

# **Supplementary Material**

## **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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## **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 31<sup>st</sup> 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-10<sup>th</sup> 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**

<b>Treatment Groups</b>	<b>Description</b>
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**

	<b>Consultation type</b>	<b>Details</b>	<b>Tariff Code</b>	<b>Cost</b>
AMBULATORY AND OTHER AMBULATORY VISITS	GP surgery consultation	Per patient contact lasting 11.7 minutes, without qualification costs, excluding direct care staff costs <sup>1</sup>	N/A	£35
	GP clinic consultation	Per patient contact lasting 17.2 minutes, without qualification costs, excluding direct care staff costs <sup>1</sup>	N/A	£50
	GP telephone consultation	Per patient contact lasting 7.1 minutes, without qualification costs, excluding direct staff care costs <sup>1</sup>	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 <sup>2</sup>  Inflated to 2014 prices using the HCHS annual price inflation <sup>1</sup>	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 <sup>2</sup>	N/A	£86

	Consultation type	Details	Tariff Code	Cost
	GP practice nurse consultation	Per 15.5 minutes surgery consultation @ £44/hour (excluding qualification costs) <sup>1</sup>	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 <sup>1</sup>	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 <sup>1</sup>	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 <sup>1</sup>	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 <sup>2</sup> Hospital and community health services annual price inflation for 2013/2014 <sup>1</sup>	N/A	£40



	<b>Consultation type</b>	<b>Details</b>	<b>Tariff Code</b>	<b>Cost</b>
	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 <sup>2</sup>  Hospital and community health services annual price inflation for 2013/2014 <sup>1</sup>	N/A	£52
OUTPATIENT HOSPITAL ATTENDANCE	Anaesthetics, outpatient attendance	Consultant Led; WF01B: First attendance Single professional <sup>3</sup>	190	£125
	Dermatology, outpatient attendance	Consultant Led; WF01B: First attendance Single professional <sup>3</sup>	330	£104
	General Medicine, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional <sup>3</sup>	300	£178
	Ophthalmology, Outpatient Attendance	Consultant Led; WF01B: First attendance Single professional <sup>3</sup>	130	£119

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

	<b>Consultation type</b>	<b>Details</b>	<b>Tariff Code</b>	<b>Cost</b>
OUTPATIENT HOSPITAL ATTENDANCE	Neurosurgery, Outpatient Attendance	Consultant led - Outpatient Attendance <sup>4</sup>	150	£182
	Palliative Medicine, Outpatient Attendance	Consultant led - Outpatient Attendance <sup>4</sup>	315	£167
	Neurology, Outpatient Attendance	Consultant led - Outpatient Attendance <sup>4</sup>	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](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**

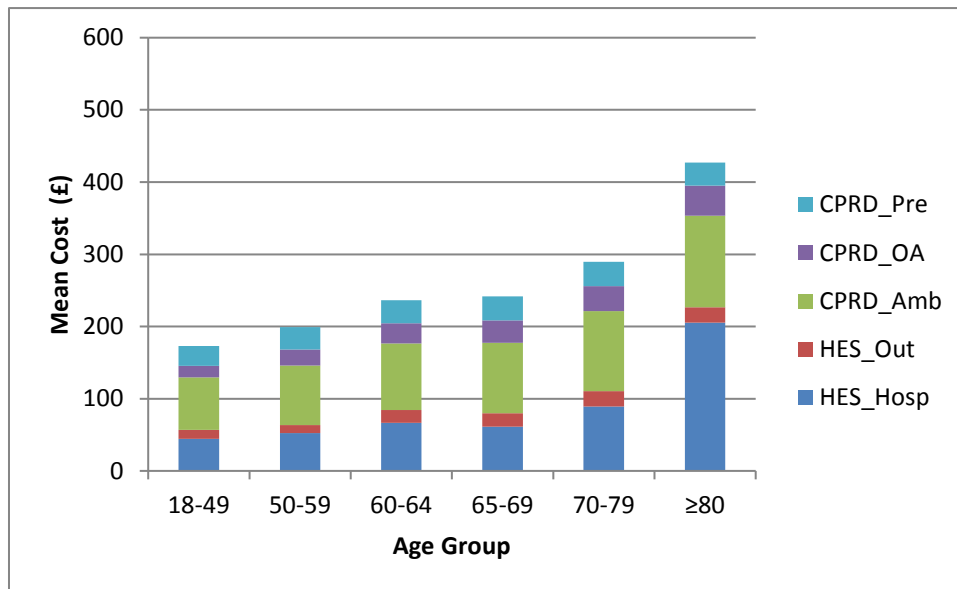
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
<b>IC Population (≤90 days)</b>						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD ambulatory visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD other ambulatory visits	16.1	22	27.7	31	34.6	41.8
CPRD prescriptions	27.6	31.1	31.9	33.3	33.9	31.9
<b>Total</b>	<b>173.2</b>	<b>199.0</b>	<b>236.2</b>	<b>241.6</b>	<b>289.6</b>	<b>427.0</b>
<b>IC Population (≤365 days)</b>						
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
<b>Total</b>	<b>189.3</b>	<b>237.8</b>	<b>294.2</b>	<b>317.4</b>	<b>391.7</b>	<b>557.0</b>
<b>IC-Free Population (≤90 days)</b>						
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
<b>Total</b>	<b>98.2</b>	<b>118.9</b>	<b>126.8</b>	<b>145.5</b>	<b>189.7</b>	<b>319.7</b>

<b>IC-Free Population (≤365 days)</b>						
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
<b>Total</b>	<b>103.8</b>	<b>135.3</b>	<b>147.7</b>	<b>174.4</b>	<b>248.6</b>	<b>401.0</b>

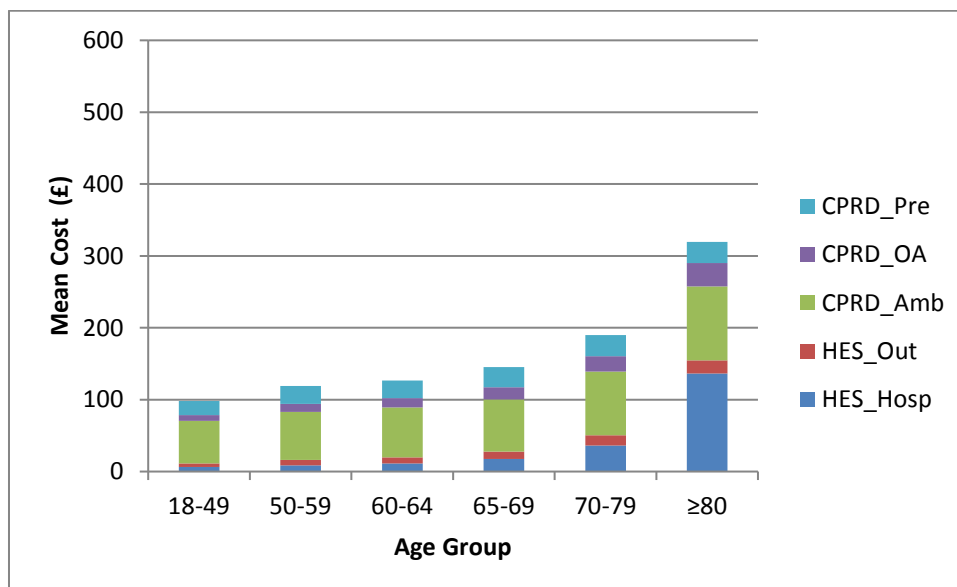
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

**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;

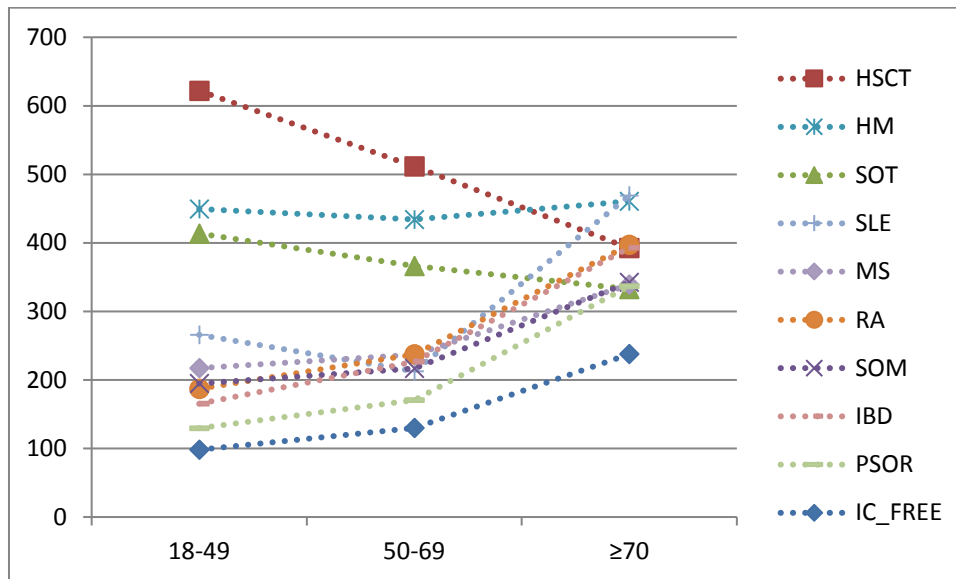
For HZ subjects with PHN: data from 7 days prior to 90 days post HZ onset included;

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.

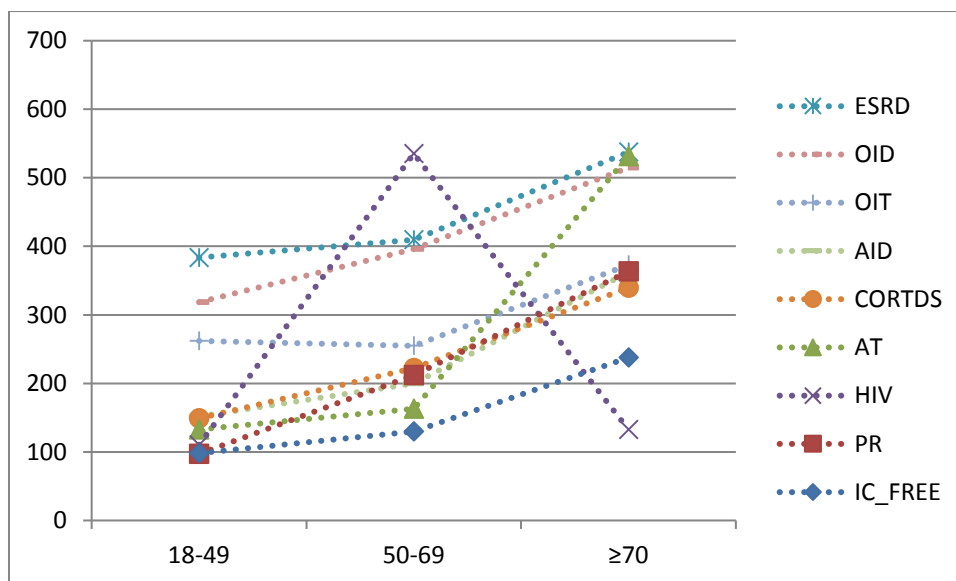


**Supplementary Figure 2: Healthcare Costs for each IC condition by age group for the analysis period 7 days prior to 90 days post initial HZ onset**

**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
<b>Total</b>	<b>21,042</b>	<b>30,860</b>	<b>2,938</b>	<b>1.47</b>	<b>18,503</b>	<b>7,862</b>	<b>1,124</b>	<b>0.42</b>

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