median, SD	80.9, 168.04	202.4, 353.33	440.2, 591.86	229.5, 1079.09

70-79	Mean	149.2	388.2	813.7	511.5
	Median, SD	88.7, 266.27	248.6, 584.03	546.1, 955.88	232.9, 952.31
≥80	Mean	242.0	607.4	1182.8	1046.5
	Median, SD	121.3, 465.00	310.5, 888.22	726.9,1 237.33	341.0, 1516.83

* Individuals with HZ only (i.e. without PHN and complications): includes only costs 7 days prior to 30 days post initial HZ onset

Individuals with HZ and PHN: includes only costs 7 days prior to 90 days post initial HZ onset

! Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset

§ Individuals with HZ and complications but no PHN: includes only costs 7 days prior to 30 days post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ,herpes zoster; PHN, post-herpetic neuralgia; HZ-Comp, HZ and complications with no PHN; YOA: years of age

FIGURE

Figure 1: Lay Language Summary

Figure 2: Inpatient Hospital Admission by HES-linked Matched IC or IC-free cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to 365 days post initial HZ onset (Panel B)

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
For HZ individuals with PHN: data from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A) and 365 days (Panel B).
Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, post-herpetic neuralgia

Figure 3 : Healthcare Costs for by HES-linked Matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset

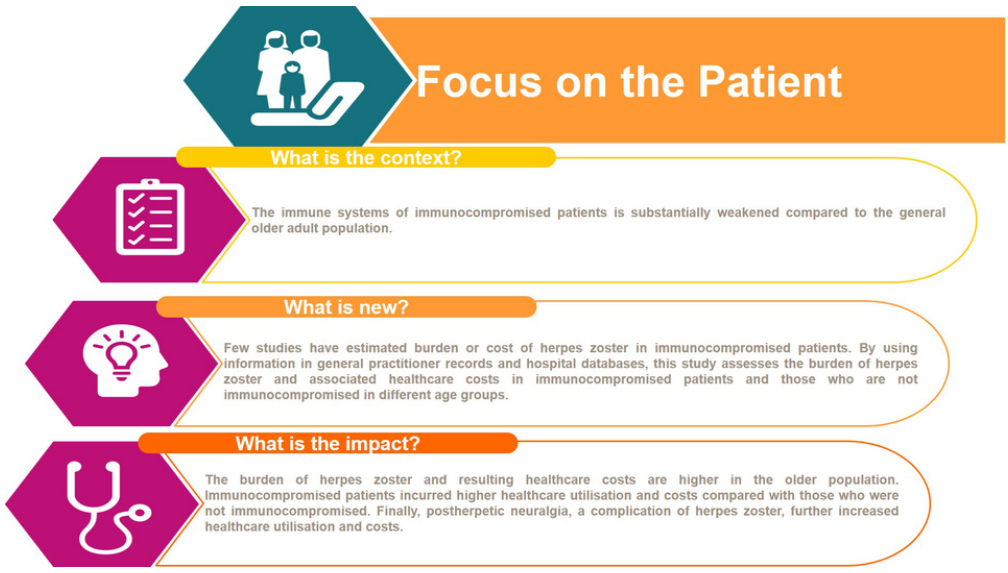
For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits; HES, Hospital Episode Statistics; HES-Out, HES Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia.

Figure 4 : Healthcare Costs for each IC condition in the HES-linked Matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.

For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.

Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM, hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, post-herpetic neuralgia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID, other immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica.



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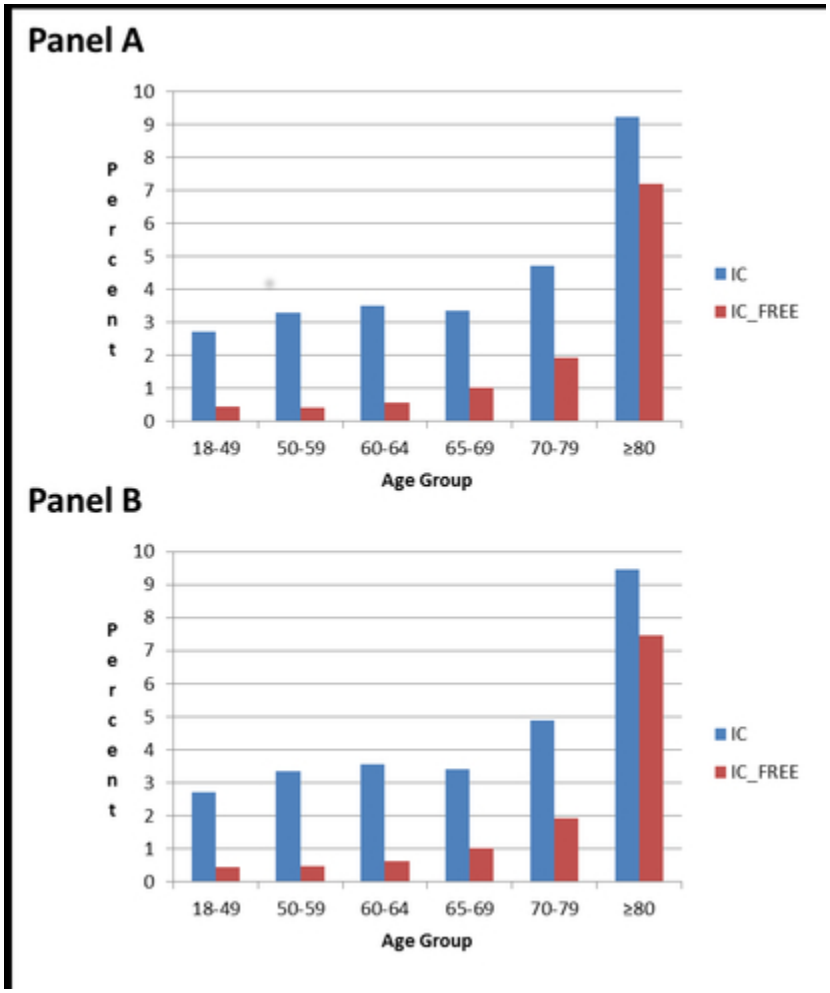

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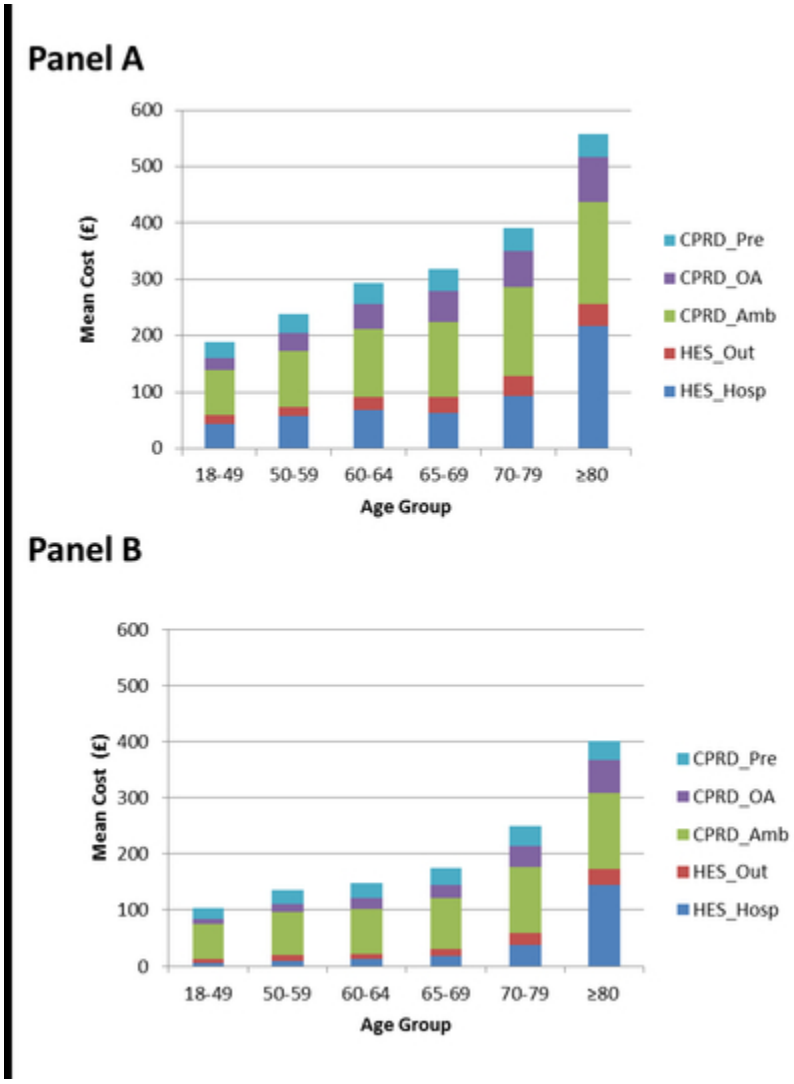

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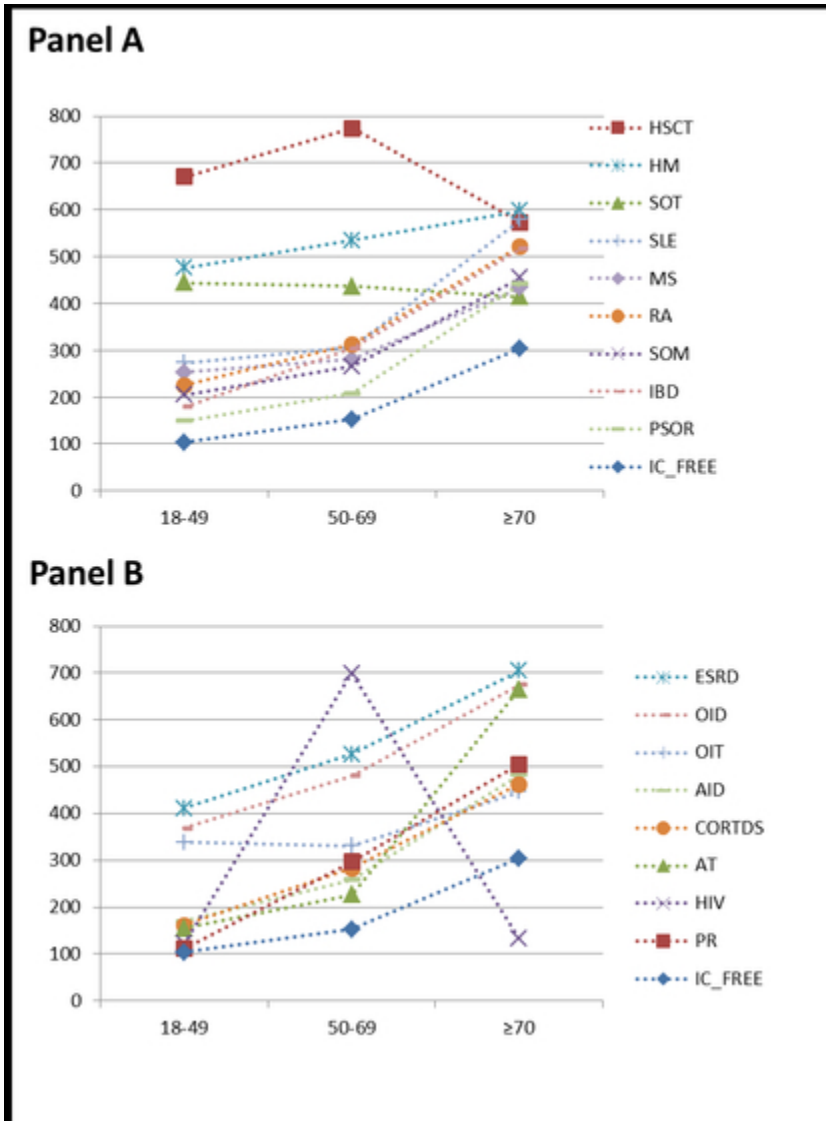

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Supplementary Material

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

Desmond Curran, Manjit Hunjan, Amale El Ghachi, Yassine El Hahi, Veronique Bianco, Germano Ferreira

BMJ Open

Immunocompromised population

The immunocompromised (IC) population, referred to as the IC cohort hereafter, included eligible subjects reporting at least one of the following conditions or therapies at any time before 31st March 2012:

- Hematopoietic stem cell transplant (HSCT);
- Solid organ transplantation (SOT);
- Solid organ malignancies (SOM);
- Hematological malignancies (HM): Leukemia, Lymphoma, Myeloma;
- Autoimmune diseases (AID):
    - Rheumatoid Arthritis (RA);
    - Systemic *Lupus erythematosus* (SLE);
    - Inflammatory Bowel Disease (IBD);
    - Psoriasis (PSOR);
    - Multiple sclerosis (MS);
    - Polymyalgia rheumatica (PR) and;
    - Autoimmune thyroiditis (AT).
- Human immunodeficiency virus (HIV);
- End-stage renal disease (ESRD);
- Corticosteroid exposure (CORTDS);
- Other immunosuppressive therapy (OIT) exposure;
- Other immunodeficiency (OID) conditions.

For autoimmune diseases, each disease was considered as a separate IC condition. Any subject with a code for any IC condition listed above at any time in their record was excluded from the IC-free cohort. Only subjects that were part of IC conditions based on treatment administration ("Corticosteroid exposure" and/or the "Other immunosuppressive therapy exposure" IC conditions) had an end of follow-up based on prescriptions and could present a gap of exposure in the IC cohort between the end of exposure in that IC condition and the beginning of the next one, if any, during which they could not be considered as IC.

IC Matching

The IC-free matched population included a random sample of the IC-free population described above matched to the subjects of the IC population with a ratio of 1:1 (IC: IC-free subjects) when possible. The matching factors were:

- Hospital Episode Statistics (HES) linkage eligibility;
- The year of birth of the subject;
- The gender of the subject, and;
- The practice geographical region.

In addition, the IC-free subjects were included in the study at their corresponding matched IC subject's index date and should not have reported any history of HZ before the matched IC index date.

Herpes Zoster (HZ) Diagnosis

HZ cases identified in the Clinical Practice Research Datalink (CPRD) database were defined as subjects reporting at least one HZ-related READ code. Incident cases were subjects with at least 12 months of active registration in CPRD and no past record of HZ diagnosis during at least 12 months prior to inclusion or even before in their available medical records. HZ cases were identified in HES using the International Classification of Diseases-10th revision (ICD-10) codes that appeared in the diagnosis fields. If HZ diagnosis codes were recorded in both HES and the CPRD, the earliest event date was considered as the onset date.

Supplementary Table 1: Post-herpetic neuralgia

Source	READ code/ICD-10 code	Complication
CPRD	A531.11	Post-herpetic neuralgia
CPRD	A531200	Post-herpetic trigeminal neuralgia
CPRD	A531300	Post-herpetic polyneuropathy
CPRD	A531500	Post-zoster neuralgia
CPRD	A531511	Post-herpetic neuralgia
CPRD	F300.00	Post-herpetic trigeminal neuralgia
HES	B02.2	Zoster with other nervous system involvement

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ICD-10, International Classifications of Diseases-10th revision.

Complications (other than post-herpetic neuralgia [PHN]) were grouped into four main categories for the analyses:

- Neurological (other than PHN): i.e. HZ meningitis, HZ encephalitis, Ramsay - Hunt syndrome;
- Ocular HZ (i.e. HZ eyelid; HZ iridocyclitis, etc);
- Disseminated HZ;
- Other HZ complications (i.e. HZ otitis externa and unspecified complications).

Healthcare costing

- HZ subjects without PHN:
  - Period = the HZ case onset date -7 prior to the case onset date + 30 days (a);
- HZ subjects reporting a PHN event within 365 days from the HZ case onset date, two analyses periods were used:
  - Period 1 = the HZ case onset date -7 prior to the case onset date + 90 days (b);
  - Period 2 = the HZ case onset date -7 prior to the case onset date + 365 days (c);

The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days after HZ event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).

Additionally, main categories of resource utilization and cost tables were presented for the following sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days and 365 days post-initial HZ onset date:

- HZ only (i.e. no PHN and no HZ-related complication);
- HZ and PHN within 1 year of HZ event;
- HZ and other HZ-related complications but no PHN (overall and by complications sub-categories):
    - Neurological;
    - Ocular;
    - Cutaneous;
    - Other complications.

A detailed mapping linking the exact event definition variables and criteria to the reference unit cost was used. The unit costs for each type of resource were obtained from the following reference sources:

- General practitioner (GP) prescribed medication costs: British National Formulary (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the prescription costs for each drug (prodcode) of interest. A detailed mapping was used to link the exact cost of prodcode quantity and packtype for each drug;
- Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014);
- HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs (National Schedule of Reference Costs, 2013/2014).

Supplementary Table 2: List of medications

Treatment Groups	Description
Antiviral	Aciclovir
	Famciclovir
	Valacyclovir
NSAIDs	Aspirin
	Ibuprofen
COX-2	Paracetamol
Topical Agents	Lidocaine
	Capsaicin
Anticonvulsants	Gabapentin
	Pregabalin
Tricyclic antidepressants	Amitriptyline
	Nortriptyline
	Desipramine
Corticosteroids	Prednisolone
Opioid analgesics	Tramadol
	Morphine
	Oxycodone
	Methadone

Supplementary Table 3: Ambulatory and Outpatient Costs

	Consultation type	Details	Tariff Code	Cost
AMBULATORY AND OTHER AMBULATORY VISITS	GP surgery consultation	Per patient contact lasting 11.7 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£35
	GP clinic consultation	Per patient contact lasting 17.2 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£50
	GP telephone consultation	Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP home visit	Per out of surgery visit lasting 23.4 minutes (including 12 minutes travel) without qualification costs, excluding direct care staff costs[2] Inflated to 2014 prices using the HCHS annual price inflation[1]	N/A	£87
	GP home visit out of hours	Ratio of direct to indirect time; Out of surgery visits (home visits and clinics; includes travel time) - 1:0.99[2]	N/A	£86

	Consultation type	Details	Tariff Code	Cost
	GP practice nurse consultation	Per 15.5 minutes surgery consultation @ £44/hour (excluding qualification costs)[1]	N/A	£11
	GP results by phone	Assume same as GP Telephone Consultation Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP time spent on phone/writing letter	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£23
	GP time on administration	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£8
AMBULATORY AND OTHER AMBULATORY VISITS	District nurse visit	Mean average cost for a face-to-face contact in district nursing services (based on NHS reference costs) was £39 in 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£40

	Consultation type	Details	Tariff Code	Cost
	Health visitor visit	Mean average cost for a face-to-face contact in health visiting services (based on NHS reference costs) was £51 in for 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£52
OUTPATIENT HOSPITAL ATTENDANCE	Anaesthetics, outpatient attendance	Consultant Led; WF01B: First attendance Single professional[3]	190	£125
	Dermatology, outpatient attendance	Consultant Led; WF01B: First attendance Single professional[3]	330	£104
	General Medicine, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	300	£178
	Ophthalmology, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	130	£119

	Consultation type	Details	Tariff Code	Cost
	A&E Attendance	Category 3 investigation with category 1-3 treatment[3]	VB03Z	£163
	Pain Management, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	191	£138

	Consultation type	Details	Tariff Code	Cost
OUTPATIENT HOSPITAL ATTENDANCE	Neurosurgery, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	150	£182
	Palliative Medicine, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	315	£167
	Neurology, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	400	£174

GP, General Practitioner; N/A, not available; NHS, National Health Service; HCHS, community health services; A&E, accident an demergency;
Source:

1. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014.
2. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2013. University of Kent, 2013
3. 2014/5 National Tariff Payment System. Annex5A National Prices, 17 December 2013
https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015
4. National Schedule of Reference costs 2013-14
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls

Supplementary Table 4: Hospital Inpatient costs

Diagnosis Code	Detail	Average tariff per admission
B020	Zoster encephalitis	£5,038.39
B021	Zoster meningitis	£2,065.47
B022	Zoster other nervous system involvement	£1,440.48
B023	Zoster with ocular diseases	£2,226.36
B027	Disseminated Zoster	£2,255.30
B028	Zoster with other complications	£2,060.70
B029	Zoster without complications	£1,790.57

Source: Hospital Episode Statistics (HES) Admission data IMS, 2013/14

HZ treatment prescriptions

All HZ treatment prescriptions, defined according to British National Formulary (BNF) indication and clinical expert input, were identified by product codes from the HZ TREATMENT CPRD Prodcodes List, and were extracted from the CPRD Therapy dataset.

Analysis datasets used

HZ treatments prescriptions (CPRD Therapy dataset);
CPRD Ambulatory Visits (CPRD Consultation dataset);
Specialists Referrals by GP (CPRD Referral dataset);
Hospitalizations (HES Inpatient: HES_DIAGNOSIS_EPI dataset);
Outpatient Visits (HESOP Clinical dataset);
Nursing home visits and Time off sick (CPRD Clinical dataset).

Supplementary Table 5: Costs by category, IC status, time period of analysis and age Groups

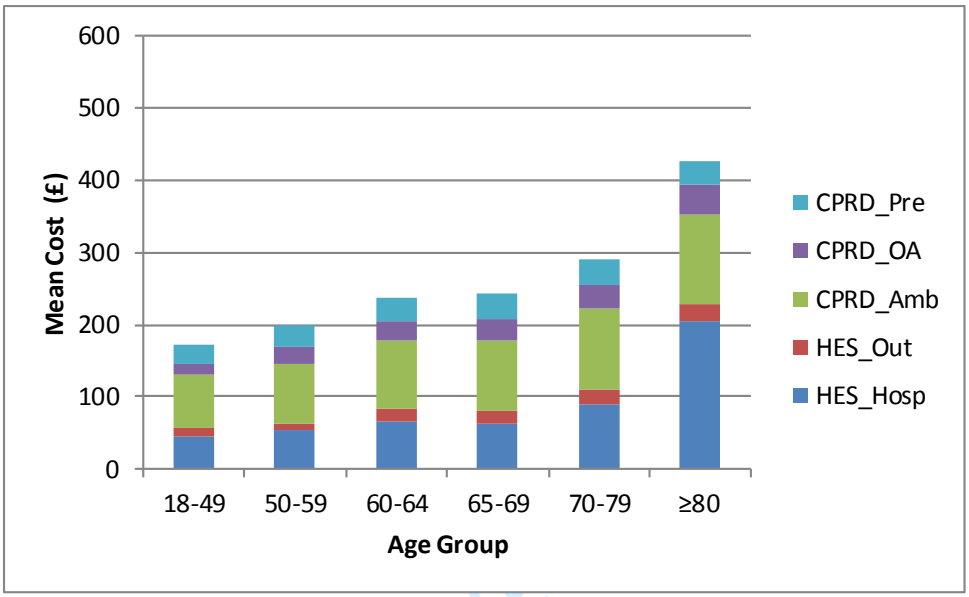
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
IC Population (≤90 days)						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD ambulatory visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD other ambulatory visits	16.1	22	27.7	31	34.6	41.8
CPRD prescriptions	27.6	31.1	31.9	33.3	33.9	31.9
Total	**173.2**	**199.0**	**236.2**	**241.6**	**289.6**	**427.0**
IC Population (≤365 days)						
Hospitalizations	44.2	56.7	68	62.4	93.8	216.5
HES outpatient consultations/visits	15.1	16.1	23.9	28.1	34.4	40.1
CPRD ambulatory visits	80.6	100.1	120.2	134.5	158.1	180.8
CPRD other ambulatory visits	20.7	31.6	44.9	54.4	63.2	78.8
CPRD prescriptions	28.7	33.3	37.3	38.1	42.2	40.8
Total	**189.3**	**237.8**	**294.2**	**317.4**	**391.7**	**557.0**
IC-Free Population (≤90 days)						
Hospitalizations	6.3	8.5	11.5	17.5	36.4	136.5
HES outpatient consultations/visits	5.2	7.8	8.2	10.4	13.9	18.2
CPRD ambulatory visits	59	66.7	69.6	72.7	88.8	102.8
CPRD other ambulatory visits	8	11.2	12.9	16.9	21.2	32.8
CPRD prescriptions	19.7	24.7	24.6	28	29.4	29.4
Total	**98.2**	**118.9**	**126.8**	**145.5**	**189.7**	**319.7**

IC-Free Population (≤365 days)						
Hospitalizations	6.3	8.9	12	17.9	37	144
HES outpatient consultations/visits	5.7	10.8	10	13.4	22.7	28.4
CPRD ambulatory visits	63	75.8	80.4	90	117.3	135.9
CPRD other ambulatory visits	8.8	14.2	18.6	23.2	36.8	58.7
CPRD prescriptions	20	25.6	26.8	29.9	34.9	34.1
Total	**103.8**	**135.3**	**147.7**	**174.4**	**248.6**	**401.0**

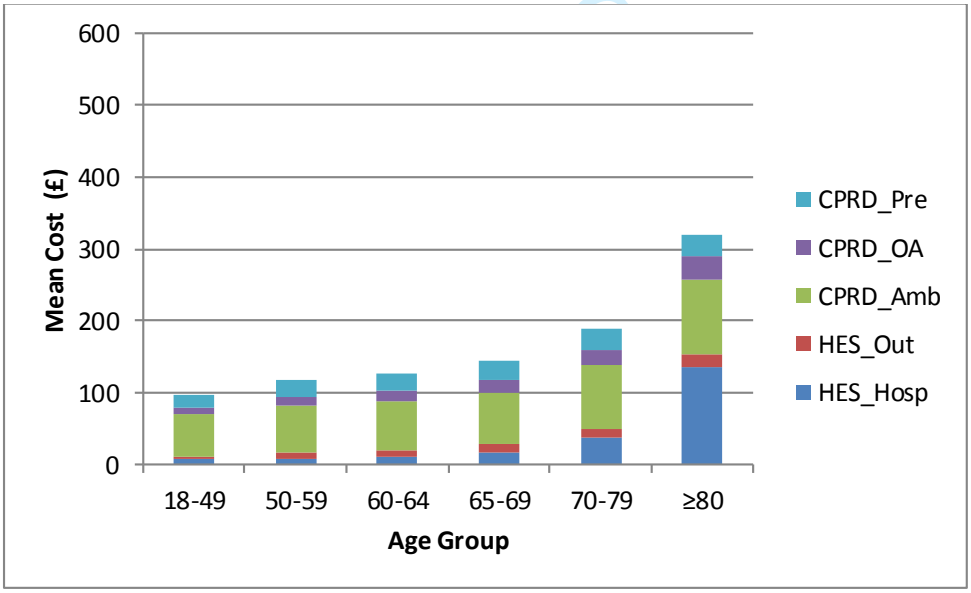
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

Supplementary Figure 1: Healthcare costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



Panel B

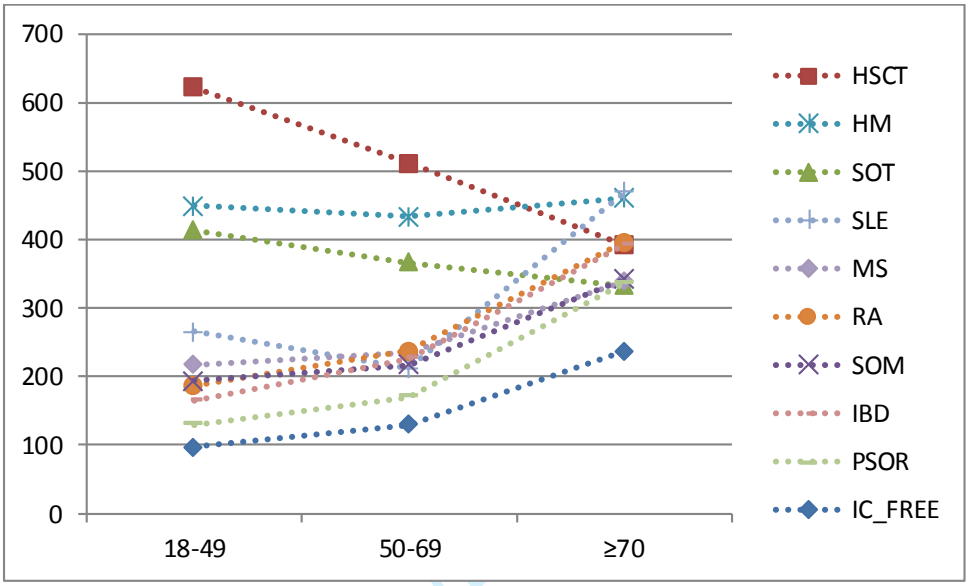


For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

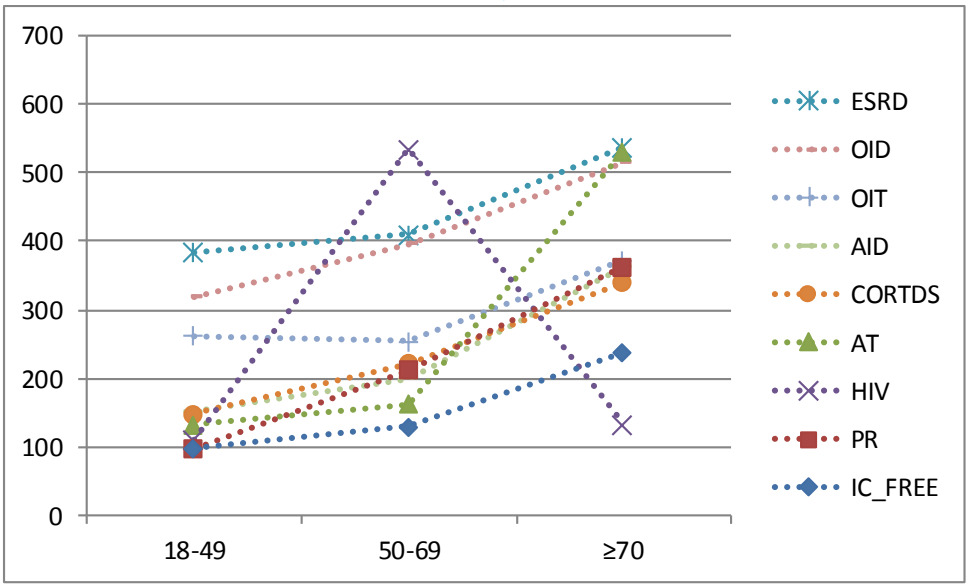
Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; CPRD, Clinical Practice Research Datalink; CPRD_Pre, CPRD Prescriptions; CPRD_OA, CPRD Other Ambulatory Visits; CPRD_Amb, CPRD Ambulatory Visits; HES_Out, HES Outpatient consultation; HES_Hosp, HES Hospital admission.

Supplementary Figure 2: Healthcare Costs for each IC condition by age group for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



Panel B



For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; HSCT, hematopoietic stem cell transplantation; HM, haematological malignancies; SOT, solid organ transplantations; SLE, systemic lupus erythematosus; MS, multiple sclerosis; RA, rheumatoid arthritis; SOM, solid organ malignancies; IBD, inflammatory bowel syndrome; PSOR, psoriasis; ESRD, end-stage renal disease; OID, other immunodeficiency; OIT, other immunosuppressive therapy; AID, autoimmune diseases; CORTDS, corticosteroid exposure; AT, autoimmune thyroiditis; HIV, human immunodeficiency virus; PR, polymyalgia rheumatica.

Supplementary Table 6: Non-HZ related Hospital Inpatient Stay for the period 7 days to 365 days post initial-HZ onset

Age groups (YOA)	IC cohort				IC-free cohort			
	N	Events	Subjects	Mean	N	Events	Subjects	Mean
18-49	3,039	1,881	259	0.62	2,078	193	56	0.09
50-59	3,408	3,267	337	0.96	2,834	251	61	0.09
60-64	2,550	2,897	293	1.14	2,308	309	63	0.13
65-69	2,753	3,867	371	1.40	2,658	434	108	0.16
70-79	5,429	9,020	838	1.66	5,454	2,556	379	0.47
≥80	3,863	9,928	840	2.57	3,171	4,119	457	1.30
Total	**21,042**	**30,860**	**2,938**	**1.47**	**18,503**	**7,862**	**1,124**	**0.42**

Abbreviations: IC, immunocompromised; HZ, herpes zoster; N, number of participant; YOA, years of age

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pages 1 and 2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8,9
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Pages 9,10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 9,10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

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Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment

TITLE PAGE

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

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ABSTRACT

Objective

Individuals with immunocompromised (IC) conditions are at a higher risk of developing herpes zoster (HZ) than IC-free individuals. This study assessed the healthcare resource utilization (HCRU) burden and costs, of HZ in IC and IC-free individuals ≥18 years of age (YOA).

Methods

We conducted an observational retrospective study in a cohort of IC (N=621,588) and IC-free (N=621,588) individuals, matched by age, gender and GP practice region, contributing to the Clinical Practice Research Datalink database from 2000 to 2012 and linked to the Hospital Episode Statistics inpatient data. HCRU (i.e. primary and secondary care consultations, hospital inpatient stays, and treatment prescriptions) was analyzed from 7 days before to: (1) 30, (2) 365 days after the HZ diagnosis date for individuals with (1) HZ only (no post-herpetic neuralgia [PHN]) and (2) individuals with HZ and PHN only. Healthcare costs were computed by multiplying the number of units of resources utilized by the unit costs, summed across all HCRU categories to obtain a total cost per subject. Values were expressed in 2014 UK pound sterling (£) and presented for HZ cases overall, stratified by age (i.e. 18-49, 50-59, 60-69, 70-79 and ≥80 YOA) and IC status.

Results

The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and IC-free individuals aged ≥80 YOA, respectively). Similarly, HZ-related mean treatment costs per subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49

YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged ≥80 YOA, respectively). Costs varied considerably by IC condition.

Conclusions

Individuals with IC conditions, have a high burden of HZ, associated with an increased risk of HZ and high HZ-related healthcare costs.

Keywords

Herpes zoster, post-herpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study is an observational retrospective descriptive study presenting the healthcare resource utilization and costs associated with herpes zoster (HZ) in both immunocompromised (IC) and IC-free populations aged ≥18 years of age in England.
- The IC population included 621,588 individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions and matched to the Hospital Episode Statistics (HES) database by age, gender and practice location to extract the IC-free population (N=621,588).
- The particularity of this study is that the design allowed calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s).
- This key study will provide data to be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in IC populations.
- A limitation of the study is that the diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts.

LIST OF ABBREVIATIONS

£, 2014 UK pound sterling

A&E, Accident and Emergency

AID, autoimmune diseases

ARDI, age-related decline in immunity

AT, Autoimmune Thyroiditis

BNF, British National Formulary

CPRD, Clinical Practice Research Datalink

GP, General Practitioner

HCRU, healthcare resource utilization

HES, Hospital Episode Statistics

HIV, human immunodeficiency virus

HM, hematological malignancies

HSCT, hematopoietic stem cell transplantation

HZ, herpes zoster

HZ-Comp, HZ and complications with no PHN

IC, immunocompromized

ICD-10, International Classification of Diseases-10th revision

ISAC, Independent Scientific Advisory Committee

PHN, post-herpetic neuralgia

PSSRU, Personal Social Services Research Unit

PY, person-years

RA, rheumatoid arthritis

SLE, systemic lupus erythematosus

SOT, solid organ transplantations

UK, United Kingdom

US, United States

VZV-CMI, varicella zoster virus cell-mediated immunity

YOA, years of age

ZVL, zoster vaccine live

INTRODUCTION

Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes zoster (HZ)[1]. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not optimal in individuals with immunocompromized (IC) conditions and the age-specific incidence and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune disease, malignancy, or organ transplantation[2].

The incidence and severity of HZ is marked with an increase in people ≥50 years of age (YOA) due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among individuals aged ≥85 YOA[3]. Further to the impact of ARDI, a study by Forbes et al. in 2014 investigated the increased risk for HZ in the UK population, associated with autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and asthma[2]. In addition to the increased risk of HZ in the various IC conditions these populations also experience increased severity of disease. In a study in Canada, Drolet et al. reported that individuals with an impaired immune status had HZ severity of illness scores, as measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with normal immune function[4 5]. In a study in the United States (US), Yawn et al. reported that although 8% of HZ cases were in individuals who were immunocompromised, these individuals represented 23.8% of the total HZ-related costs[6]. The increase in healthcare costs was associated with higher rates of post-herpetic neuralgia (PHN) and non-pain complications in this group of individuals[6].

This study aims to estimate the healthcare resource utilization of HZ in selected IC populations and in an IC-free (i.e., immunocompetent) population aged ≥18 YOA in England. The clinical burden of disease epidemiological results of the study are reported elsewhere[7], and may be summarized as follows: the prevalence of IC conditions increased from 7.6% in individuals aged 18-44 YOA to 42.2% in individuals aged ≥80 YOA; the incidence rate of HZ in the IC cohort was 3.5/1000 PY in individuals aged 18-49 YOA increasing to 12.6/1000 PY in individuals aged ≥80 YOA. In this manuscript, we focus on the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations.

METHODS

The study was conducted as an observational retrospective descriptive study (e-track number: 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥18 YOA). The IC population included individuals who were registered in the Clinical Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥12-month follow-up before being diagnosed with any of the selected 16 IC conditions (See Supplemental Material). The CPRD IC population cohort was linked to the Hospital Episode Statistics (HES) database and matched, using a 1:1 ratio, to a cohort of CPRD-HES linked IC-free population (N=621,588), by age, gender and practice location[8]. Individuals with a missing date of IC diagnosis were excluded from the study population. Clinical diagnoses were based on READ codes used in CPRD and with the International Classifications of Diseases-10th revision (ICD-10) codes in the HES database.

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency database research (ISAC protocol number 14_222R). The study was conducted in accordance with all applicable regulatory

requirements, with the Guidelines for Good Pharmacoepidemiology Practices[9], all applicable patient privacy requirements and the guiding principles of the Declaration of Helsinki.

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[7]. Healthcare resource data associated with an incident HZ episode during the study follow-up were extracted for IC and matched IC-free CPRD-HES-linked individuals. Only reported records (resource utilization) with available event dates during the individuals' eligibility period and those that occurred 7 days before the initial HZ onset date, up to 365 days after the initial HZ onset date, were extracted. Consequently, individuals who recorded the first PHN event date after 365 days post HZ event date were classified as not having PHN.

Patient and Public Involvement

This is a retrospective database analysis carried out following ethical committee approval. No patient or the public was involved in the study design or in the recruitment or the conduct of this study. No specific dissemination of study results to participants was done. However, we provided a lay language summary contextualizing the results and potential clinical research relevance and impact in Figure 1.

Data sources

Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation, Clinical, Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI dataset; (3) HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource utilization was defined as: HZ-treatment related prescribed medications; Consultations and care provided by

General Practitioners (GPs) or others in the GP practice); HES secondary care outpatient visits (HES outpatient events); and HES inpatient hospitalizations (HES inpatient events).

For each patient, healthcare costs stratified by subcategory of interest (HES Inpatient Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by their unit costs. These were then summed over all resource use categories to obtain a total cost for each patient. Values were expressed in 2014 UK pound sterling (£).

Healthcare resource costs

For each patient, the cost of each prescription was calculated by merging the product code, package type and prescribed quantity with the associated standard package size and unit cost. The unit cost of a product in a prescription instance (i.e. one distinct record in the CPRD therapy) was calculated using the cost described in the British National Formulary (BNF), 2015 (as listed price if included or indicative price based on price in BNF).

Ambulatory visits included consultations with GPs and nurses in primary or community care. Visits included consultations at the practice or at the home of the patient, during working hours and out of hours. Consultations for which no clinical intervention was recorded were not included in the cost estimate for GP practice related healthcare utilization, for example: information technology data migration, administrative recording of received information. Administrative resource use in primary care was considered, including time on the phone, writing reports, referrals, etc. A referral to secondary care noted in a patient's record, *per se*, was not allocated the cost of the secondary care appointment. The most conservative option for the cost per unit as included in the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care, 2014 were applied e.g.

GP consultation costs excluded qualification, direct staff care and travel costs[10]. Where specific costs for 2013/14 were not available, 2012/13 costs, were adjusted by applying the Hospital and Community Health Services inflation index[10]. Administration costs were based on unit costs as stated in the PSSRU, 2014.

Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient resource utilization concerned HZ related referrals for non-inpatient hospital consultations, derived from the HES Outpatient data. Additionally, visits to the Accident and Emergency (A&E) department in hospitals were also recorded and costed. Inpatient hospitalization costs were based on the average cost per episode using HES data for 2013/14 (calculated from the total average payment by result spell cost and the average number of episodes per spell). Hospital outpatient costs were sourced from National Tariff costs (2014) for specific consultant led outpatient consultations; conservative costs were allocated i.e. wherever applicable costs for first attendance by a single professional appointment were used[11]. Costs allocated to A&E visits were based on the cost of a category 3 investigation with category 1-3 treatment[11]. Only events related to HZ were costed out. Resources related to HZ complications were considered using ICD-10 Code B020.

No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in CPRD. Further details, including information on the IC populations included, ICD-10 codes for HZ and PHN, and unit healthcare costs are provided in the Supplementary Material, specifically in Supplementary Tables 1 to 4.

RESULTS

The CPRD-HES-linked matched IC and IC-free population cohorts (n=621,588 each) included approximately 44% males and 56% females with a mean age of approximately 56 years. The age

distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥80 YOA (11.01%).

The proportion of inpatient hospital admissions by age group for the CPRD-HES-linked matched IC and IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel A) or 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 2. Hospital admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset (Panel B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus* 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and IC-free individuals aged ≥80 YOA, respectively). Multiple HZ-related hospital visits were reported for some individuals. As such, Table 1 presents the mean number of healthcare resources utilized by IC Status, Age Group and Analysis period. The mean number of hospitalizations per HZ case for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free individuals aged 18-49 YOA, respectively and 0.173 and 0.115 in IC and IC-free individuals aged ≥80 YOA, respectively. A similar pattern of higher healthcare resource utilization with increasing age and in IC individuals was observed for all resources for which costs were assigned. A similar mean number of sick leave certificates were observed between the IC and the IC-free cohorts with the mean decreasing with age. Nursing home care / admissions were only recorded for individuals aged ≥70 YOA in CPRD.

Figure 3 and Table 2 present the overall healthcare costs by CPRD-HES-linked matched IC cohort and age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs increase with age and are consistently higher in the IC cohort compared with the IC-free cohort. Although the absolute cost difference between IC and IC-free individuals increases with age from £85.5 in individuals aged 18-49 YOA to £156.1 in individuals aged ≥80 YOA the relative

difference is higher in younger individuals (i.e. 75.8%-99.2% in <70 YOA) compared with older individuals (i.e. 38.9%-57.6% in ≥70 YOA). It is also noteworthy that the means are consistently higher than medians, and as is common for healthcare cost data, the distribution is skewed to the right. Supplementary Table 5 and Supplementary Figures 1 and 2 provide additional data on healthcare Costs for the analysis period 7 days prior to 90 days post initial HZ onset.

Figure 4 presents the overall healthcare costs by each IC condition in the CPRD-HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset. For all IC conditions, the costs were higher than those for the IC-free group, in particular for the hematopoietic stem cell transplantation (HSCT), hematological malignancies (HM) and solid organ transplantations (SOT) conditions. In general, there was a similar trend of increasing costs with increasing age-groups. A few outliers were observed due to small sample sizes. For example, only 3 and 8 individuals aged ≥70 YOA were included in the HIV and HSCT groups, respectively. Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis (AT) and SOT were included, respectively.

Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean healthcare costs were approximately 2 to 4 times higher for individuals with HZ complications compared to individuals with HZ only.

Supplementary Table 6 presents the non-HZ related hospital inpatient stay for the period 7 days to 365 days post initial-HZ onset. The mean number of non-HZ related hospitalizations were consistently higher in IC patients compared to and IC-free patients and increased with age.

DISCUSSION

In this study, we presented the healthcare resource utilization and costs associated with HZ in both IC and IC-free populations using large electronic health record databases in the UK. An important feature of this study was that the design enabled the calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level in the same pre-defined population(s), see Yanni et. al. for further detail on epidemiological outcomes[7]. In this study, every effort was made to include only resources directly related to HZ. For example, only hospitalized patients were included who had an ICD-10 HZ diagnosis identified in the HES database. Similarly, only medications potentially related to HZ treatment were included (see Supplementary Material Tables 2 and 4). HZ-related mean treatment costs per patient were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA, respectively increasing to £557 *versus* £401 in IC and IC-free individuals aged ≥80 YOA, respectively).

Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the mean healthcare costs per HZ patient, from an National Health Services perspective, of £85.6 and £400.9 in individuals aged <65 YOA and ≥65 YOA, respectively[12]. A later UK study that used the HES and the health improvement network databases, estimated the mean cost of treating a HZ patient to be £65.5 in the first month of diagnosis, with patients aged ≥70 YOA having a mean cost of £83 in the first month and £15.80 in months 2 and 3[13]. The costs of treating individuals with PHN were much higher, i.e. mean cost per patient was estimated to be £921 in all individuals and £909.60 in individuals aged ≥70 YOA[13]. Another study evaluated mean healthcare costs (excluding hospitalization costs) to be £75.63 per HZ patient with mean direct costs for treating PHN episodes

(PHN pain occurring or persisting for 3 months) of £340.04[14]. These values augmented with hospitalization costs were used as inputs in a cost-effectiveness model evaluating a HZ vaccine using the population of England and Wales[3]. The costs estimated by van Hoek et al. are consistent with the values estimated in our study for IC-free individuals by age group[3].

In a previous study, mean prescription costs per HZ patient were reported to be £40.52[14]. In our study, the mean prescription costs per HZ patient ranged from £19.7 to £40.8 depending on the age group, IC status and analysis period included. Our study aimed to include only medications considered to be directly related to HZ; i.e. excluded medications that may be linked to IC conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from other conditions). This restriction and the introduction of generic versions of medications such as acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed to the reduced overall medication costs reported in this study.

Many studies on HCRU and costs include a number of days prior to diagnosis, e.g. 14 or 21 days, as there may be a delay in diagnosis and HCRU may be utilized prior to diagnosis[6,15]. In this analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days post HZ onset, although it is recognized that HZ episodes can last for longer. The costs of PHN were analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days prior to 365 days post HZ onset. The rationale for the time periods studied was that using analysis period 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2 only could overestimate these costs. The most frequently used definition of PHN is: pain persisting or appearing at least 90 days following rash onset. The median duration of PHN has been reported to be 10.3 and 12.9 months in individuals aged ≤69 and ≥70 YOA respectively[16], and is likely to be longer in individuals who are immunocompromised[5].

The healthcare costs associated with PHN and complications were higher than those for individuals with HZ only. However, as reported elsewhere, when considering the overall cost of disease at a population level, the overall healthcare-associated cost is higher for HZ only[17]. This is primarily a result of the higher incidence rates of HZ only.

Few studies have investigated healthcare resource utilization and costs in IC individuals. Schroder et al. carried out a study using the German Pharmacoepidemiological Research Database, which consists of claims data from four statutory health insurances[18]. They reported that during the quarter of the HZ diagnosis or during the two following quarters, 10% of all HZ patients with an IC condition were hospitalized (with a HZ diagnosis), whereas among IC-free HZ patients, 4.2% were hospitalized. White et al. reported that in their study using the US Market Scan Research Database, direct medical costs were nearly twice as high in IC patients compared with IC-free patients[19]. Li et al. carried out a study using the US Truven Health MarketScan Commercial and Medicare Supplemental Insurance databases[15]. They concluded that patients with the studied IC conditions (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer) had significantly higher healthcare utilization and cost when developing HZ than their comparable matches without HZ. Insurance databases include not only the healthcare resource utilization but also costs. In the CPRD and HES Databases only the resource utilization is captured. As such the overall costs need to be calculated by assigning unit costs to the resource utilization. There are advantages however of using the CPRD and HES in that the databases offer more diversity than might be observed using insurance databases, the latter of which may be somewhat limited by bias associated with factors such as age, race, and income. A strength of the CPRD database is that it is considered to be broadly representative of the characteristics of patients and GP practices in the UK[20,21].

This study has several limitations. Diagnoses were derived from administrative codes, which are recognized to be subject to miscoding or under-coding and are not validated against medical charts[22]. Increasing healthcare resource utilization and cost is likely to be related to increased severity of IC conditions. In a study, Schroder et al. categorized individuals as low IC and high IC[18]. However, insufficient details are recorded in the CPRD and HES databases to allow adequate definition of patients' severity of immunosuppression e.g. laboratory parameters, immunosuppressive medication details such as chemotherapy. In addition, many IC individuals had prescriptions that included more than one immunosuppressing medicine. In this study we selected 16 IC conditions in our definition of an IC population but perhaps other researchers would select different IC conditions. As such our study is exploratory in nature and was not intended to be definitive.

CONCLUSION

Immunosuppression is known to be associated with an increased risk of HZ in the UK[2,7]. In this descriptive analysis, involving a large representative national data source, the results suggest that individuals with IC conditions were associated with higher HZ related healthcare utilization and costs than IC-free individuals[6,7,15]. The results from this study could be used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in these populations.

AUTHOR CONTRIBUTIONS

VB, AEG, YEH, GF, MH and DC participated in the conception and design of the study. VB, AEG, YEH, GF and MH participated in the collection or generation of the study data. VB, AEG and YEH performed the study. AEG, YEH, MH and DC contributed to the material. VB, AEG, YEH, GF, MH and DC were involved in the analysis or interpretation of the data. All named authors provided substantial intellectual and scientific input during the manuscript development, critically reviewing the content, revising the manuscript and giving final approval before submission. The work described was carried out in accordance with the ICMJE recommendations for conducting, reporting, editing and publishing scholarly work in medical journals. All authors had full access to the data and gave final approval before submission.

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CONFLICTS OF INTEREST

VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the GSK group of companies between 2012 and Feb 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.

DATA SHARING STATEMENT

All data used in this study are presented in the manuscript, references to the original material are provided. Please contact the corresponding author shall you require any additional information

ETHICAL APPROVAL

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

FUNDING

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TABLES

Table 1: Mean number of healthcare resources by IC status, age group and analysis period

	IC cohort		IC-Free cohort	
	90 Day	365 Day	90 Day	365 Day
HES Hospital admission				
18-49	0.035	0.035	0.005	0.005
50-59	0.042	0.046	0.006	0.007
60-64	0.053	0.055	0.009	0.010
65-69	0.049	0.050	0.014	0.014
70-79	0.072	0.076	0.029	0.030
≥80	0.163	0.173	0.108	0.115
HES Outpatient consultation				
18-49	0.095	0.116	0.041	0.045
50-59	0.086	0.122	0.062	0.086
60-64	0.136	0.180	0.065	0.078
65-69	0.146	0.217	0.085	0.108
70-79	0.165	0.267	0.113	0.181
≥80	0.173	0.313	0.149	0.231
CPRD Ambulatory visits				
18-49	2.816	3.168	2.186	2.360
50-59	3.334	4.175	2.466	2.907
60-64	3.733	5.081	2.598	3.115
65-69	4.089	6.009	2.774	3.610
70-79	4.534	6.959	3.413	4.767
≥80	4.881	7.422	3.811	5.367
CPRD Other ambulatory visits				
18-49	0.319	0.411	0.155	0.170
50-59	0.433	0.623	0.218	0.277

60-64	0.545	0.885	0.251	0.360
65-69	0.607	1.064	0.330	0.454
70-79	0.686	1.251	0.417	0.722
≥80	0.860	1.616	0.668	1.183
CPRD Prescriptions (All treatments)				
18-49	1.247	1.363	0.890	0.931
50-59	1.670	1.994	1.143	1.227
60-64	1.969	2.602	1.379	1.489
65-69	2.129	2.894	1.473	1.717
70-79	2.310	3.295	1.814	2.347
≥80	2.405	3.743	1.844	2.575
CPRD Referrals*				
18-49	0.018	0.020	0.011	0.012
50-59	0.021	0.026	0.018	0.022
60-64	0.031	0.040	0.020	0.024
65-69	0.031	0.044	0.015	0.023
70-79	0.033	0.054	0.031	0.047
≥80	0.040	0.065	0.029	0.048
CPRD Sick leave*				
18-49	0.162	0.175	0.155	0.161
50-59	0.156	0.178	0.173	0.182
60-64	0.060	0.069	0.080	0.087
65-69	0.017	0.017	0.008	0.008
70-79	0.001	0.001	0.002	0.003
≥80	0.000	0.000	0.000	0.000
CPRD Nursing home care/admission*				
18-69	0.000	0.000	0.000	0.000
70-79	0.001	0.001	0.001	0.001

≥80	0.004	0.004	0.003	0.003

* No costs were assigned for CPRD Referrals, CPRD Sick leave, CPRD Nursing home care / admission

Abbreviations: IC, immunocompromized; HES, Hospital Episode Statistics; CPRD, Clinical Practice Research Datalink; Costs were assigned for HES Hospital admission, HES Outpatient consultation, CPRD Ambulatory Visits, CPRD Other Ambulatory Visits, CPRD Prescriptions.

Table 2: Mean cost (£) of healthcare resource utilization by IC status, age group and analysis period*

Age groups (YOA)	Statistic	Mean cost (£)			
		IC cohort		IC-free cohort	
		90 Day	365 Day	90 Day	365 Day
18-49	Mean	173.3	189.3	98.2	103.8
	Median, SE	86.1, 6.03	86.9, 6.81	59.6, 3.06	62.0, 3.35
50-59	Mean	199.0	237.8	118.9	135.3
	Median, SE	106.6, 6.37	108.8, 9.05	74.6, 3.72	74.8, 4.68
60-64	Mean	236.2	294.2	126.8	147.7
	Median, SE	120.2, 9.39	124.1, 12.01	78.9, 4.48	80.9, 5.81
65-69	Mean	241.6	317.4	145.5	174.4
	Median, SE	132.2, 8.52	140.0, 11.25	87.9, 4.64	90.7, 5.97
70-79	Mean	289.6	391.7	189.8	248.6
	Median, SE	154.2, 7.21	163.9, 10.11	108.8, 4.97	113.6, 6.88
≥80	Mean	427.0	557.1	319.7	401.0
	Median, SE	176.2, 13.12	188.6, 17.05	143.0, 11.20	154.0, 13.63

* post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; HZ: herpes zoster; IC, immunocompromized; YOA: years of age, SE: Standard Error

Table 3: Mean cost (£) of healthcare resource utilization by IC status, age group, analysis period and HZ complication status

Age groups (YOA)		Mean cost (£), IC			
		HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	Mean	156.6	302.4	746.6	573.3
	Median, SE	81.8, 5.60	194.7, 33.83	465.7, 77.58	176.5, 87.70
50-59	Mean	168.1	468.0	998.9	562.6
	Median, SE	93.9, 5.05	262.8, 49.39	588.8, 89.42	226.0, 89.23
60-64	Mean	190.8	538.7	1135.5	780.5
	Median, SE	108.8, 7.59	297.7, 51.60	688.2, 76.50	226.4, 175.40
65-69	Mean	195.6	489.3	1064.3	551.8
	Median, SE	109.6, 8.04	305.4, 31.80	738.9, 50.39	204.9, 104.01
70-79	Mean	228.9	540.4	1200.2	847.5
	Median, SE	129.0, 6.18	324.5, 27.02	808.4, 44.67	337.4, 111.20
≥80	Mean	307.6	779.5	1536.0	1396.4
	Median, SE	148.6, 11.11	384.3, 40.82	937.3, 64.54	516.5, 151.71
		Mean cost (£), IC-free			
		HZ only*	PHN Day 90#	PHN Day 365!	HZ-Comp§
18-49	Mean	91.6	216.1	391.9	246.4
	Median, SE	54.9, 2.67	137.7, 39.25	261.9, 48.41	106.6, 58.73
50-59	Mean	106.8	262.8	540.8	275.1
	Median, SE	72.0, 2.76	208.2, 25.72	391.3, 45.62	118.1, 124.73
60-64	Mean	114.1	270.5	556.1	192.7
	Median, SE	74.6, 4.34	191.9, 23.69	409.4, 46.78	78.1, 56.06
65-69	Mean	123.7	287.7	595.5	592.6
	Median, SE	80.9, 3.45	202.4, 22.35	440.2, 37.43	229.5, 179.85

70-79	Mean	149.2	388.2	813.7	511.5
	Median, SE	88.7, 3.93	248.6, 21.27	546.1, 34.81	232.9, 89.19
≥80	Mean	242.0	607.4	1182.8	1046.5
	Median, SE	121.3, 9.08	310.5, 41.96	726.9,1 58.46	341.0, 149.46

* Individuals with HZ only (i.e. without PHN and complications): includes only costs 7 days prior to 30 days post initial HZ onset

Individuals with HZ and PHN: includes only costs 7 days prior to 90 days post initial HZ onset

! Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset

§ Individuals with HZ and complications but no PHN: includes only costs 7 days prior to 30 days post initial HZ onset

Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ,herpes zoster; PHN, post-herpetic neuralgia; HZ-Comp: HZ and complications with no PHN; SE: Standard Errors; YOA: years of age

FIGURE

Figure 1: Lay Language Summary

Figure 2: Inpatient Hospital Admission by HES-linked matched IC or IC-free cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to 365 days post initial HZ onset (Panel B)

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
For HZ individuals with PHN: data from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A) and 365 days (Panel B).
Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, post-herpetic neuralgia

Figure 3 : Healthcare Costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits; HES, Hospital Episode Statistics; HES-Out, HES Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia.

Figure 4 : Healthcare Costs for each IC condition in the HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset

For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.

For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.

Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM, hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, post-herpetic neuralgia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID, other immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica.

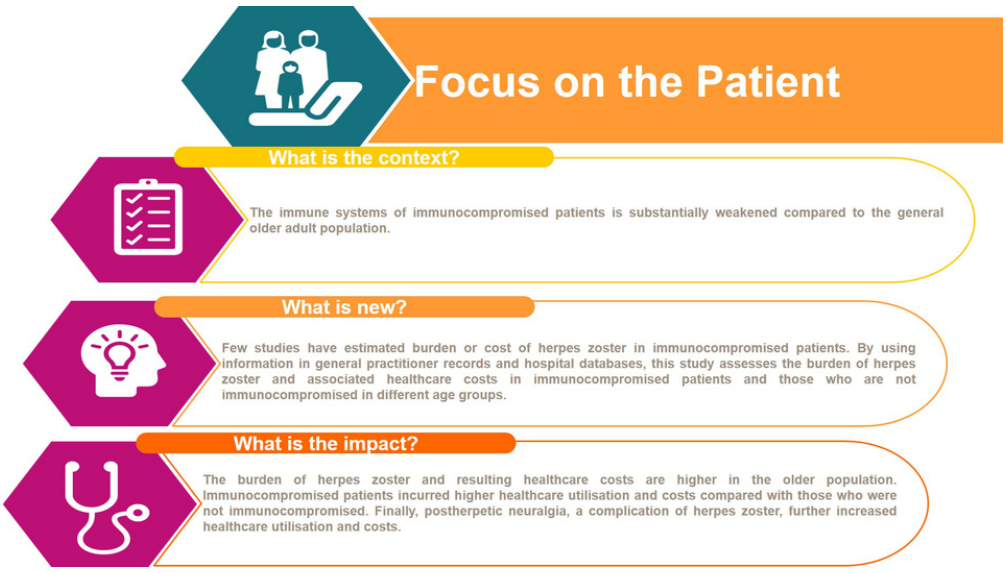

Figure 1: Lay Language Summary

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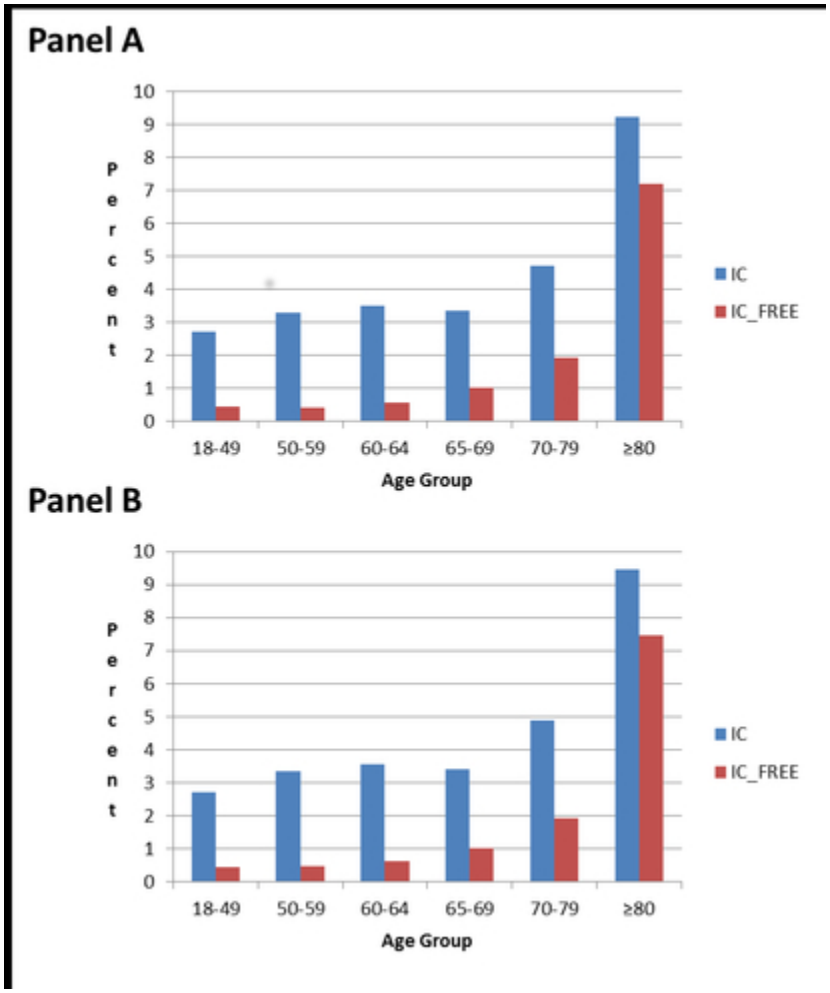

Figure 2: Inpatient Hospital Admission by HES-linked matched IC or IC-free cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to 365 days post initial HZ onset (Panel B)

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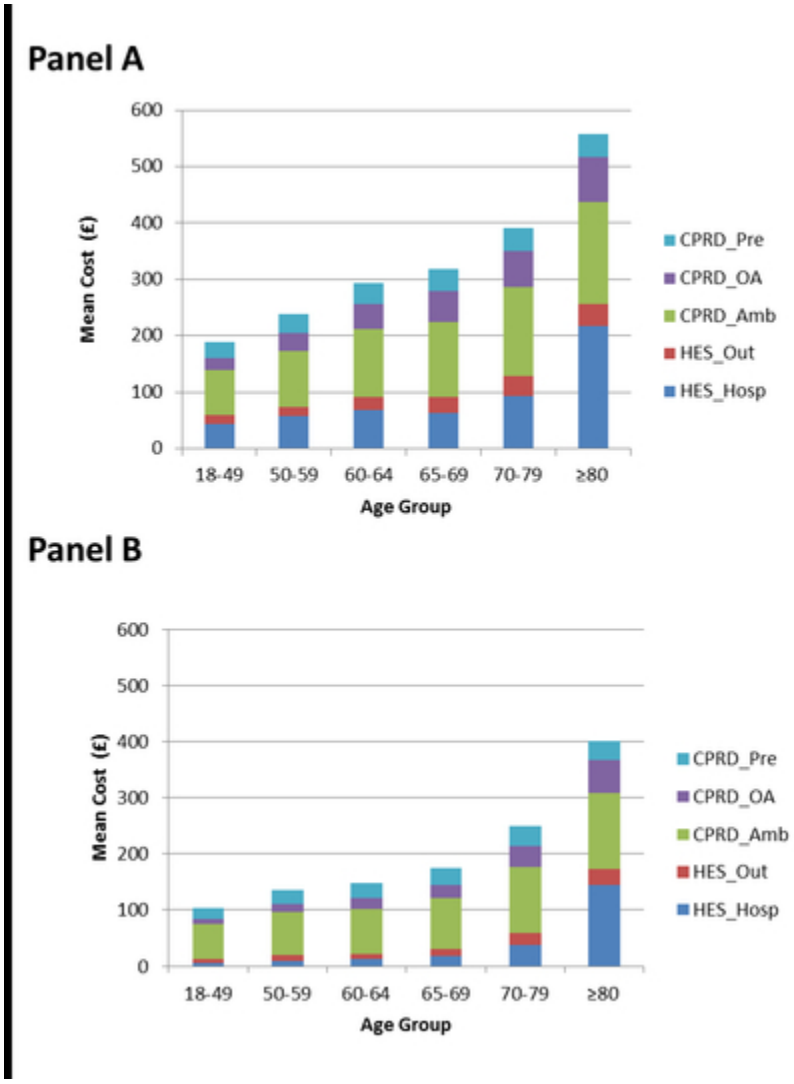

Figure 3 : Healthcare Costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset

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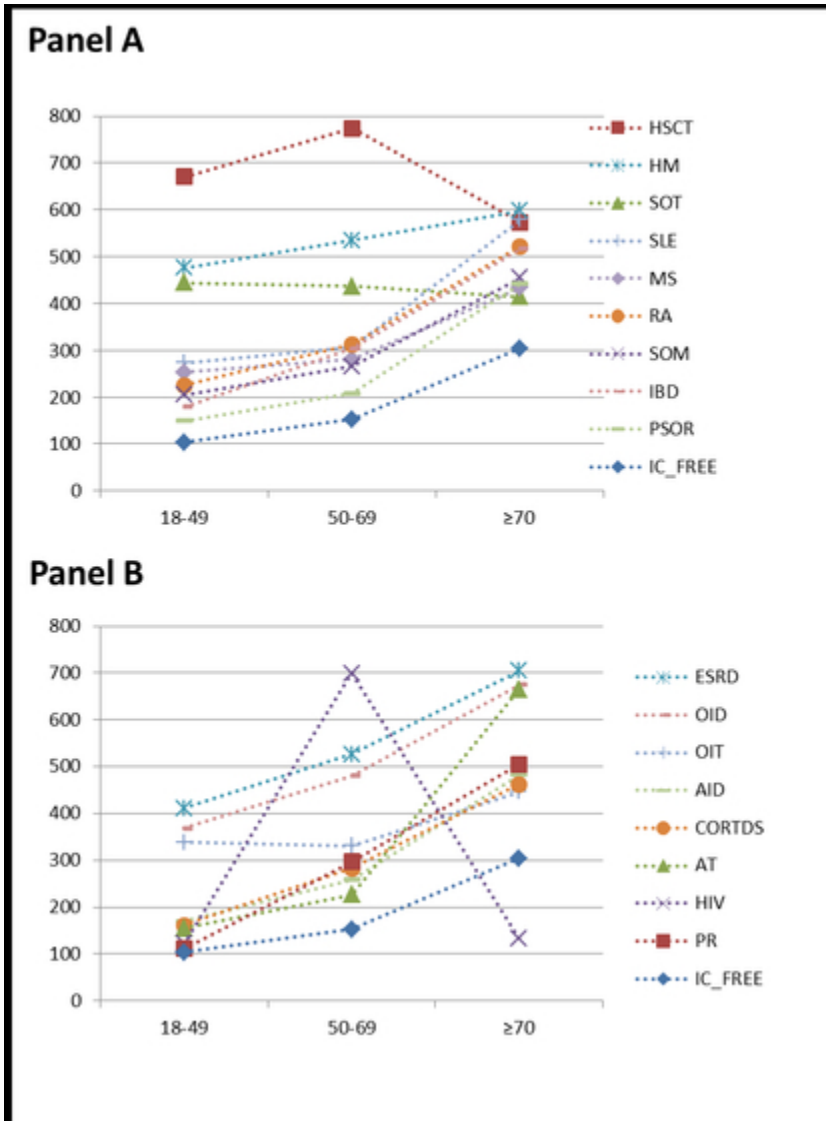


Figure 4 : Healthcare Costs for each IC condition in the HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset

34x47mm (300 x 300 DPI)

Supplementary Material

HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS

Desmond Curran, Manjit Hunjan, Amale El Ghachi, Yassine El Hahi, Veronique Bianco, Germano Ferreira

BMJ Open

Immunocompromised population

The immunocompromised (IC) population, referred to as the IC cohort hereafter, included eligible subjects reporting at least one of the following conditions or therapies at any time before 31st March 2012:

- Hematopoietic stem cell transplant (HSCT);
- Solid organ transplantation (SOT);
- Solid organ malignancies (SOM);
- Hematological malignancies (HM): Leukemia, Lymphoma, Myeloma;
- Autoimmune diseases (AID):
    - Rheumatoid Arthritis (RA);
    - Systemic *Lupus erythematosus* (SLE);
    - Inflammatory Bowel Disease (IBD);
    - Psoriasis (PSOR);
    - Multiple sclerosis (MS);
    - Polymyalgia rheumatica (PR) and;
    - Autoimmune thyroiditis (AT).
- Human immunodeficiency virus (HIV);
- End-stage renal disease (ESRD);
- Corticosteroid exposure (CORTDS);
- Other immunosuppressive therapy (OIT) exposure;
- Other immunodeficiency (OID) conditions.

For autoimmune diseases, each disease was considered as a separate IC condition. Any subject with a code for any IC condition listed above at any time in their record was excluded from the IC-free cohort. Only subjects that were part of IC conditions based on treatment administration ("Corticosteroid exposure" and/or the "Other immunosuppressive therapy exposure" IC conditions) had an end of follow-up based on prescriptions and could present a gap of exposure in the IC cohort between the end of exposure in that IC condition and the beginning of the next one, if any, during which they could not be considered as IC.

IC Matching

The IC-free matched population included a random sample of the IC-free population described above matched to the subjects of the IC population with a ratio of 1:1 (IC: IC-free subjects) when possible. The matching factors were:

- Hospital Episode Statistics (HES) linkage eligibility;
- The year of birth of the subject;
- The gender of the subject, and;
- The practice geographical region.

In addition, the IC-free subjects were included in the study at their corresponding matched IC subject's index date and should not have reported any history of HZ before the matched IC index date.

Herpes Zoster (HZ) Diagnosis

HZ cases identified in the Clinical Practice Research Datalink (CPRD) database were defined as subjects reporting at least one HZ-related READ code. Incident cases were subjects with at least 12 months of active registration in CPRD and no past record of HZ diagnosis during at least 12 months prior to inclusion or even before in their available medical records. HZ cases were identified in HES using the International Classification of Diseases-10th revision (ICD-10) codes that appeared in the diagnosis fields. If HZ diagnosis codes were recorded in both HES and the CPRD, the earliest event date was considered as the onset date.

Supplementary Table 1: Post-herpetic neuralgia

Source	READ code/ICD-10 code	Complication
CPRD	A531.11	Post-herpetic neuralgia
CPRD	A531200	Post-herpetic trigeminal neuralgia
CPRD	A531300	Post-herpetic polyneuropathy
CPRD	A531500	Post-zoster neuralgia
CPRD	A531511	Post-herpetic neuralgia
CPRD	F300.00	Post-herpetic trigeminal neuralgia
HES	B02.2	Zoster with other nervous system involvement

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ICD-10, International Classifications of Diseases-10th revision.

Complications (other than post-herpetic neuralgia [PHN]) were grouped into four main categories for the analyses:

- Neurological (other than PHN): i.e. HZ meningitis, HZ encephalitis, Ramsay - Hunt syndrome;
- Ocular HZ (i.e. HZ eyelid; HZ iridocyclitis, etc);
- Disseminated HZ;
- Other HZ complications (i.e. HZ otitis externa and unspecified complications).

Healthcare costing

- HZ subjects without PHN:
  - Period = the HZ case onset date -7 prior to the case onset date + 30 days (a);
- HZ subjects reporting a PHN event within 365 days from the HZ case onset date, two analyses periods were used:
  - Period 1 = the HZ case onset date -7 prior to the case onset date + 90 days (b);
  - Period 2 = the HZ case onset date -7 prior to the case onset date + 365 days (c);

The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days after HZ event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).

Additionally, main categories of resource utilization and cost tables were presented for the following sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days and 365 days post-initial HZ onset date:

- HZ only (i.e. no PHN and no HZ-related complication);
- HZ and PHN within 1 year of HZ event;
- HZ and other HZ-related complications but no PHN (overall and by complications sub-categories):
    - Neurological;
    - Ocular;
    - Cutaneous;
    - Other complications.

A detailed mapping linking the exact event definition variables and criteria to the reference unit cost was used. The unit costs for each type of resource were obtained from the following reference sources:

- General practitioner (GP) prescribed medication costs: British National Formulary (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the prescription costs for each drug (prodcode) of interest. A detailed mapping was used to link the exact cost of prodcode quantity and packtype for each drug;
- Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014);
- HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs (National Schedule of Reference Costs, 2013/2014).

Supplementary Table 2: List of medications

Treatment Groups	Description
Antiviral	Aciclovir
	Famciclovir
	Valacyclovir
NSAIDs	Aspirin
	Ibuprofen
COX-2	Paracetamol
Topical Agents	Lidocaine
	Capsaicin
Anticonvulsants	Gabapentin
	Pregabalin
Tricyclic antidepressants	Amitriptyline
	Nortriptyline
	Desipramine
Corticosteroids	Prednisolone
Opioid analgesics	Tramadol
	Morphine
	Oxycodone
	Methadone

Supplementary Table 3: Ambulatory and Outpatient Costs

	Consultation type	Details	Tariff Code	Cost
AMBULATORY AND OTHER AMBULATORY VISITS	GP surgery consultation	Per patient contact lasting 11.7 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£35
	GP clinic consultation	Per patient contact lasting 17.2 minutes, without qualification costs, excluding direct care staff costs[1]	N/A	£50
	GP telephone consultation	Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP home visit	Per out of surgery visit lasting 23.4 minutes (including 12 minutes travel) without qualification costs, excluding direct care staff costs[2] Inflated to 2014 prices using the HCHS annual price inflation[1]	N/A	£87
	GP home visit out of hours	Ratio of direct to indirect time; Out of surgery visits (home visits and clinics; includes travel time) - 1:0.99[2]	N/A	£86

	Consultation type	Details	Tariff Code	Cost
	GP practice nurse consultation	Per 15.5 minutes surgery consultation @ £44/hour (excluding qualification costs)[1]	N/A	£11
	GP results by phone	Assume same as GP Telephone Consultation Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs[1]	N/A	£21
	GP time spent on phone/writing letter	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£23
	GP time on administration	Ratio of direct to indirect time; Face-to-face time (excludes travel time). Using cost of GP consultation in surgery[1]	N/A	£8
AMBULATORY AND OTHER AMBULATORY VISITS	District nurse visit	Mean average cost for a face-to-face contact in district nursing services (based on NHS reference costs) was £39 in 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£40

	Consultation type	Details	Tariff Code	Cost
	Health visitor visit	Mean average cost for a face-to-face contact in health visiting services (based on NHS reference costs) was £51 in for 2012/2013[2] Hospital and community health services annual price inflation for 2013/2014[1]	N/A	£52
OUTPATIENT HOSPITAL ATTENDANCE	Anaesthetics, outpatient attendance	Consultant Led; WF01B: First attendance Single professional[3]	190	£125
	Dermatology, outpatient attendance	Consultant Led; WF01B: First attendance Single professional[3]	330	£104
	General Medicine, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	300	£178
	Ophthalmology, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional[3]	130	£119

	Consultation type	**Details**	**Tariff Code**	**Cost**
	A&E Attendance	Category 3 investigation with category 1-3 treatment[3]	VB03Z	£163
	Pain Management, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	191	£138

	Consultation type	Details	Tariff Code	Cost
OUTPATIENT HOSPITAL ATTENDANCE	Neurosurgery, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	150	£182
	Palliative Medicine, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	315	£167
	Neurology, Outpatient Attendance	Consultant led - Outpatient Attendance[4]	400	£174

GP, General Practitioner; N/A, not available; NHS, National Health Service; HCHS, community health services; A&E, accident and emergency;
Source:
1. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014.
2. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2013. University of Kent, 2013
3. 2014/5 National Tariff Payment System. Annex 5A National Prices, 17 December 2013
https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015
4. National Schedule of Reference costs 2013-14
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls

Supplementary Table 4: Hospital Inpatient costs

Diagnosis Code	Detail	Average tariff per admission
B020	Zoster encephalitis	£5,038.39
B021	Zoster meningitis	£2,065.47
B022	Zoster other nervous system involvement	£1,440.48
B023	Zoster with ocular diseases	£2,226.36
B027	Disseminated Zoster	£2,255.30
B028	Zoster with other complications	£2,060.70
B029	Zoster without complications	£1,790.57

Source: Hospital Episode Statistics (HES) Admission data IMS, 2013/14

HZ treatment prescriptions

All HZ treatment prescriptions, defined according to British National Formulary (BNF) indication and clinical expert input, were identified by product codes from the HZ TREATMENT CPRD Prodcodes List, and were extracted from the CPRD Therapy dataset.

Analysis datasets used

The Clinical Practice Research Datalink (CPRD)-GOLD 2014Q3;

- HZ treatments prescriptions (CPRD Therapy dataset);
- CPRD Ambulatory Visits (CPRD Consultation dataset);
- Specialists Referrals by GP (CPRD Referral dataset);
- Nursing home visits and Time off sick (CPRD Clinical dataset).

The CPRD GOLD, referred to as CPRD, is a large computerised database of linked anonymised longitudinal medical records from primary care in the UK, drawn from General Practitioners' (GPs') computer systems used for clinical records in their practices. At the time of data extraction, the CPRD included data from 15,436,637 subjects from 684 practices in the UK. The population in the database matched the age and gender distribution of the UK population as a whole. Mean follow-up of subjects was approximately 7 years (median 5.0 years).

Information in the CPRD includes records of clinical events (medical diagnoses), referrals to secondary care and specialists, primary care prescriptions, immunisations and vaccinations, diagnostic tests, lifestyle (smoking and alcohol status) as well as that related to other routine General Practitioner (GP) medical services. More recently the CPRD was linked to certain key secondary care data and mortality data from the ONS.

READ codes comprise coded clinical terms used by clinicians to record outputs of patient assessments as well as health and social care procedures. Medical codes used in CPRD, referred to as medcodes, are CPRD-generated numerical representations of alphanumeric READ codes and are used to identify medical diagnoses in the database.

The Hospital Episode Statistics

HES inpatient Set 9 (2013Q3);

- Hospitalizations (HES Inpatient: HES_DIAGNOSIS_EPI dataset);

HES outpatient Set 9;

- Outpatient Visits (HESOP Clinical dataset);

At the time of data extraction, HES included information related to inpatient admissions, outpatient and accident & emergency activity in NHS (National Health Service) hospitals that were restricted to England only. Records are collated from over 125 million patients annually. ICD-10 clinical coding is used to record diagnoses in HES.

Records for approximately 60% of patients registered in GP practices in CPRD are eligible for linking with their HES records. Record linkage is dependent on agreement by the GP and is limited to subjects in CPRD with a valid NHS number in England.

A combination of the subject's NHS number, gender, date of birth and postcode is used to link patient records. This process is managed by an independent party to HES and CPRD.

A large proportion of subjects with IC conditions and HZ-related or potential complications received care in a hospital setting at some point during their disease history. Although, generally, communication from hospitals (e.g. via discharge letters) inform GPs about care received by their patients, not all of these events are encoded by GPs in patients' notes and therefore there are discrepancies between the CPRD and HES-linked data.

Supplementary Table 5: Costs by category, IC status, time period of analysis and age Groups

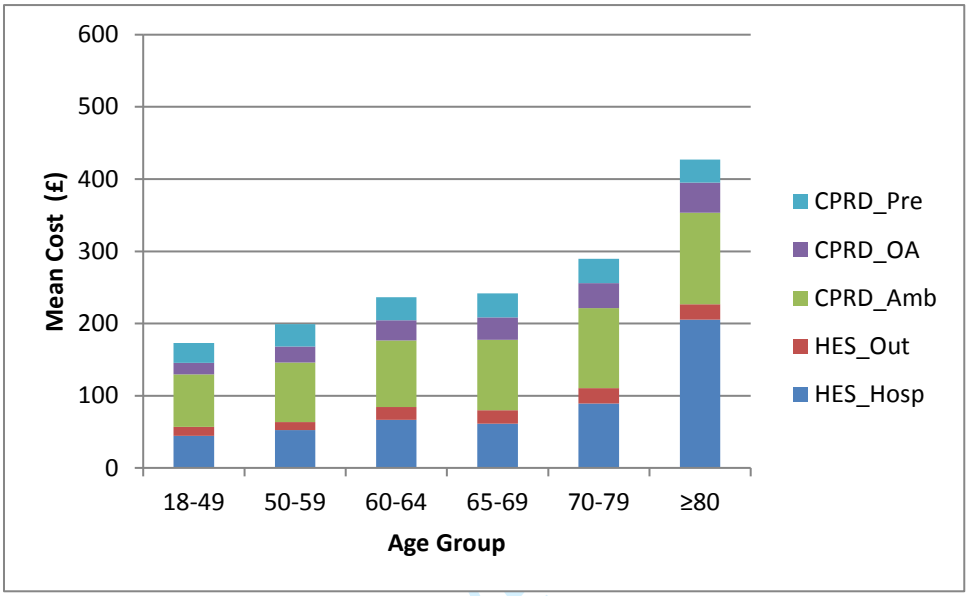
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
IC Population (≤90 days)						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD ambulatory visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD other ambulatory visits	16.1	22	27.7	31	34.6	41.8
CPRD prescriptions	27.6	31.1	31.9	33.3	33.9	31.9
Total	**173.2**	**199.0**	**236.2**	**241.6**	**289.6**	**427.0**
IC Population (≤365 days)						
Hospitalizations	44.2	56.7	68	62.4	93.8	216.5
HES outpatient consultations/visits	15.1	16.1	23.9	28.1	34.4	40.1
CPRD ambulatory visits	80.6	100.1	120.2	134.5	158.1	180.8
CPRD other ambulatory visits	20.7	31.6	44.9	54.4	63.2	78.8
CPRD prescriptions	28.7	33.3	37.3	38.1	42.2	40.8
Total	**189.3**	**237.8**	**294.2**	**317.4**	**391.7**	**557.0**
IC-Free Population (≤90 days)						
Hospitalizations	6.3	8.5	11.5	17.5	36.4	136.5
HES outpatient consultations/visits	5.2	7.8	8.2	10.4	13.9	18.2
CPRD ambulatory visits	59	66.7	69.6	72.7	88.8	102.8
CPRD other ambulatory visits	8	11.2	12.9	16.9	21.2	32.8
CPRD prescriptions	19.7	24.7	24.6	28	29.4	29.4
Total	**98.2**	**118.9**	**126.8**	**145.5**	**189.7**	**319.7**

IC-Free Population (≤365 days)						
Hospitalizations	6.3	8.9	12	17.9	37	144
HES outpatient consultations/visits	5.7	10.8	10	13.4	22.7	28.4
CPRD ambulatory visits	63	75.8	80.4	90	117.3	135.9
CPRD other ambulatory visits	8.8	14.2	18.6	23.2	36.8	58.7
CPRD prescriptions	20	25.6	26.8	29.9	34.9	34.1
Total	**103.8**	**135.3**	**147.7**	**174.4**	**248.6**	**401.0**

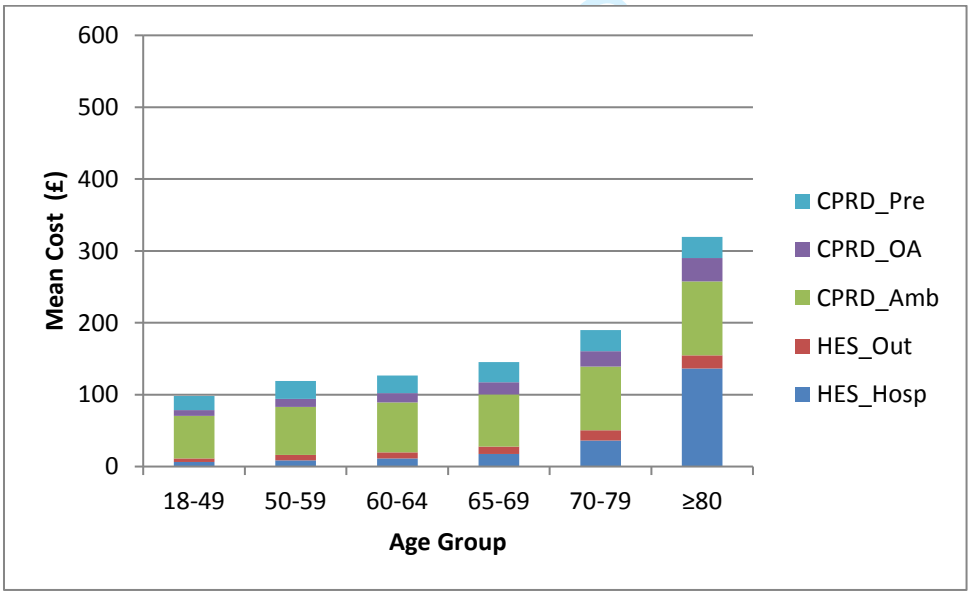
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

Supplementary Figure 1: Healthcare costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



Panel B

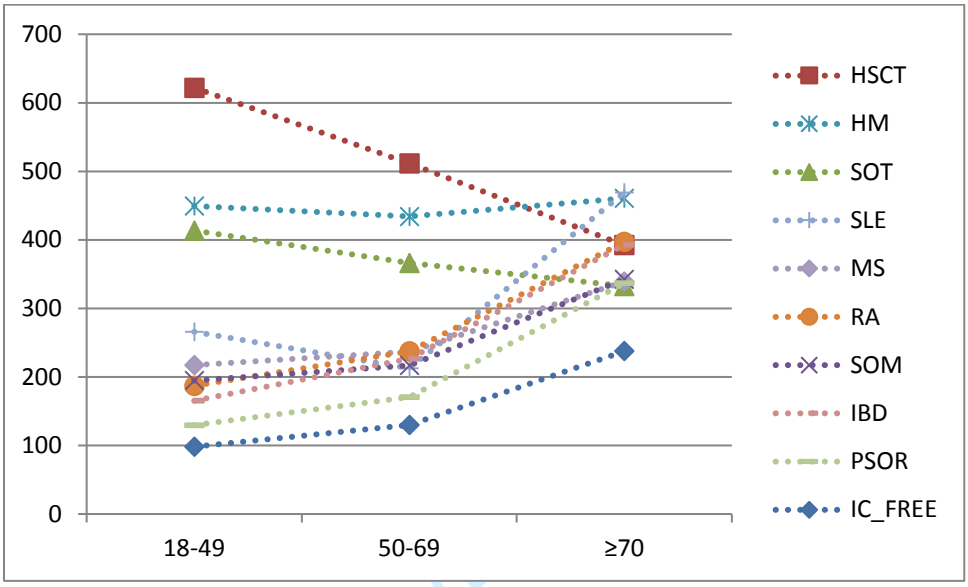


For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

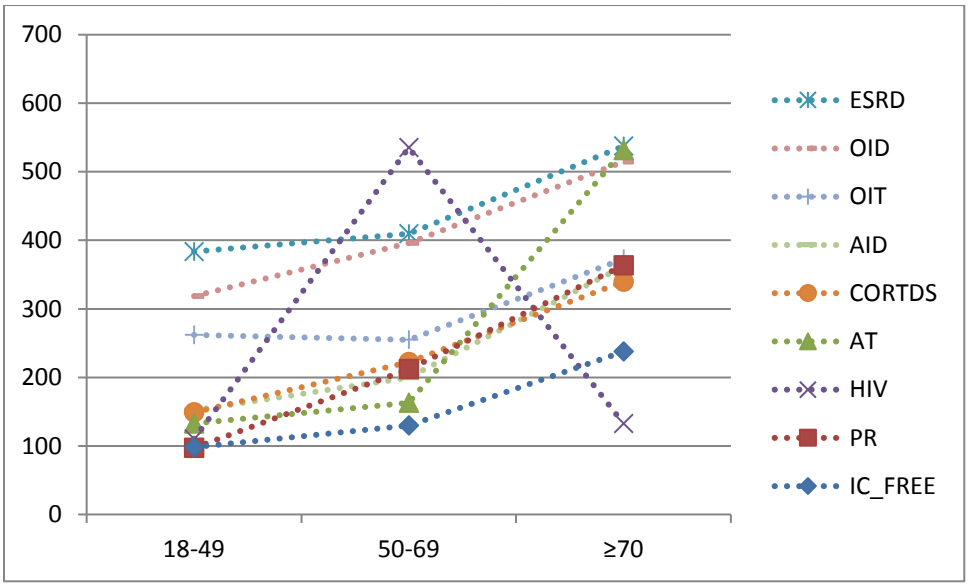
Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; CPRD, Clinical Practice Research Datalink; CPRD_Pre, CPRD Prescriptions; CPRD_OA, CPRD Other Ambulatory Visits; CPRD_Amb, CPRD Ambulatory Visits; HES_Out, HES Outpatient consultation; HES_Hosp, HES Hospital admission.

Supplementary Figure 2: Healthcare Costs for each IC condition by age group for the analysis period 7 days prior to 90 days post initial HZ onset

Panel A



Panel B



For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; HSCT, hematopoietic stem cell transplantation; HM, haematological malignancies; SOT, solid organ transplantations; SLE, systemic lupus erythematosus; MS, multiple sclerosis; RA, rheumatoid arthritis; SOM, solid organ malignancies; IBD, inflammatory bowel syndrome; PSOR, psoriasis; ESRD, end-stage renal disease; OID, other immunodeficiency; OIT, other immunosuppressive therapy; AID, autoimmune diseases; CORTDS, corticosteroid exposure; AT, autoimmune thyroiditis; HIV, human immunodeficiency virus; PR, polymyalgia rheumatica.

Supplementary Table 6: Non-HZ related Hospital Inpatient Stay for the period 7 days to 365 days post initial-HZ onset

Age groups (YOA)	IC cohort				IC-free cohort			
	N	Events	Subjects	Mean	N	Events	Subjects	Mean
18-49	3,039	1,881	259	0.62	2,078	193	56	0.09
50-59	3,408	3,267	337	0.96	2,834	251	61	0.09
60-64	2,550	2,897	293	1.14	2,308	309	63	0.13
65-69	2,753	3,867	371	1.40	2,658	434	108	0.16
70-79	5,429	9,020	838	1.66	5,454	2,556	379	0.47
≥80	3,863	9,928	840	2.57	3,171	4,119	457	1.30
Total	**21,042**	**30,860**	**2,938**	**1.47**	**18,503**	**7,862**	**1,124**	**0.42**

Abbreviations: IC, immunocompromised; HZ, herpes zoster; N, number of participant; YOA, years of age

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pages 1 and 2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8,9
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Pages 9,10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 9,10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.