

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023502
Article Type:	Research
Date Submitted by the Author:	09-Apr-2018
Complete List of Authors:	Curran, Desmond; GlaxoSmithKline, Value Evidence Hunjan, Manjit; GlaxoSmithKline El Ghachi, Amale; Aixial France; Hoffmann-La Roche Ltd El-Hahi, Yassine; Valesta, Mechelen, Belgium c/o GSK, ; Bianco, Veronique; GSK Vaccines, Research and Development Center Ferreira, Germano; P-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium
Keywords:	Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment

SCHOLARONE™
Manuscripts

1
2
3
4 **1 TITLE PAGE**

5
6 **2 HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN**
7
8 **3 IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN**
9
10 **4 OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS**

11
12
13
14 **5 Desmond Curran^a, Manjit Hunjan^b, Amale El Ghachi^c, Yassine El Hahi^d, Veronique**
15
16 **6 Bianco^e, Germano Ferreira^f**

17
18
19 **7 Affiliations**

20
21
22 ^aGSK, Wavre, Belgium; desmond.x.curran@gsk.com

23
24 ^bGSK, Uxbridge, United Kingdom; manjit.k.hunjan@gsk.com

25
26
27 ^cAIXIAL, Boulogne-Billancourt, France c/o GSK, Wavre, Belgium; current affiliation F.

28
29 Hoffmann-La Roche Ltd., Basel, Switzerland ; amale.el_ghachi@roche.com

30
31 ^dValesta, Mechelen, Belgium c/o GSK, Wavre, Belgium; yassine.x.el-hahi@gsk.com

32
33 ^eGSK, Rockville, Maryland, United States; veronique.x.bianco@gsk.com

34
35
36 ^fP-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium; germano.ferreira@p-
37
38
39 95.com

40
41
42 **16 Corresponding author**

43
44
45 Desmond Curran

46
47 GSK, Avenue Fleming 20, 1300 Wavre, Belgium.

48
49 Email: desmond.x.curran@gsk.com

50
51
52
53
54
55
56
57
58
59
60

21 **ABSTRACT**

22 *[[298/300 words]]*

23 **Objective**

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

27 **Methods**

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

39 **Results**

40 The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% versus
41 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% versus 7.5% in IC

1
2
3 42 and IC-free individuals aged ≥ 80 YOA, respectively). Similarly, HZ-related mean treatment costs
4
5 43 per subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged
6
7 44 18-49 YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged ≥ 80 YOA,
8
9 45 respectively). Costs varied considerably by IC condition.
10
11
12

13 46 **Conclusions**

14
15
16 47 Individuals with IC conditions, not only have a higher risk of HZ than IC-free individuals, but
17
18 48 also incur higher HZ-related healthcare costs.
19
20
21 49

22 23 24 50 **Keywords**

25
26
27 51 Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden,
28
29 52 herpes zoster treatment.
30
31
32 53

54 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 55 • The study is an observational retrospective descriptive study presenting the healthcare
56 resource utilization and costs associated with HZ in both IC and IC-free populations aged
57 ≥ 18 years of age (YOA) in England.
- 58 • The IC population included 621,588 individuals who were registered in the Clinical
59 Practice Research Datalink (CPRD) from January 2000 to March 2012 with ≥ 12 -month
60 follow-up before being diagnosed with any of the selected 16 IC conditions and matched
61 to the Hospital Episode Statistics (HES) database by age, gender and practice location to
62 extract the IC-free population (N=621,588).
- 63 • The particularity of this study is that the design allowed calculation of IC condition
64 prevalence rates, HZ incidence rates and occurrence of HZ-related healthcare utilization
65 and costs at individual level in the same pre-defined population(s).
- 66 • This key study will provide data to be used in economic analyses to evaluate the value of
67 vaccination in reducing the burden of HZ in IC populations.
- 68 • A limitation of the study is that the diagnoses were derived from administrative codes,
69 which are recognized to be subject to miscoding or under-coding and are not validated
70 against medical charts.

71

1
2
3 **72 LIST OF ABBREVIATIONS**
4

5 73 £, 2014 UK pound sterling
6
7

8
9 74 A&E, Accident and Emergency
10

11
12 75 AID, autoimmune diseases
13
14

15 76 ARDI, age-related decline in immunity
16
17

18 77 AT, Autoimmune Thyroiditis
19
20

21
22 78 BNF, British National Formulary
23
24

25 79 CPRD, Clinical Practice Research Datalink
26
27

28 80 GP, General Practitioner
29
30

31 81 HCRU, healthcare resource utilization
32
33

34
35 82 HES, Hospital Episode Statistics
36
37

38 83 HIV, human immunodeficiency virus
39
40

41 84 HM, hematological malignancies
42
43

44
45 85 HSCT, hematopoietic stem cell transplantation
46
47

48 86 HZ, herpes zoster
49
50

51 87 HZ-Comp, HZ and complications with no PHN
52
53

54
55 88 IC, immunocompromized
56
57

- 1
2
3 89 ICD-10, International Classification of Diseases-10th revision
4
5
6 90 ISAC, Independent Scientific Advisory Committee
7
8
9 91 PHN, postherpetic neuralgia
10
11
12
13 92 PSSRU, Personal Social Services Research Unit
14
15
16 93 PY, person-years
17
18
19 94 RA, rheumatoid arthritis
20
21
22
23 95 SLE, systemic lupus erythematosus
24
25
26 96 SOT, solid organ transplantations
27
28
29 97 UK, United Kingdom
30
31
32
33 98 US, United States
34
35
36 99 VZV-CMI, varicella zoster virus cell-mediated immunity
37
38
39 100 YOA, years of age
40
41
42
43 101 ZVL, zoster vaccine live
44
45
46 102
47
48
49
50
51
52
53
54
55
56
57
58
59
60

103 INTRODUCTION

104 *[[2,819/4,000 words; 6/5 tables+figures but journal allow flexibility]]*

105 Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes
106 zoster (HZ)¹. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons
107 for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not
108 optimal in individuals with immunocompromized (IC) conditions and the age-specific incidence
109 and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human
110 immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune
111 disease, malignancy, or organ transplantation².

112 The incidence and severity of HZ is marked with an increase in people ≥ 50 years of age (YOA)
113 due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of
114 HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among
115 individuals aged ≥ 85 YOA³. Further to the impact of ARDI, a study by Forbes et al. in 2014
116 investigated the increased risk for HZ in the UK population, associated with autoimmune
117 conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic
118 conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney
119 disease, and asthma². In addition to the increased risk of HZ in the various IC conditions these
120 populations also experience increased severity of disease. In a study in Canada, Drolet et al.
121 reported that individuals with an impaired immune status had HZ severity of illness scores, as
122 measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with
123 normal immune function^{4,5}. In a study in the United States (US), Yawn et al. reported that
124 although 8% of HZ cases were in individuals who were immunocompromised, these individuals
125 represented 23.8% of the total HZ-related costs⁶. The increase in healthcare costs was associated

1
2
3 126 with higher rates of postherpetic neuralgia (PHN) and non-pain complications in this group of
4
5 127 individuals⁶.

6
7
8 128 This study aims to estimate the healthcare resource utilization of HZ in selected IC populations
9
10 129 and in an IC-free (i.e., immunocompetent) population aged ≥ 18 YOA in England. The clinical
11
12 130 burden of disease epidemiological results of the study are reported elsewhere⁷. The prevalence of
13
14 131 IC conditions increased from 7.6% in individuals aged 18-44 YOA to 42.2% in individuals aged
15
16 132 ≥ 80 YOA. The incidence rate of HZ in the IC cohort was 3.5/1000 PY in individuals aged 18-49
17
18 133 YOA increasing to 12.6/1000 PY in individuals aged ≥ 80 YOA. In this manuscript, we focus on
19
20 134 the healthcare resource utilization and costs associated with HZ in both IC and IC-free
21
22 135 populations.
23
24
25
26
27

28 136 **METHODS**

29
30 137 The study was conducted as an observational retrospective descriptive study (e-track number:
31
32 138 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥ 18 YOA). The IC
33
34 139 population included individuals who were registered in the Clinical Practice Research Datalink
35
36 140 (CPRD) from January 2000 to March 2012 with ≥ 12 -month follow-up before being diagnosed
37
38 141 with any of the selected 16 IC conditions (See Supplemental Text). The CPRD IC population
39
40 142 cohort linked to the Hospital Episode Statistics (HES) database was matched to a cohort of HES
41
42 143 linked IC-free population (N=621,588), by age, gender and practice location. Individuals with a
43
44 144 missing date of IC diagnosis were excluded from the study population. Clinical diagnoses were
45
46 145 based on READ codes used in CPRD and with the International Classifications of Diseases-10th
47
48 146 revision (ICD-10) codes in the HES database.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 147 The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for
4
5 148 the Medicines and Healthcare Products Regulatory Agency database research (ISAC protocol
6
7 149 number 14_222R). The study was conducted in accordance with all applicable regulatory
8
9 150 requirements, with the Guidelines for Good Pharmacoepidemiology Practices⁸, all applicable
10
11 151 subject privacy requirements and the guiding principles of the Declaration of Helsinki.
12
13
14

15 152 Healthcare resource data were extracted for IC and Matched IC-free HES-linked individuals who
16
17 153 were incident HZ cases during the study follow-up. Only reported records (resource utilization)
18
19 154 with available event dates during the individuals' eligibility period and those that occurred 7 days
20
21 155 before the initial HZ onset date, up to 365 days after the initial HZ onset date, were extracted.
22
23 156 Individuals who recorded the first PHN event date after 365 days post HZ event date were
24
25 157 excluded.
26
27
28
29

30 158 **Data sources**

31
32
33 159 Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation,
34
35 160 Clinical, Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI
36
37 161 dataset; (3) HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource
38
39 162 utilization was defined as: HZ-treatment related prescribed medications (CPRD tbl:therapy);
40
41 163 Consultations and care provided by General Practitioners (GPs) or others in the GP practice
42
43 164 (CPRD tbl:consultations); HES secondary care outpatient visits (HES outpatient events); and
44
45 165 HES inpatient hospitalizations (HES inpatient events).
46
47
48
49

50 166 For each subject, healthcare costs stratified by subcategory of interest (HES Inpatient
51
52 167 Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other
53
54 168 Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by
55
56
57
58
59
60

1
2
3 169 their unit costs. These were then summed over all resource use categories to obtain a total cost for
4
5 170 each subject. Values were expressed in 2014 UK pound sterling (£).
6
7

8 9 171 **Healthcare resource costs**

10
11 172 For each subject, the cost of each prescription was calculated by merging the product code,
12
13 173 package type and prescribed quantity (prodcode-packtype-quantity) with the associated standard
14
15 174 package size and unit cost. The unit cost of a product in a prescription instance (i.e. one distinct
16
17 175 record in the CPRD therapy) was calculated using the cost described in the British National
18
19 176 Formulary (BNF), 2015 (as listed price if included or indicative price based on price in BNF).
20
21
22
23

24 177 Ambulatory visits included consultations with GPs and nurses in primary or community care.

25
26 178 Visits included consultations at the practice or at the home of the patient, during working hours

27
28 179 and out of hours. Consultations for which no clinical intervention was recorded were not included

29
30 180 in the cost estimate for GP practice related healthcare utilization, for example: information

31
32 181 technology data migration, administrative recording of received information. Administrative

33
34 182 resource use in primary care was considered, including time on the phone, writing reports,

35
36 183 referrals, etc. A referral to secondary care noted in a patient's record, *per se*, was not allocated the

37
38 184 cost of the secondary care appointment. The most conservative option for the cost per unit as

39
40 185 included in the Personal Social Services Research Unit (PSSRU) Costs of Health and Social

41
42 186 Care, 2014 were applied e.g. GP consultation costs excluded qualification, direct staff care and

43
44 187 travel costs⁹. Where specific costs for 2013/14 were not available, 2012/13 costs, were adjusted

45
46 188 by applying the Hospital and Community Health Services inflation index⁹. Administration costs

47
48 189 were based on unit costs as stated in the PSSRU, 2014.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 190 Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient
4
5 191 resource utilization concerned HZ related referrals for non-inpatient hospital consultations,
6
7 192 derived from the HES Outpatient data. Additionally, visits to the Accident and Emergency
8
9 193 (A&E) department in hospitals were also recorded and costed. Inpatient hospitalization costs
10
11 194 were based on the average cost per episode using HES data for 2013/14 (calculated from the total
12
13 195 average payment by result spell cost and the average number of episodes per spell). Hospital
14
15 196 outpatient costs were sourced from National Tariff costs (2014) for specific consultant led
16
17 197 outpatient consultations; conservative costs were allocated i.e. wherever applicable costs for first
18
19 198 attendance by a single professional appointment were used¹⁰. Costs allocated to A&E visits were
20
21 199 based on the cost of a category 3 investigation with category 1-3 treatment¹⁰. Only events related
22
23 200 to HZ were costed out. Resources related to HZ complications were considered using ICD-10
24
25 201 Code B020.

26
27
28
29
30
31 202 No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in
32
33 203 CPRD. Further details are provided in the Supplementary Text.

34 35 36 37 204 **RESULTS**

38
39 205 The HES-linked matched IC and IC-free population cohorts (n=621,588 each) included
40
41 206 approximately 44% males and 56% females with a mean age of approximately 56 years. The age
42
43 207 distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA
44
45 208 (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥ 80 YOA (11.01%).

46
47
48
49 209 The proportion of inpatient hospital admissions by age group for the HES-linked Matched IC and
50
51 210 IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel A) or
52
53 211 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 1. Hospital

1
2
3 212 admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset
4
5 213 (Panel B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The
6
7 214 percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus*
8
9 215 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC
10
11 216 and IC-free individuals aged ≥ 80 YOA, respectively). Multiple HZ-related hospital visits were
12
13 217 reported for some individuals. As such, Table 1 presents the mean number of healthcare
14
15 218 resources utilized by IC Status, Age Group and Analysis period. The mean number of
16
17 219 hospitalizations per HZ case for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free
18
19 220 individuals aged 18-49 YOA, respectively and 0.173 and 0.115 in IC and IC-free individuals
20
21 221 aged ≥ 80 YOA, respectively. A similar pattern of higher healthcare resource utilization with
22
23 222 increasing age and in IC individuals was observed for all resources for which costs were
24
25 223 assigned. A similar mean number of sick leave certificates were observed between the IC and the
26
27 224 IC-free cohorts with the mean decreasing with age. Nursing home care / admissions were only
28
29 225 recorded for individuals aged ≥ 70 YOA in CPRD.

30
31 226 Figure 2 and Table 2 present the overall healthcare costs by HES-linked matched IC cohort and
32
33 227 age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs
34
35 228 increase with age and are consistently higher in the IC cohort compared with the IC-free cohort.
36
37 229 Although the absolute cost difference between IC and IC-free individuals increases with age from
38
39 230 £85.5 in individuals aged 18-49 YOA to £156.1 in individuals aged ≥ 80 YOA the relative
40
41 231 difference is higher in younger individuals (i.e. 75.8%-99.2% in < 70 YOA) compared with older
42
43 232 individuals (i.e. 38.9%-57.6% in ≥ 70 YOA).

44
45 233 Figure 3 presents the overall healthcare costs by each IC condition in the HES-linked matched IC
46
47 234 and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ
48
49
50
51
52

1
2
3 235 onset. For all IC conditions, the costs were higher than those for the IC-free group, in particular
4
5 236 for the hematopoietic stem cell transplantation (HSCT), hematological malignancies (HM) and
6
7 237 solid organ transplantations (SOT) conditions. In general, there was a similar trend of increasing
8
9 238 costs with increasing age-groups. A few outliers were observed due to small sample sizes. For
10
11 239 example, only 3 and 8 individuals aged ≥ 70 YOA were included in the HIV and HSCT groups,
12
13 240 respectively. Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis (AT)
14
15 241 and SOT were included, respectively.
16
17
18
19

20 242 Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean
21
22 243 healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis
23
24 244 period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean
25
26 245 healthcare costs were approximately 2 to 4 times higher for individuals with HZ complications
27
28 246 compared to individuals with HZ only.
29
30
31
32

33 247 **DISCUSSION**

34
35 248 In this study, we presented the healthcare resource utilization and costs associated with HZ in
36
37 249 both IC and IC-free populations. An important feature of this study was that the design enabled
38
39 250 the calculation of IC condition prevalence rates, HZ incidence rates and occurrence of HZ-related
40
41 251 healthcare utilization and costs at individual level in the same pre-defined population(s).
42
43
44

45 252 Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the
46
47 253 mean healthcare costs per HZ subject, from an National Health Services perspective, of £85.6 and
48
49 254 £400.9 in individuals aged <65 YOA and ≥ 65 YOA, respectively¹¹. A later UK study that used
50
51 255 the HES and the health improvement network databases, estimated the mean cost of treating a HZ
52
53 256 patient to be £65.5 in the first month of diagnosis, with patients aged ≥ 70 YOA having a mean
54
55
56
57
58
59
60

1
2
3 257 cost of £83 in the first month and £15.80 in months 2 and 3¹². The costs of treating individuals
4
5 258 with PHN were much higher, i.e. mean cost per subject was estimated to be £921 in all
6
7 259 individuals and £909.60 in individuals aged ≥ 70 YOA¹². Another study evaluated mean
8
9 260 healthcare costs (excluding hospitalization costs) to be £75.63 per HZ patient with mean direct
10
11 261 costs for treating PHN episodes (PHN pain occurring or persisting for 3 months) of £340.04¹³.
12
13
14 262 These values augmented with hospitalization costs were used as inputs in a cost-effectiveness
15
16 263 model evaluating a HZ vaccine using the population of England and Wales³. The costs estimated
17
18 264 by van Hoek et al. are consistent with the values estimated in our study for IC-free individuals by
19
20 265 age group³.

21
22
23
24
25 266 In a previous study, mean prescription costs per HZ subject were reported to be £40.52¹³. In our
26
27 267 study, the mean prescription costs per HZ subject ranged from £19.7 to £40.8 depending on the
28
29 268 age group, IC status and analysis period included. Our study aimed to include only medications
30
31 269 considered to be directly related to HZ; i.e. excluded medications that may be linked to IC
32
33 270 conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from
34
35 271 other conditions). This restriction and the introduction of generic versions of medications such as
36
37 272 acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed
38
39 273 to the reduced overall medication costs reported in this study.

40
41
42
43
44 274 In this analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days
45
46 275 post HZ onset, although it is recognized that HZ episodes can last for longer. The costs of PHN
47
48 276 were analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days
49
50 277 prior to 365 days post HZ onset. The rationale for the time periods studied was that using analysis
51
52 278 period 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2
53
54 279 only could overestimate these costs. The most frequently used definition of PHN is: pain
55
56
57
58
59
60

1
2
3 280 persisting or appearing at least 90 days following rash onset. The median duration of PHN has
4
5 281 been reported to be 10.3 and 12.9 months in individuals aged ≤ 69 and ≥ 70 YOA respectively¹⁴,
6
7 282 and is likely to be longer in individuals who are immunocompromised⁵.
8
9

10
11 283 The healthcare costs associated with PHN and complications were higher than those for
12
13 284 individuals with HZ only. However, as reported elsewhere, when considering the overall cost of
14
15 285 disease at a population level, the overall healthcare-associated cost is higher for HZ only¹⁵. This
16
17 286 is primarily a result of the higher incidence rates of HZ only.
18
19

20
21 287 Few studies have investigated healthcare resource utilization and costs in IC individuals.
22
23 288 Schroder et al. carried out a study using the German Pharmacoepidemiological Research
24
25 289 Database , which consists of claims data from four statutory health insurances¹⁶. They reported
26
27 290 that during the quarter of the HZ diagnosis or during the two following quarters, 10% of all HZ
28
29 291 patients with an IC condition were hospitalized (with a HZ diagnosis), whereas among IC-free
30
31 292 HZ patients, 4.2% were hospitalized. White et al. reported that in their study using the US Market
32
33 293 Scan Research Database, direct medical costs were nearly twice as high in IC patients compared
34
35 294 with IC-free patients¹⁷. Li et al. carried out a study using the US Truven Health MarketScan
36
37 295 Commercial and Medicare Supplemental Insurance databases¹⁸. They concluded that patients
38
39 296 with the studied IC conditions (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer)
40
41 297 had significantly higher healthcare utilization and cost when developing HZ than their
42
43 298 comparable matches without HZ.
44
45
46
47
48

49
50 299 This study has several limitations. Diagnoses were derived from administrative codes, which are
51
52 300 recognized to be subject to miscoding or under-coding and are not validated against medical
53
54 301 charts. Increasing healthcare resource utilization and cost is likely to be related to increased
55
56
57
58

1
2
3 302 severity of IC conditions. In a study, Schroder et al. categorized individuals as low IC and high
4
5 303 IC¹⁶. However, insufficient details are recorded in the CPRD and HES databases to allow
6
7 304 adequate definition of patients' severity of immunosuppression e.g. laboratory parameters,
8
9
10 305 immunosuppressive medication details such as chemotherapy. In addition, many IC individuals
11
12 306 had prescriptions that included more than one immunosuppressing medicine.
13
14

15 307 **CONCLUSION**

16
17
18 308 In conclusion, individuals with IC conditions incurred higher healthcare utilization and costs than
19
20 309 IC-free individuals. The current HZ vaccine which is licensed in the UK is a live vaccine (zoster
21
22 310 vaccine live [ZVL]), and is contraindicated for use in immunosuppressed or immunodeficient
23
24 311 individuals in whom administration of ZVL may result in disseminated disease². New HZ
25
26 312 vaccines which may be used in IC populations are currently under development^{19 20}. The results
27
28
29 313 from this study could be used in economic analyses to evaluate the value of vaccination in
30
31 314 reducing the burden of HZ in these populations.
32
33
34

35 315 **AUTHOR CONTRIBUTIONS**

36
37 316 VB, AEG, YEH, GF, MH and DC participated in the conception and design of the study. VB,
38
39 317 AEG, YEH, GF and MH participated in the collection or generation of the study data. VB, AEG
40
41 318 and YEH performed the study. AEG, YEH, MH and DC contributed to the material. VB, AEG,
42
43
44 319 YEH, GF, MH and DC were involved in the analysis or interpretation of the data. All named
45
46 320 authors provided substantial intellectual and scientific input during the manuscript development,
47
48 321 critically reviewing the content, revising the manuscript and giving final approval before
49
50 322 submission. The work described was carried out in accordance with the ICMJE recommendations
51
52 323 for conducting, reporting, editing and publishing scholarly work in medical journals. All authors
53
54 324 had full access to the data and gave final approval before submission.
55
56
57
58
59
60

325 **ACKNOWLEDGEMENTS**

326 The authors would like to thank Emmanuelle Espié, Yanni Emad, Morgane Guinnec, François
327 Haguinet for their contribution to the study. They would also like to thank the Business &
328 Decision Life Sciences platform for editorial assistance and coordination, on behalf of GSK.
329 Gregory Collet coordinated manuscript development and editorial support. Kathleen Daly
330 provided editing support.

331 **CONFLICTS OF INTEREST**

332 VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the
333 GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the
334 GSK group of companies between 2012 and Feb 2015, during which the study was designed and
335 implemented. Later, as an employee of P-95 epidemiology and pharmacovigilance, GF provided
336 contracted consultancy services to the GSK group of companies for this and other GSK-
337 sponsored studies. P-95 provides contracted services to the GSK group of companies, beyond the
338 scope of this study.

339 **DATA SHARING STATEMENT**

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

342 **ETHICAL APPROVAL**

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

1
2
3 345 **FUNDING**
4

5 346 GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK
6
7 347 study identifier: e-track number: 201615) activities and overall data management (collection,
8
9 348 analysis and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated
10
11 349 with the development and the publishing of the present manuscript. All authors had full access to
12
13
14 350 the data and the corresponding author was responsible for submission of the publication.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

351 **REFERENCES**

- 352 1. Oxman M. Zoster vaccine: current status and future prospects. *Clin Infect Dis* 2010;**51**(2):197-
353 213.
- 354 2. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster:
355 population based case-control study. *BMJ* 2014;**348**:g2911.
- 356 3. van Hoek AJ, Gay N, Melegaro A. Estimating the cost-effectiveness of vaccination against
357 herpes zoster in England and Wales. *Vaccine* 2009;**27**:1454-67.
- 358 4. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due
359 to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain
360 inventory. *J Pain* 2004;**5**(6):344-56.
- 361 5. Drolet M, Brisson M, Schmader K, et al. Predictors of postherpetic neuralgia among patients
362 with herpes zoster: a prospective study. *J Pain* 2010;**11**(11):1211-21.
- 363 6. Yawn BP, Itzler RF, Wollan PC, et al. Health care utilization and cost burden of herpes zoster
364 in a community population. *Mayo Clin Proc* 2009;**84**(9):787-94.
- 365 7. Yanni E, Ferreira G, El Hahi Y, et al. The burden of herpes zoster in 16 selected
366 immunocompromised populations in England: a cohort study in the Clinical Practice Research
367 Datalink 2000-2012. *BMJ Open* 2016;**[submitted]**.
- 368 8. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology
369 Practices (GPP). Secondary Guidelines for Good Pharmacoepidemiology Practices (GPP) 2015.
370 https://www.pharmacoepi.org/resources/guidelines_08027.cfm.

- 1
2
3 371 9. Curtis LPSSRU. Unit costs of Health & Social Care 2014. Secondary Unit costs of Health &
4
5 372 Social Care 2014 2014. <http://www.pssru.ac.uk/project-pages/unit-costs/2014/>.
6
7
8
9 373 10. National Tariff Payment System. Annex 5A National Prices. Secondary Annex 5A National
10
11 374 Prices 2014/2015. [https://www.gov.uk/government/publications/national-tariff-payment-system-](https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015)
12
13 375 [2014-to-2015](https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015).
14
15
16 376 11. Scott FT, Johnson RW, Leedham-Green M, et al. The burden of Herpes Zoster: a prospective
17
18 377 population based study. *Vaccine* 2006;**24**(9):1308-14.
19
20
21
22 378 12. Taieb V, Schwarzbard J, Butt T, et al. The Epidemiological and Cost Burden of Herpes
23
24 379 Zoster (Hz) and Post-Herpetic Neuralgia (Phn) in the UK. *Value Health* 2015;**18**(7):A589.
25
26
27
28 380 13. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-
29
30 381 herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;**137**(1):38-47.
31
32
33 382 14. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the
34
35 383 prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost Eff Resour Alloc*
36
37 384 2010;**8**:7.
38
39
40
41 385 15. Gater A, Uhart M, McCool R, et al. The humanistic, economic and societal burden of herpes
42
43 386 zoster in Europe: a critical review. *BMC Public Health* 2015;**15**:193.
44
45
46
47 387 16. Schröder C, Enders D, Schink T, et al. Incidence of herpes zoster amongst adults varies by
48
49 388 severity of immunosuppression. *J Infect* 2017;**S0163-4453**(17):30228-1.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 389 17. White RR, Lenhart G, Singhal PK, et al. Incremental 1-Year Medical Resource Utilization
4
5 390 and Costs for Patients with Herpes Zoster from a Set of US Health Plans. *Pharmacoeconomics*
6
7 391 2009;**27**(9):781-92.
- 9
10
11 392 18. Li A, Chen SY, Burstin SJ, et al. Cost of Herpes Zoster in Patients With Selected Immune-
12
13 393 Compromised Conditions in the United States. *Open Forum Infect Dis* 2016;**3**(2):ofw067.
- 15
16
17 394 19. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit
18
19 395 vaccine in older adults. *N Engl J Med* 2015;**372**(22):2087-96.
- 21
22 396 20. Mullane KM, Winston DJ, Wertheim MS, et al. Safety and immunogenicity of heat-treated
23
24 397 zoster vaccine (ZVHT) in immunocompromised adults. *J Infect Dis* 2013;**208**(9):1375-85.

25
26
27
28 398
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

399 **TABLES**

400 **Table 1 : Mean number of healthcare resources by IC status, age group and analysis**
 401 **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				

1					
2					
3	18-49	0.319	0.411	0.155	0.170
4					
5	50-59	0.433	0.623	0.218	0.277
6					
7	60-64	0.545	0.885	0.251	0.360
8					
9	65-69	0.607	1.064	0.330	0.454
10					
11	70-79	0.686	1.251	0.417	0.722
12					
13	≥80	0.860	1.616	0.668	1.183
14					
15	CPRD Prescriptions (All treatments)				
16	18-49	1.247	1.363	0.890	0.931
17					
18	50-59	1.670	1.994	1.143	1.227
19					
20	60-64	1.969	2.602	1.379	1.489
21					
22	65-69	2.129	2.894	1.473	1.717
23					
24	70-79	2.310	3.295	1.814	2.347
25					
26	≥80	2.405	3.743	1.844	2.575
27					
28	CPRD Referrals*				
29	18-49	0.018	0.020	0.011	0.012
30					
31	50-59	0.021	0.026	0.018	0.022
32					
33	60-64	0.031	0.040	0.020	0.024
34					
35	65-69	0.031	0.044	0.015	0.023
36					
37	70-79	0.033	0.054	0.031	0.047
38					
39	≥80	0.040	0.065	0.029	0.048
40					
41	CPRD Sick leave*				
42	18-49	0.162	0.175	0.155	0.161
43					
44	50-59	0.156	0.178	0.173	0.182
45					
46	60-64	0.060	0.069	0.080	0.087
47					
48	65-69	0.017	0.017	0.008	0.008
49					
50	70-79	0.001	0.001	0.002	0.003
51					
52	≥80	0.000	0.000	0.000	0.000
53					
54	CPRD Nursing home care/admission*				
55					
56					
57					
58					
59					
60					

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

402

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

404 Abbreviations: IC, immunocompromized; HES, Hospital Episode Statistics; CPRD, Clinical Practice Research Datalink;

405 Costs were assigned for HES Hospital admission, HES Outpatient consultation, CPRD Ambulatory Visits, CPRD Other

406 Ambulatory Visits, CPRD Prescriptions.

407

For peer review only

1
2
3 **408 Table 2 : Mean cost (£) of healthcare resource utilization by IC status, age group and**
4
5
6 **409 analysis period***
7

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

410

411 * post initial HZ onset

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

413

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

Mean cost (£), IC				
Age groups (YOA)	HZ only*	PHN Day 90 [#]	PHN Day 365 ¹	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 ¹	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

416
 417 * Individuals with HZ only (i.e. without PHN and complications): includes only costs 7 days prior to 30 days post initial HZ onset

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

419 ¹ Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset

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

421 Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ: ,herpes zoster; PHN, postherpetic neuralgia; HZ-

422 Comp, HZ and complications with no PHN; YOA: years of age

423

1
2
3 424 **FIGURE**

4
5 425 **Figure 1 : Inpatient Hospital Admission by HES-linked Matched IC or IC-free**
6
7
8 426 **cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A)**
9
10 427 **and 7 days prior to 365 days post initial HZ onset (Panel B)**

11
12
13 428
14
15
16 429 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data
17 430 from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A) and 365 days (Panel B)
18 431 Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, postherpetic neuralgia
19 432
20
21
22 433

1
2
3 434 **Figure 2 : Healthcare Costs for by HES-linked Matched IC (Panel A) and IC-free**
4
5
6 435 **cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset**
7

8
9 436

10
11 437 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data
12 438 from 7 days prior until 365 days after HZ onset

13
14 439 Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-
15 440 OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits; HES, Hospital Episode Statistics; HES-Out,
16 441 HES Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN,
17 442 postherpetic neuralgia;
18
19 443

1
2
3 444 **Figure 3 : Healthcare Costs for each IC condition in the HES-linked Matched IC**
4
5
6 445 **and IC-free cohort by age group for the analysis period 7 days prior to 365 days post**
7
8 446 **initial HZ onset**
9

10
11 447

12
13
14 448 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included; For HZ individuals with PHN: data
15 449 from 7 days prior until 365 days after HZ onset.

16 450 Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid
17 451 exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM,
18 452 hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel
19 453 syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, postherpetic neuralgia; RA, rheumatoid arthritis; SLE,
20 454 systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID,
21 455 other immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica;
22
23
24

25 456
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

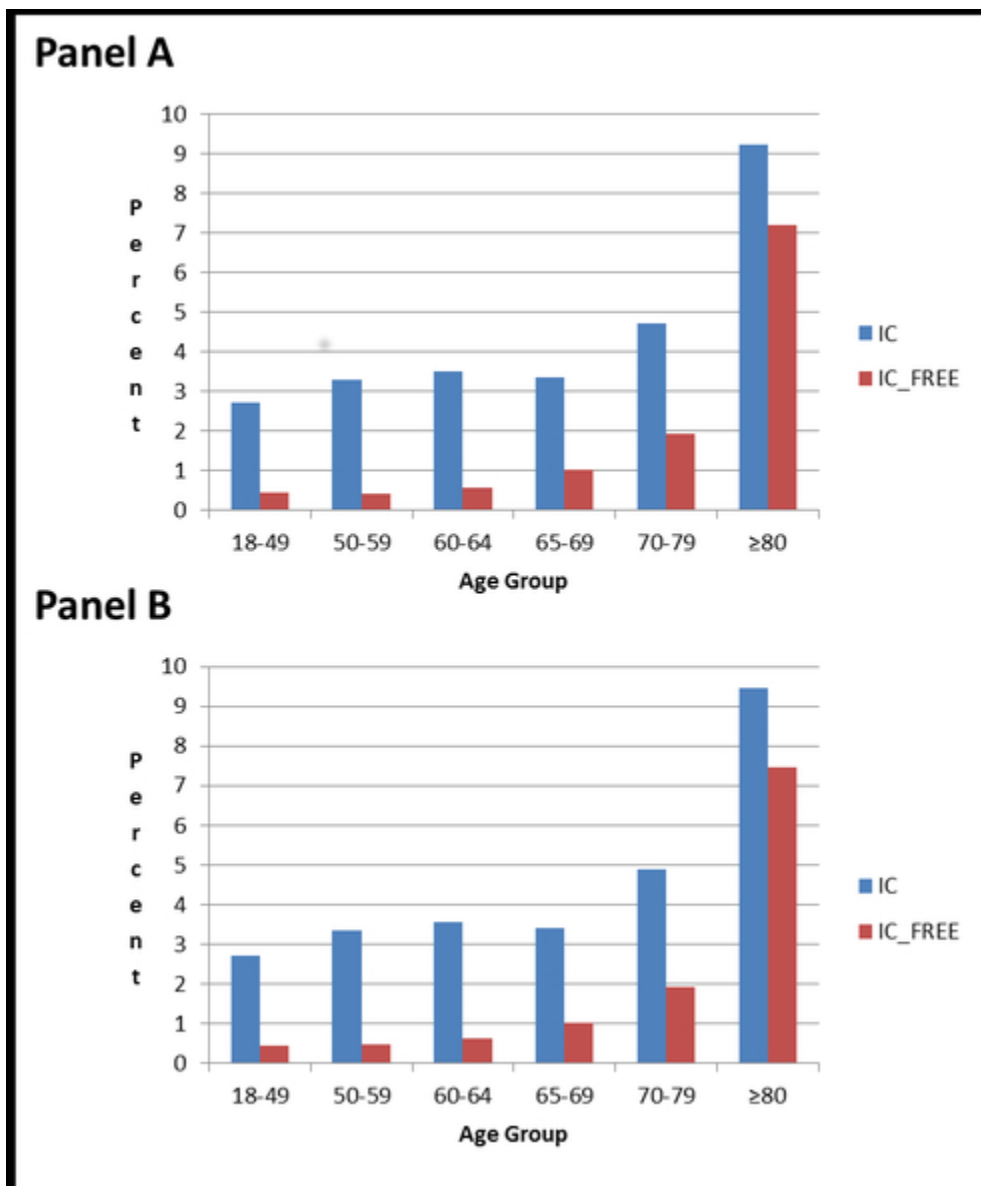
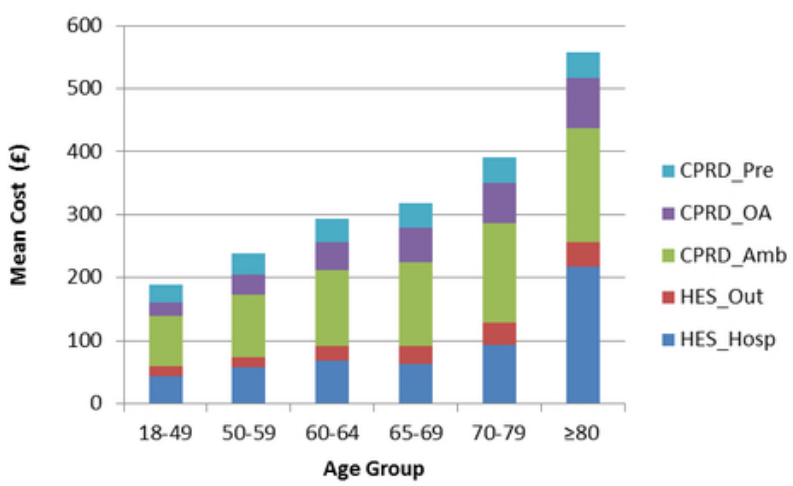


Figure 1

41x50mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Panel A



Panel B

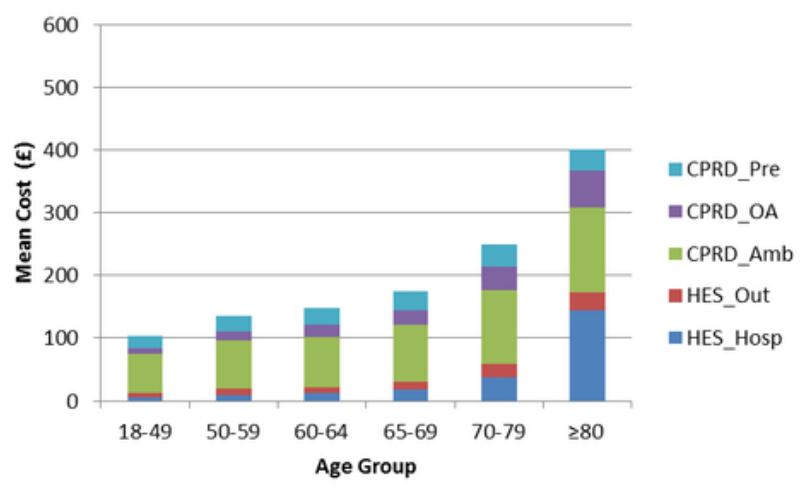


Figure 2

45x59mm (300 x 300 DPI)

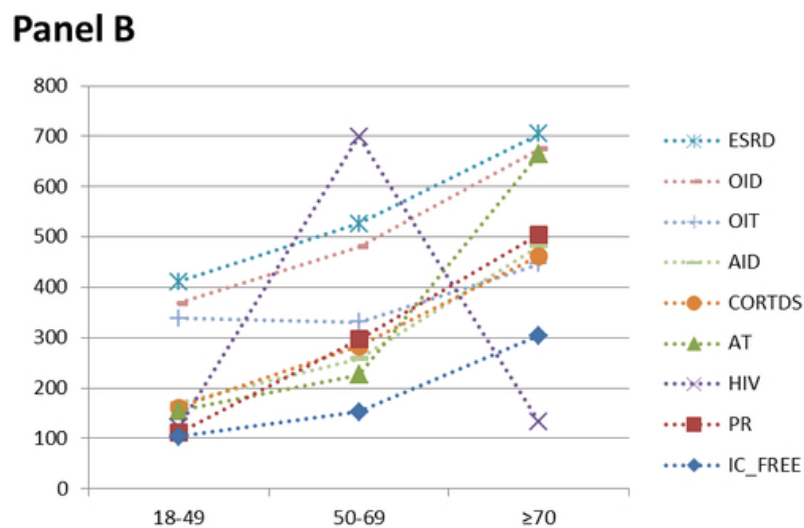
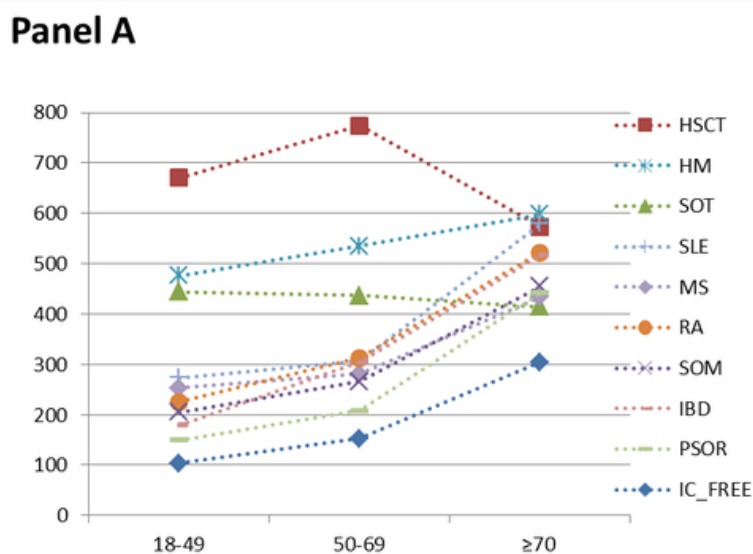


Figure 3

47x64mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

18 IC Population

19 The immunocompromised (IC) population, referred to as the IC cohort hereafter, included eligible
20 subjects reporting at least one of the following conditions or therapies at any time before 31st March
21 2012:

- 22 • Hematopoietic stem cell transplant (HSCT);
- 23 • Solid organ transplantation (SOT);
- 24 • Solid organ malignancies (SOM);
- 25 • Hematological malignancies (HM): Leukemia, Lymphoma, Myeloma;
- 26 • Autoimmune diseases (AID):
 - 27 ○ Rheumatoid Arthritis (RA);
 - 28 ○ Systemic *Lupus erythematosus* (SLE);
 - 29 ○ Inflammatory Bowel Disease (IBD);
 - 30 ○ Psoriasis (PSOR);
 - 31 ○ Multiple sclerosis (MS);
 - 32 ○ Polymyalgia rheumatica (PR) and;
 - 33 ○ Autoimmune thyroiditis (AT).
- 34 • Human immunodeficiency virus (HIV);
- 35 • End-stage renal disease (ESRD);
- 36 • Corticosteroid exposure (CORTDS);
- 37 • Other immunosuppressive therapy (OIT) exposure;
- 38 • Other immunodeficiency (OID) conditions.

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

46 **IC Matching**

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

49 The matching factors were:

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

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

57 **Herpes Zoster (HZ) Diagnosis**

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

65 **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

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

68

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

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

76

77 **Healthcare costing**

- 78 • HZ subjects without PHN:

- 1
2
3 79 ○ Period = the HZ case onset date -7 prior to the case onset date + 30 days (a);
4
5
6 80 ● HZ subjects reporting a PHN event within 365 days from the HZ case onset date, two
7
8 81 analyses periods were used:
9
10
11 82 ○ Period 1 = the HZ case onset date -7 prior to the case onset date + 90 days (b);
12
13 83 ○ Period 2 = the HZ case onset date -7 prior to the case onset date + 365 days (c);
14
15

16 84 The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days after HZ
17 85 event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).
18

19 86
20 87 Additionally, main categories of resource utilization and cost tables were presented for the following
21 88 sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days and 365 days
22 89 post-initial HZ onset date:

- 23
24 90 ● HZ only (i.e. no PHN and no HZ-related complication);
25
26 91 ● HZ and PHN within 1 year of HZ event;
27
28 92 ● HZ and other HZ-related complications but no PHN (overall and by complications
29
30 93 sub-categories:
31
32 94 ○ Neurological;
33
34 95 ○ Ocular;
35
36 96 ○ Cutaneous;
37
38 97 ○ Other complications.
39
40

41 98
42 99 A detailed mapping linking the exact event definition variables and criteria to the reference unit cost
43 100 was used. The unit costs for each type of resource were obtained from the following reference
44 101 sources:

- 45
46 102 ● General practitioner (GP) prescribed medication costs: British National Formulary
47
48 103 (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the
49
50 104 prescription costs for each drug (prodcode) of interest. A detailed mapping was used
51
52 105 to link the exact cost of prodcode quantity and packtype for each drug;
53
54
55
56
57
58
59
60

- 1
2
3 106 • Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L,
4
5 107 Personal Social Services Research Unit. Unit costs of Health & Social Care 2014.
6
7 108 University of Kent, 2014);
8
9 109 • HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs
10
11 110 (National Schedule of Reference Costs, 2013/2014).
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

111 **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

112

113 **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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	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

For peer review only

	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

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

115 Source:

- 116 1. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2014. University of Kent, 2014.
- 117 2. Curtis L, Personal Social Services Research Unit. Unit costs of Health & Social Care 2013. University of Kent, 2013
- 118 3. 2014/5 National Tariff Payment System. Annex 5A National Prices, 17 December 2013
- 119 <https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015>
- 120 4. National Schedule of Reference costs 2013-14
- 121 [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls)
- 122 [NET_updated.xls](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls)

124 **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

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

126

127 **HZ treatment prescriptions**

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

131

132 **Analysis datasets used**

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

139

140 **Supplementary Table 5: Costs by Category, IC Status, Time period of Analysis**
 141 **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

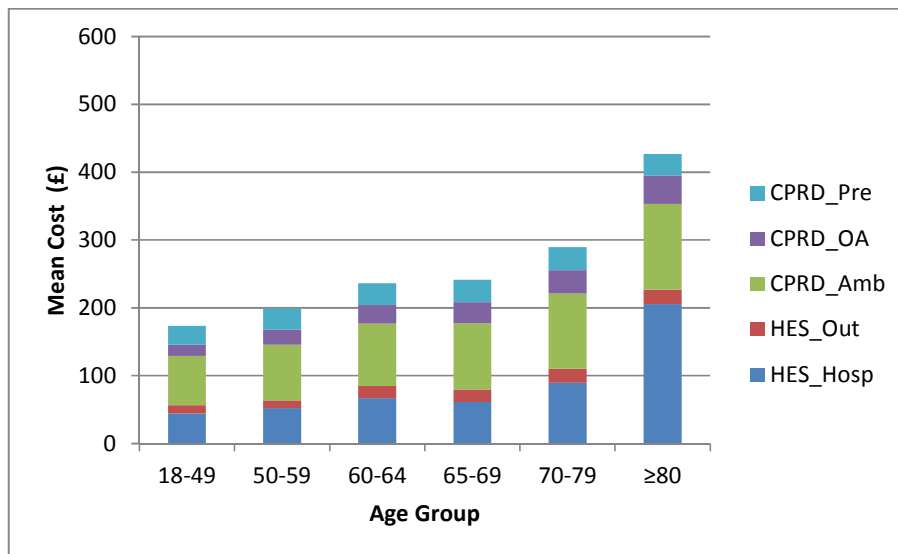
CPRD Prescriptions	28.7	33.3	37.3	38.1	42.2	40.8
Total	189.3	237.8	294.2	317.4	391.7	557.0
IC-Free Population (≤90 days)						
Hospitalizations	6.3	8.5	11.5	17.5	36.4	136.5
HES Outpatient consultations/visits	5.2	7.8	8.2	10.4	13.9	18.2
CPRD Ambulatory Visits	59	66.7	69.6	72.7	88.8	102.8
CPRD Other Ambulatory 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

1
2
3 142 HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years
4 143 of age
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

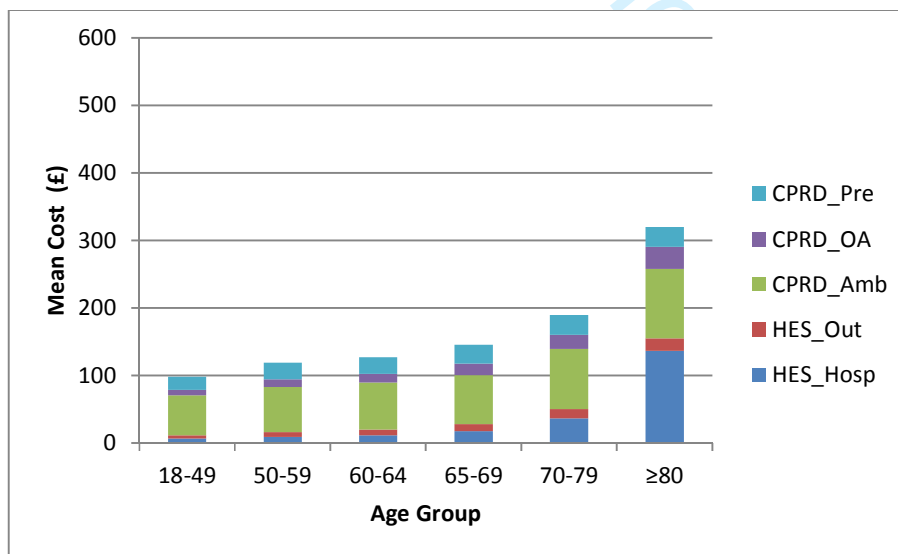
1
2
3 144 **Supplementary Figure 1: Healthcare costs for by HES-linked matched IC (Panel**
4
5 145 **A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 90 days**
6
7 146 **post initial HZ onset**
8
9

10 147 **Panel A**



148

149 **Panel B**



150

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

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

153

154 Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia;

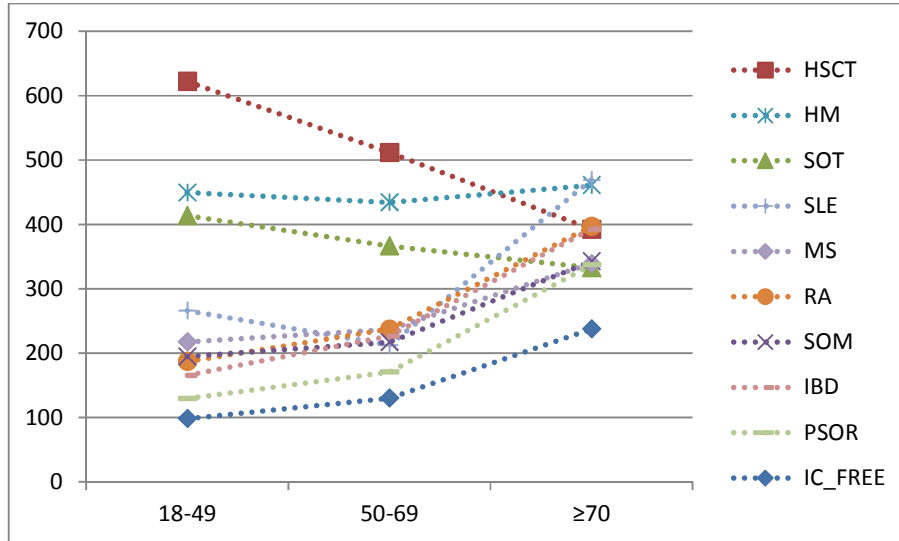
155 CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-OA, CPRD Other Ambulatory

1
2
3 156 Visits; CPRD-Amb, CPRD Ambulatory Visits; HES-Out, HES Outpatient consultation; HES-Hosp, HES Hospital
4 157 admission;
5 158
6 159
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

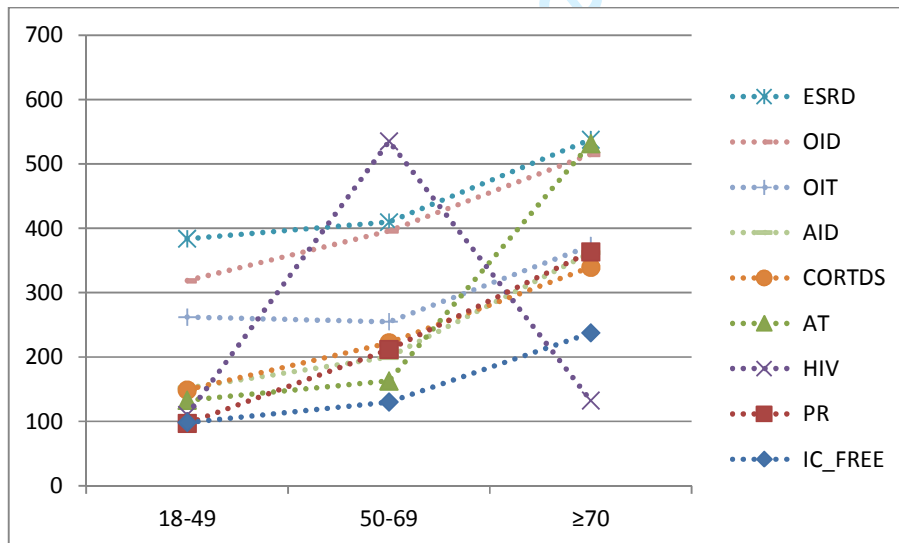
For peer review only

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

162 **Panel A**



164 **Panel B**



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

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

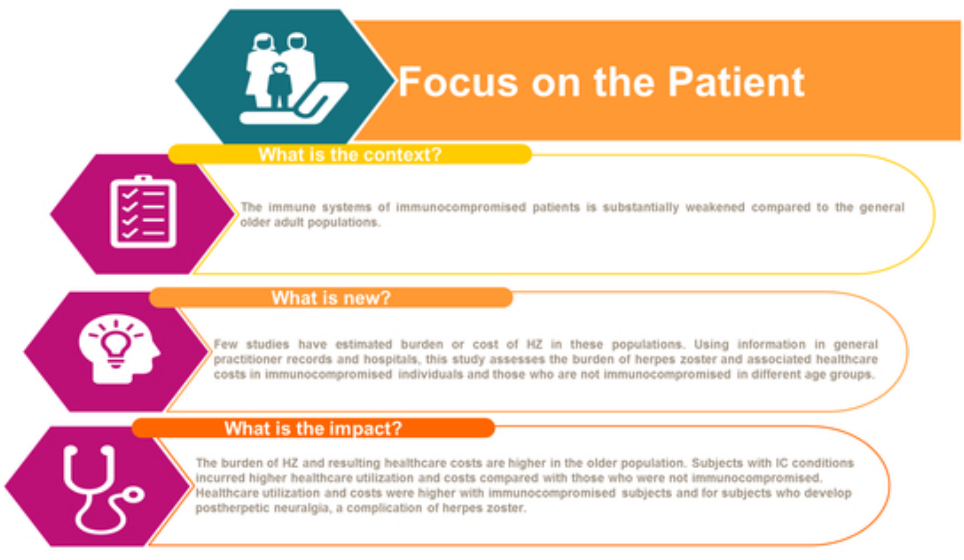
168

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

1
2
3 174 immunosuppressive therapy; AID, autoimmune diseases; CORTDS, corticosteroid exposure; AT,
4 175 autoimmune thyroiditis; HIV, human immunodeficiency virus; PR, polymyalgia rheumatica
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



47x26mm (300 x 300 DPI)

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 1 and 2,3 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Page 6
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	N/A

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Pages 9,10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023502.R1
Article Type:	Research
Date Submitted by the Author:	03-Dec-2018
Complete List of Authors:	Curran, Desmond; GlaxoSmithKline, Value Evidence Hunjan, Manjit; GlaxoSmithKline El Ghachi, Amale; Aixial France; Hoffmann-La Roche Ltd El-Hahi, Yassine; Valesta, Mechelen, Belgium c/o GSK; Accord Research Bianco, Veronique; GSK Vaccines, Research and Development Center Ferreira, Germano; P-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment

SCHOLARONE™
Manuscripts

1
2
3
4 **1 TITLE PAGE**

5
6 **2 HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN**
7
8 **3 IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN**
9
10 **4 OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS**

11
12
13
14 **5 Desmond Curran^a, Manjit Hunjan^b, Amale El Ghachi^c, Yassine El Hahi^d, Veronique**

15
16 **6 Bianco^e, Germano Ferreira^f**

17
18
19 **7 Affiliations**

20
21
22 ^aGSK, Wavre, Belgium; desmond.x.curran@gsk.com

23
24 ^bGSK, Uxbridge, United Kingdom; manjit.k.hunjan@gsk.com

25
26
27 ^cAIXIAL, Boulogne-Billancourt, France c/o GSK, Wavre, Belgium; current affiliation F.

28
29
30 Hoffmann-La Roche Ltd., Basel, Switzerland ; amale.el_ghachi@roche.com

31
32 ^dValesta, Mechelen, Belgium c/o GSK, Wavre, Belgium; current affiliation Accord Research

33
34 s.r.o., Prague, Czech Republic ; yassineelhahi@gmail.com

35
36
37 ^eGSK, Rockville, Maryland, United States; veronique.x.bianco@gsk.com

38
39 ^fP-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium; germano.ferreira@p-

40
41 [95.com](mailto:germano.ferreira@p-95.com)

42
43
44 **17 Corresponding author**

45
46
47 Desmond Curran

48
49 GSK, Avenue Fleming 20, 1300 Wavre, Belgium.

50
51 Email: desmond.x.curran@gsk.com

52
53
54 21

22 ABSTRACT

23 [[298/300 words]]

24 Objective

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

28 Methods

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

39 Results

40 The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% *versus*
41 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and
42 IC-free individuals aged ≥ 80 YOA, respectively). Similarly, HZ-related mean treatment costs per

1
2
3 43 subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49
4
5 44 YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged \geq 80 YOA,
6
7 45 respectively). Costs varied considerably by IC condition.
8
9
10

11 46 **Conclusions**

12
13
14 47 Individuals with IC conditions, not only have a higher risk of HZ than IC-free individuals, but also
15
16 48 incur higher HZ-related healthcare costs.
17
18
19
20
21

22 50 **Keywords**

23
24
25 51 Herpes zoster, post-herpetic neuralgia, immunocompromized, hospitalization, healthcare burden,
26
27 52 herpes zoster treatment.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

54 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

71

1
2
3 **72 LIST OF ABBREVIATIONS**
4

5 73 £, 2014 UK pound sterling
6

7 74 A&E, Accident and Emergency
8

9 75 AID, autoimmune diseases
10

11 76 ARDI, age-related decline in immunity
12

13 77 AT, Autoimmune Thyroiditis
14

15 78 BNF, British National Formulary
16

17 79 CPRD, Clinical Practice Research Datalink
18

19 80 GP, General Practitioner
20

21 81 HCRU, healthcare resource utilization
22

23 82 HES, Hospital Episode Statistics
24

25 83 HIV, human immunodeficiency virus
26

27 84 HM, hematological malignancies
28

29 85 HSCT, hematopoietic stem cell transplantation
30

31 86 HZ, herpes zoster
32

33 87 HZ-Comp, HZ and complications with no PHN
34

35 88 IC, immunocompromized
36

37 89 ICD-10, International Classification of Diseases-10th revision
38

39 90 ISAC, Independent Scientific Advisory Committee
40

41 91 PHN, post-herpetic neuralgia
42

43 92 PSSRU, Personal Social Services Research Unit
44

45 93 PY, person-years
46

47 94 RA, rheumatoid arthritis
48

49 95 SLE, systemic lupus erythematosus
50

51 96 SOT, solid organ transplantations
52
53
54
55
56
57
58
59
60

- 1
2
3 97 UK, United Kingdom
4
5 98 US, United States
6
7 99 VZV-CMI, varicella zoster virus cell-mediated immunity
8
9 100 YOA, years of age
10
11 101 ZVL, zoster vaccine live
12
13
14 102
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

103 INTRODUCTION

104 *[[2,819/4,000 words; 6/5 tables+figures but journal allows flexibility]]*

105 Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes
106 zoster (HZ)¹. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons
107 for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not
108 optimal in individuals with immunocompromized (IC) conditions and the age-specific incidence
109 and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human
110 immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune
111 disease, malignancy, or organ transplantation².

112 The incidence and severity of HZ is marked with an increase in people ≥ 50 years of age (YOA)
113 due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of
114 HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among
115 individuals aged ≥ 85 YOA³. Further to the impact of ARDI, a study by Forbes et al. in 2014
116 investigated the increased risk for HZ in the UK population, associated with autoimmune
117 conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic
118 conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney
119 disease, and asthma². In addition to the increased risk of HZ in the various IC conditions these
120 populations also experience increased severity of disease. In a study in Canada, Drolet et al.
121 reported that individuals with an impaired immune status had HZ severity of illness scores, as
122 measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with normal
123 immune function^{4,5}. In a study in the United States (US), Yawn et al. reported that although 8% of
124 HZ cases were in individuals who were immunocompromised, these individuals represented 23.8%

1
2
3 125 of the total HZ-related costs⁶. The increase in healthcare costs was associated with higher rates of
4
5 126 post-herpetic neuralgia (PHN) and non-pain complications in this group of individuals⁶.
6
7

8
9 127 This study aims to estimate the healthcare resource utilization of HZ in selected IC populations and
10
11 128 in an IC-free (i.e., immunocompetent) population aged ≥ 18 YOA in England. The clinical burden
12
13 129 of disease epidemiological results of the study are reported elsewhere⁷, and may be summarized as
14
15 130 follows: the prevalence of IC conditions increased from 7.6% in individuals aged 18-44 YOA to
16
17 131 42.2% in individuals aged ≥ 80 YOA; the incidence rate of HZ in the IC cohort was 3.5/1000 PY
18
19 132 in individuals aged 18-49 YOA increasing to 12.6/1000 PY in individuals aged ≥ 80 YOA. In this
20
21 133 manuscript, we focus on the healthcare resource utilization and costs associated with HZ in both
22
23 134 IC and IC-free populations.
24
25
26
27

28 135 **METHODS**

29
30 136 The study was conducted as an observational retrospective descriptive study (e-track number:
31
32 137 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥ 18 YOA). The IC
33
34 138 population included individuals who were registered in the Clinical Practice Research Datalink
35
36 139 (CPRD) from January 2000 to March 2012 with ≥ 12 -month follow-up before being diagnosed with
37
38 140 any of the selected 16 IC conditions (See Supplemental Material). The CPRD IC population cohort
39
40 141 linked to the Hospital Episode Statistics (HES) database was matched to a cohort of HES linked
41
42 142 IC-free population (N=621,588), by age, gender and practice location. Individuals with a missing
43
44 143 date of IC diagnosis were excluded from the study population. Clinical diagnoses were based on
45
46 144 READ codes used in CPRD and with the International Classifications of Diseases-10th revision
47
48 145 (ICD-10) codes in the HES database.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 146 The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for
4
5 147 the Medicines and Healthcare Products Regulatory Agency database research (ISAC protocol
6
7 148 number 14_222R). The study was conducted in accordance with all applicable regulatory
8
9
10 149 requirements, with the Guidelines for Good Pharmacoepidemiology Practices⁸, all applicable
11
12 150 patient privacy requirements and the guiding principles of the Declaration of Helsinki.

13
14
15 151 The matched IC and IC-free cohorts were followed up from the index date until the earliest of the
16
17 152 following events: transfer out of the practice date, the last GP practice collections date, death date
18
19 153 or the end of the study⁷. Healthcare resource data associated with an incident HZ episode during
20
21 154 the study follow-up were extracted for IC and Matched IC-free HES-linked individuals. Only
22
23 155 reported records (resource utilization) with available event dates during the individuals' eligibility
24
25 156 period and those that occurred 7 days before the initial HZ onset date, up to 365 days after the
26
27 157 initial HZ onset date, were extracted. Consequently, individuals who recorded the first PHN event
28
29 158 date after 365 days post HZ event date were classified as not having PHN.
30
31
32
33

34 35 159 **Patient and Public Involvement**

36
37
38 160 This is a retrospective database analysis carried out following ethical committee approval. No
39
40 161 patient or the public was involved in the study design or in the recruitment or the conduct of this
41
42 162 study. No specific dissemination of study results to participants was done. However, we provided
43
44 163 a lay language summary contextualizing the results and potential clinical research relevance and
45
46 164 impact in Figure 1.
47
48
49

50 51 165 **Data sources**

52
53 166 Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation, Clinical,
54
55 167 Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI dataset; (3)
56
57
58

1
2
3 168 HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource utilization
4
5 169 was defined as: HZ-treatment related prescribed medications (CPRD tbl:therapy); Consultations
6
7 170 and care provided by General Practitioners (GPs) or others in the GP practice
8
9
10 171 (CPRD tbl:consultations); HES secondary care outpatient visits (HES outpatient events); and HES
11
12 172 inpatient hospitalizations (HES inpatient events).

13
14
15 173 For each patient, healthcare costs stratified by subcategory of interest (HES Inpatient
16
17 174 Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other
18
19 175 Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by
20
21 176 their unit costs. These were then summed over all resource use categories to obtain a total cost for
22
23 177 each patient. Values were expressed in 2014 UK pound sterling (£).

24 25 26 27 28 178 **Healthcare resource costs**

29
30
31 179 For each patient, the cost of each prescription was calculated by merging the product code, package
32
33 180 type and prescribed quantity (prodcodetype-quantity) with the associated standard package
34
35 181 size and unit cost. The unit cost of a product in a prescription instance (i.e. one distinct record in
36
37 182 the CPRD therapy) was calculated using the cost described in the British National Formulary
38
39 183 (BNF), 2015 (as listed price if included or indicative price based on price in BNF).

40
41
42
43 184 Ambulatory visits included consultations with GPs and nurses in primary or community care. Visits
44
45 185 included consultations at the practice or at the home of the patient, during working hours and out
46
47 186 of hours. Consultations for which no clinical intervention was recorded were not included in the
48
49 187 cost estimate for GP practice related healthcare utilization, for example: information technology
50
51 188 data migration, administrative recording of received information. Administrative resource use in
52
53 189 primary care was considered, including time on the phone, writing reports, referrals, etc. A referral
54
55
56
57
58

1
2
3 190 to secondary care noted in a patient's record, *per se*, was not allocated the cost of the secondary
4
5 191 care appointment. The most conservative option for the cost per unit as included in the Personal
6
7 192 Social Services Research Unit (PSSRU) Costs of Health and Social Care, 2014 were applied e.g.
8
9
10 193 GP consultation costs excluded qualification, direct staff care and travel costs⁹. Where specific
11
12 194 costs for 2013/14 were not available, 2012/13 costs, were adjusted by applying the Hospital and
13
14 195 Community Health Services inflation index⁹. Administration costs were based on unit costs as
15
16
17 196 stated in the PSSRU, 2014.

18
19
20 197 Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient resource
21
22 198 utilization concerned HZ related referrals for non-inpatient hospital consultations, derived from the
23
24 199 HES Outpatient data. Additionally, visits to the Accident and Emergency (A&E) department in
25
26
27 200 hospitals were also recorded and costed. Inpatient hospitalization costs were based on the average
28
29 201 cost per episode using HES data for 2013/14 (calculated from the total average payment by result
30
31 202 spell cost and the average number of episodes per spell). Hospital outpatient costs were sourced
32
33
34 203 from National Tariff costs (2014) for specific consultant led outpatient consultations; conservative
35
36 204 costs were allocated i.e. wherever applicable costs for first attendance by a single professional
37
38 205 appointment were used¹⁰. Costs allocated to A&E visits were based on the cost of a category 3
39
40 206 investigation with category 1-3 treatment¹⁰. Only events related to HZ were costed out. Resources
41
42
43 207 related to HZ complications were considered using ICD-10 Code B020.

44
45
46 208 No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in CPRD.
47
48 209 Further details, including information on the IC populations included, ICD-10 codes for HZ and
49
50 210 PHN, and unit healthcare costs are provided in the Supplementary Material, specifically in
51
52
53 211 Supplementary Tables 1 to 4.

212 RESULTS

213 The HES-linked matched IC and IC-free population cohorts (n=621,588 each) included
214 approximately 44% males and 56% females with a mean age of approximately 56 years. The age
215 distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA
216 (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥ 80 YOA (11.01%).

217 The proportion of inpatient hospital admissions by age group for the HES-linked Matched IC and
218 IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel A) or
219 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 2. Hospital
220 admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset (Panel
221 B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The
222 percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus*
223 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and
224 IC-free individuals aged ≥ 80 YOA, respectively). Multiple HZ-related hospital visits were reported
225 for some individuals. As such, Table 1 presents the mean number of healthcare resources utilized
226 by IC Status, Age Group and Analysis period. The mean number of hospitalizations per HZ case
227 for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free individuals aged 18-49 YOA,
228 respectively and 0.173 and 0.115 in IC and IC-free individuals aged ≥ 80 YOA, respectively. A
229 similar pattern of higher healthcare resource utilization with increasing age and in IC individuals
230 was observed for all resources for which costs were assigned. A similar mean number of sick leave
231 certificates were observed between the IC and the IC-free cohorts with the mean decreasing with
232 age. Nursing home care / admissions were only recorded for individuals aged ≥ 70 YOA in CPRD.
233 Figure 3 and Table 2 present the overall healthcare costs by HES-linked matched IC cohort and
234 age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs increase

1
2
3 235 with age and are consistently higher in the IC cohort compared with the IC-free cohort. Although
4
5 236 the absolute cost difference between IC and IC-free individuals increases with age from £85.5 in
6
7 237 individuals aged 18-49 YOA to £156.1 in individuals aged ≥ 80 YOA the relative difference is
8
9
10 238 higher in younger individuals (i.e. 75.8%-99.2% in <70 YOA) compared with older individuals
11
12 239 (i.e. 38.9%-57.6% in ≥ 70 YOA). It is also noteworthy that the means are consistently higher than
13
14 240 medians, and as is common for healthcare cost data, the distribution is skewed to the right.
15
16
17 241 Supplementary Table 5 and Supplementary Figures 1 and 2 provide additional data on healthcare
18
19 242 Costs for the analysis period 7 days prior to 90 days post initial HZ onset.

20
21
22 243 Figure 4 presents the overall healthcare costs by each IC condition in the HES-linked matched IC
23
24 244 and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ
25
26
27 245 onset. For all IC conditions, the costs were higher than those for the IC-free group, in particular for
28
29 246 the hematopoietic stem cell transplantation (HSCT), hematological malignancies (HM) and solid
30
31 247 organ transplantations (SOT) conditions. In general, there was a similar trend of increasing costs
32
33
34 248 with increasing age-groups. A few outliers were observed due to small sample sizes. For example,
35
36 249 only 3 and 8 individuals aged ≥ 70 YOA were included in the HIV and HSCT groups, respectively.
37
38
39 250 Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis (AT) and SOT were
40
41 251 included, respectively.

42
43
44 252 Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean
45
46 253 healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis
47
48 254 period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean healthcare
49
50
51 255 costs were approximately 2 to 4 times higher for individuals with HZ complications compared to
52
53 256 individuals with HZ only.
54
55
56
57
58
59
60

1
2
3 257 Supplementary Table 6 presents the non-HZ related hospital inpatient stay for the period 7 days to
4
5 258 365 days post initial-HZ onset. The mean number of non-HZ related hospitalizations were
6
7 259 consistently higher in IC patients compared to and IC-free patients and increased with age.
9
10
11 260

14 261 **DISCUSSION**

16 262 In this study, we presented the healthcare resource utilization and costs associated with HZ in both
17
18 263 IC and IC-free populations using large electronic health record databases in the UK. An important
19
20 264 feature of this study was that the design enabled the calculation of IC condition prevalence rates,
21
22 265 HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level
23
24 266 in the same pre-defined population(s), see Yanni et. al. for further detail on epidemiological
25
26 267 outcomes⁷. In this study, every effort was made to include only resources directly related to HZ.
27
28 268 For example, only hospitalized patients were included who had an ICD-10 HZ diagnosis identified
29
30 269 in the HES database. Similarly, only medications potentially related to HZ treatment were included
31
32 270 (see Supplementary Material Tables 2 and 4). HZ-related mean treatment costs per patient were
33
34 271 higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA,
35
36 272 respectively increasing to £557 *versus* £401 in IC and IC-free individuals aged ≥ 80 YOA,
37
38 273 respectively).
39
40
41
42
43
44

45 274 Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the
46
47 275 mean healthcare costs per HZ patient, from an National Health Services perspective, of £85.6 and
48
49 276 £400.9 in individuals aged <65 YOA and ≥ 65 YOA, respectively¹¹. A later UK study that used the
50
51 277 HES and the health improvement network databases, estimated the mean cost of treating a HZ
52
53 278 patient to be £65.5 in the first month of diagnosis, with patients aged ≥ 70 YOA having a mean cost
54
55
56
57
58
59
60

1
2
3 279 of £83 in the first month and £15.80 in months 2 and 3¹². The costs of treating individuals with
4
5 280 PHN were much higher, i.e. mean cost per patient was estimated to be £921 in all individuals and
6
7 281 £909.60 in individuals aged ≥ 70 YOA¹². Another study evaluated mean healthcare costs (excluding
8
9 282 hospitalization costs) to be £75.63 per HZ patient with mean direct costs for treating PHN episodes
10
11 283 (PHN pain occurring or persisting for 3 months) of £340.04¹³. These values augmented with
12
13 284 hospitalization costs were used as inputs in a cost-effectiveness model evaluating a HZ vaccine
14
15 285 using the population of England and Wales³. The costs estimated by van Hoek et al. are consistent
16
17 286 with the values estimated in our study for IC-free individuals by age group³.

18
19
20
21
22 287 In a previous study, mean prescription costs per HZ patient were reported to be £40.52¹³. In our
23
24 288 study, the mean prescription costs per HZ patient ranged from £19.7 to £40.8 depending on the age
25
26 289 group, IC status and analysis period included. Our study aimed to include only medications
27
28 290 considered to be directly related to HZ; i.e. excluded medications that may be linked to IC
29
30 291 conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from other
31
32 292 conditions). This restriction and the introduction of generic versions of medications such as
33
34 293 acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed
35
36 294 to the reduced overall medication costs reported in this study.

37
38
39
40
41 295 Many studies on HCRU and costs include a number of days prior to diagnosis, e.g. 14 or 21 days,
42
43 296 as there may be a delay in diagnosis and HCRU may be utilized prior to diagnosis^{6,14}. In this
44
45 297 analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days post HZ
46
47 298 onset, although it is recognized that HZ episodes can last for longer. The costs of PHN were
48
49 299 analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days prior to
50
51 300 365 days post HZ onset. The rationale for the time periods studied was that using analysis period
52
53 301 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2 only could
54
55
56
57
58
59
60

1
2
3 302 overestimate these costs. The most frequently used definition of PHN is: pain persisting or
4
5 303 appearing at least 90 days following rash onset. The median duration of PHN has been reported to
6
7 304 be 10.3 and 12.9 months in individuals aged ≤ 69 and ≥ 70 YOA respectively¹⁵, and is likely to be
8
9 305 longer in individuals who are immunocompromised⁵.

10
11
12
13 306 The healthcare costs associated with PHN and complications were higher than those for individuals
14
15 307 with HZ only. However, as reported elsewhere, when considering the overall cost of disease at a
16
17 308 population level, the overall healthcare-associated cost is higher for HZ only¹⁶. This is primarily a
18
19 309 result of the higher incidence rates of HZ only.

20
21
22
23 310 Few studies have investigated healthcare resource utilization and costs in IC individuals. Schroder
24
25 311 et al. carried out a study using the German Pharmacoepidemiological Research Database, which
26
27 312 consists of claims data from four statutory health insurances¹⁷. They reported that during the quarter
28
29 313 of the HZ diagnosis or during the two following quarters, 10% of all HZ patients with an IC
30
31 314 condition were hospitalized (with a HZ diagnosis), whereas among IC-free HZ patients, 4.2% were
32
33 315 hospitalized. White et al. reported that in their study using the US Market Scan Research Database,
34
35 316 direct medical costs were nearly twice as high in IC patients compared with IC-free patients¹⁸. Li
36
37 317 et al. carried out a study using the US Truven Health MarketScan Commercial and Medicare
38
39 318 Supplemental Insurance databases¹⁹. They concluded that patients with the studied IC conditions
40
41 319 (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer) had significantly higher
42
43 320 healthcare utilization and cost when developing HZ than their comparable matches without HZ.
44
45 321 Insurance databases include not only the healthcare resource utilization but also costs. In the CPRD
46
47 322 and HES Databases only the resource utilization is captured. As such the overall costs need to be
48
49 323 calculated by assigning unit costs to the resource utilization. There are advantages however of using
50
51 324 the CPRD and HES in that the databases offer more diversity than might be observed using
52
53
54
55
56
57
58
59
60

1
2
3 325 insurance databases, the latter of which may be somewhat limited by bias associated with factors
4
5 326 such as age, race, and income.
6
7

8
9 327 This study has several limitations. Diagnoses were derived from administrative codes, which are
10
11 328 recognized to be subject to miscoding or under-coding and are not validated against medical charts.
12
13 329 Increasing healthcare resource utilization and cost is likely to be related to increased severity of IC
14
15 330 conditions. In a study, Schroder et al. categorized individuals as low IC and high IC¹⁷. However,
16
17 331 insufficient details are recorded in the CPRD and HES databases to allow adequate definition of
18
19 332 patients' severity of immunosuppression e.g. laboratory parameters, immunosuppressive
20
21 333 medication details such as chemotherapy. In addition, many IC individuals had prescriptions that
22
23 334 included more than one immunosuppressing medicine.
24
25
26
27

28 335 **CONCLUSION**

29
30 336 In conclusion, individuals with IC conditions, seeking healthcare in the UK, incurred higher
31
32 337 healthcare utilization and costs than IC-free individuals^{6,7,14}. The results from this study could be
33
34 338 used in economic analyses to evaluate the value of vaccination in reducing the burden of HZ in
35
36 339 these populations.
37
38
39

40
41 340
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

341 **AUTHOR CONTRIBUTIONS**

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

351 **ACKNOWLEDGEMENTS**

352 The authors would like to thank Emmanuelle Espié, Yanni Emad, Morgane Guinnec, François
353 Haguinet for their contribution to the study. They would also like to thank the Business & Decision
354 Life Sciences platform for editorial assistance and coordination, on behalf of GSK. Gregory Collet
355 coordinated manuscript development and editorial support. Kathleen Daly provided editing
356 support. This study is based in part on data from the Clinical Practice Research Datalink obtained
357 under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the
358 interpretation and conclusions contained in this report are those of the authors alone.

359 **CONFLICTS OF INTEREST**

360 VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the
361 GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the GSK
362 group of companies between 2012 and Feb 2015, during which the study was designed and
363 implemented. Later, as an employee of P-95 epidemiology and pharmacovigilance, GF provided

1
2
3 364 contracted consultancy services to the GSK group of companies for this and other GSK-sponsored
4
5 365 studies. P-95 provides contracted services to the GSK group of companies, beyond the scope of
6
7
8 366 this study.
9

10 11 367 **DATA SHARING STATEMENT**

12
13 368 All data used in this study are presented in the manuscript, references to the original material are
14
15 369 provided. Please contact the corresponding author shall you require any additional information
16
17

18 19 370 **ETHICAL APPROVAL**

20
21 371 Approval was obtained from the Clinical Practice Research Datalink Independent Scientific
22
23 372 Advisory Committee (14_222R).
24
25

26 27 373 **FUNDING**

28
29 374 GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK study
30
31 375 identifier: e-track number: 201615) activities and overall data management (collection, analysis
32
33 376 and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated with the
34
35 377 development and the publishing of the present manuscript. All authors had full access to the data
36
37
38 378 and the corresponding author was responsible for submission of the publication.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 379 **REFERENCES**
4

- 5 380 1. Oxman M. Zoster vaccine: current status and future prospects. Clin Infect Dis 2010;**51**(2):197-
6
7 381 213.
8
9
10
11 382 2. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster:
12
13 383 population based case-control study. BMJ 2014;**348**:g2911.
14
15
16 384 3. van Hoek AJ, Gay N, Melegaro A. Estimating the cost-effectiveness of vaccination against
17
18 385 herpes zoster in England and Wales. Vaccine 2009;**27**:1454-67.
19
20
21
22 386 4. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due
23
24 387 to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain
25
26 388 inventory. J Pain 2004;**5**(6):344-56.
27
28
29
30 389 5. Drolet M, Brisson M, Schmader K, et al. Predictors of postherpetic neuralgia among patients
31
32 390 with herpes zoster: a prospective study. J Pain 2010;**11**(11):1211-21.
33
34
35
36 391 6. Yawn BP, Itzler RF, Wollan PC, et al. Health care utilization and cost burden of herpes zoster
37
38 392 in a community population. Mayo Clin Proc 2009;**84**(9):787-94.
39
40
41 393 7. Yanni E, Ferreira G, El Hahi Y, et al. The burden of herpes zoster in 16 selected
42
43 394 immunocompromised populations in England: a cohort study in the Clinical Practice Research
44
45 395 Datalink 2000-2012. BMJ Open 2018;**8**:e020528.
46
47
48
49 396 8. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology
50
51 397 Practices (GPP). Secondary Guidelines for Good Pharmacoepidemiology Practices (GPP) 2015.
52
53 398 https://www.pharmacoepi.org/resources/guidelines_08027.cfm.
54
55
56
57
58
59
60

- 1
2
3 399 9. Curtis LPSSRU. Unit costs of Health & Social Care 2014. Secondary Unit costs of Health &
4
5 400 Social Care 2014 2014. <http://www.pssru.ac.uk/project-pages/unit-costs/2014/>.
6
7
8
9 401 10. National Tariff Payment System. Annex 5A National Prices. Secondary Annex 5A National
10
11 402 Prices 2014/2015. [https://www.gov.uk/government/publications/national-tariff-payment-system-](https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015)
12
13 403 [2014-to-2015](https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015).
14
15
16 404 11. Scott FT, Johnson RW, Leedham-Green M, et al. The burden of Herpes Zoster: a prospective
17
18 405 population based study. *Vaccine* 2006;**24**(9):1308-14.
19
20
21
22 406 12. Taieb V, Schwarzbard J, Butt T, et al. The Epidemiological and Cost Burden of Herpes
23
24 407 Zoster (Hz) and Post-Herpetic Neuralgia (Phn) in the UK. *Value Health* 2015;**18**(7):A589.
25
26
27
28 408 13. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-
29
30 409 herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;**137**(1):38-47.
31
32
33 410 14. Li A, Chen SY, Burstin SJ, et al. Cost of Herpes Zoster in Patients With Selected Immune-
34
35 411 Compromised Conditions in the United States. *Open Forum Infect Dis* 2016;**3**(2):ofw067.
36
37
38
39 412 15. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the
40
41 413 prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost Eff Resour Alloc*
42
43 414 2010;**8**:7.
44
45
46
47 415 16. Gater A, Uhart M, McCool R, et al. The humanistic, economic and societal burden of herpes
48
49 416 zoster in Europe: a critical review. *BMC Public Health* 2015;**15**:193.
50
51
52
53 417 17. Schröder C, Enders D, Schink T, et al. Incidence of herpes zoster amongst adults varies by
54
55 418 severity of immunosuppression. *J Infect* 2017;**S0163-4453**(17):30228-1.
56
57
58
59
60

1
2
3 419 18. White RR, Lenhart G, Singhal PK, et al. Incremental 1-Year Medical Resource Utilization
4
5 420 and Costs for Patients with Herpes Zoster from a Set of US Health Plans. *Pharmacoeconomics*
6
7 421 2009;27(9):781-92.
8
9

10
11 422
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

423 **TABLES**424 **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

1					
2					
3	60-64	0.545	0.885	0.251	0.360
4					
5	65-69	0.607	1.064	0.330	0.454
6					
7	70-79	0.686	1.251	0.417	0.722
8					
9	≥80	0.860	1.616	0.668	1.183
10					
11	CPRD Prescriptions (All treatments)				
12	18-49	1.247	1.363	0.890	0.931
13					
14	50-59	1.670	1.994	1.143	1.227
15					
16	60-64	1.969	2.602	1.379	1.489
17					
18	65-69	2.129	2.894	1.473	1.717
19					
20	70-79	2.310	3.295	1.814	2.347
21					
22	≥80	2.405	3.743	1.844	2.575
23					
24	CPRD Referrals*				
25	18-49	0.018	0.020	0.011	0.012
26					
27	50-59	0.021	0.026	0.018	0.022
28					
29	60-64	0.031	0.040	0.020	0.024
30					
31	65-69	0.031	0.044	0.015	0.023
32					
33	70-79	0.033	0.054	0.031	0.047
34					
35	≥80	0.040	0.065	0.029	0.048
36					
37	CPRD Sick leave*				
38	18-49	0.162	0.175	0.155	0.161
39					
40	50-59	0.156	0.178	0.173	0.182
41					
42	60-64	0.060	0.069	0.080	0.087
43					
44	65-69	0.017	0.017	0.008	0.008
45					
46	70-79	0.001	0.001	0.002	0.003
47					
48	≥80	0.000	0.000	0.000	0.000
49					
50	CPRD Nursing home care/admission*				
51	18-69	0.000	0.000	0.000	0.000
52					
53	70-79	0.001	0.001	0.001	0.001
54					
55					
56					
57					
58					
59					
60					

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

≥80	0.004	0.004	0.003	0.003
-----	-------	-------	-------	-------

425
426
427
428
429
430

* 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.

For peer review only

431 **Table 2: Mean cost (£) of healthcare resource utilization by IC status, age group and**
 432 **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

433

434 * post initial HZ onset

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

436 Deviation

437

438 **Table 3: Mean cost (£) of healthcare resource utilization by IC status, age group, analysis**
 439 **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

440

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

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

443 [†] Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset

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

445 Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ, herpes zoster; PHN, post-herpetic neuralgia; HZ-Comp,

446 HZ and complications with no PHN; YOA: years of age

447

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

448 **FIGURE**

449 **Figure 1: Lay Language Summary**

For peer review only

1
2
3 450 **Figure 2: Inpatient Hospital Admission by HES-linked Matched IC or IC-free cohort over**
4
5 451 **the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to**
6
7 452 **365 days post initial HZ onset (Panel B)**
8
9

10 453
11
12
13 454 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
14
15 455 For HZ individuals with PHN: data from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A)
16 456 and 365 days (Panel B).
17 457 Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, post-herpetic neuralgia
18
19 458
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **459 Figure 3 : Healthcare Costs for by HES-linked Matched IC (Panel A) and IC-free cohort**
4
5 **460 (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset**
6
7

8 461
9
10
11 462 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
12
13 463 For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
14 464 Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-
15 465 OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits; HES, Hospital Episode Statistics; HES-Out, HES
16 466 Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic
17 467 neuralgia.
18
19 468
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 469 **Figure 4 : Healthcare Costs for each IC condition in the HES-linked Matched IC and IC-**
4
5 470 **free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ**
6
7
8 471 **onset**
9

10 472
11
12
13 473 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
14 474 For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
15
16 475 Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid
17 476 exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM,
18 477 hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel
19 478 syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, post-herpetic neuralgia; RA, rheumatoid arthritis; SLE,
20 479 systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID, other
21 480 immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica.
22
23
24 481

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60




Focus on the Patient

What is the context?




The immune systems of immunocompromised patients is substantially weakened compared to the general older adult population.

What is new?



Few studies have estimated burden or cost of herpes zoster in immunocompromised patients. By using information in general practitioner records and hospital databases, this study assesses the burden of herpes zoster and associated healthcare costs in immunocompromised patients and those who are not immunocompromised in different age groups.

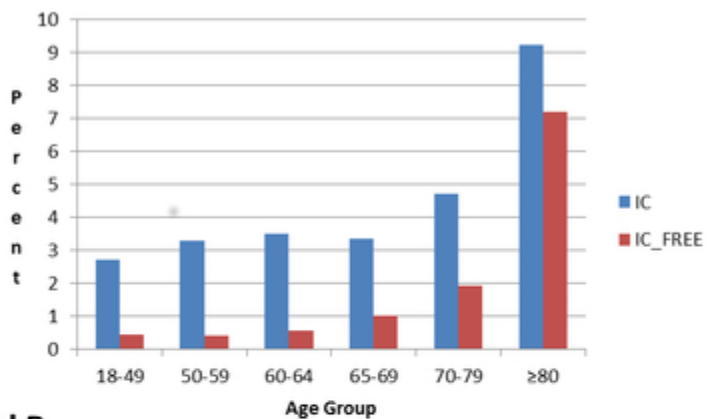
What is the impact?



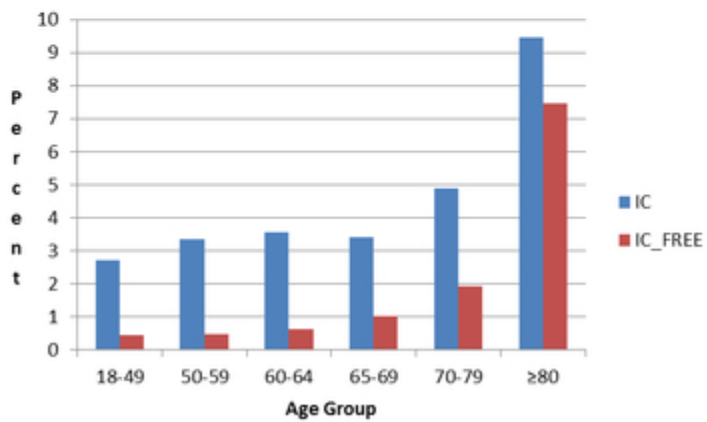
The burden of herpes zoster and resulting healthcare costs are higher in the older population. Immunocompromised patients incurred higher healthcare utilisation and costs compared with those who were not immunocompromised. Finally, postherpetic neuralgia, a complication of herpes zoster, further increased healthcare utilisation and costs.

81x45mm (300 x 300 DPI)

Panel A



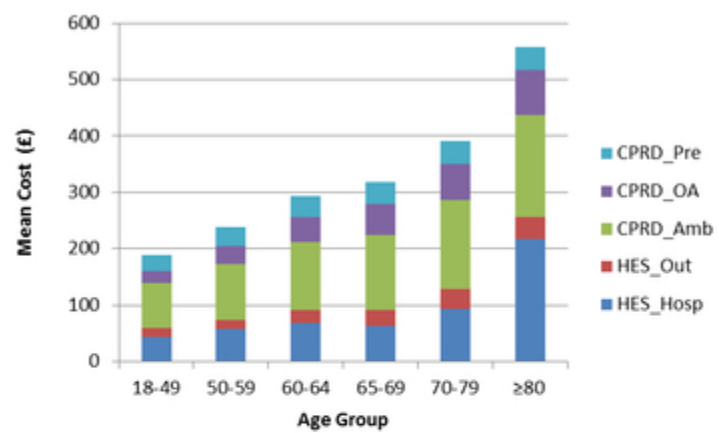
Panel B



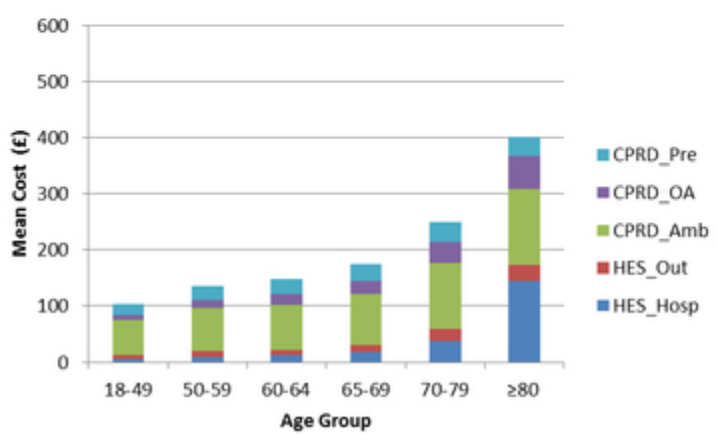
34x41mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Panel A

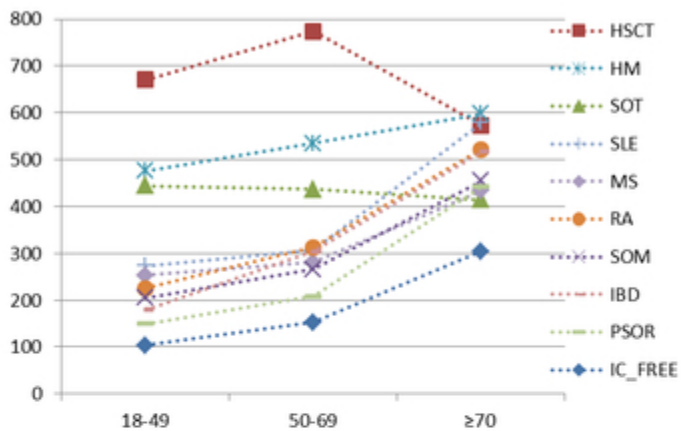


Panel B

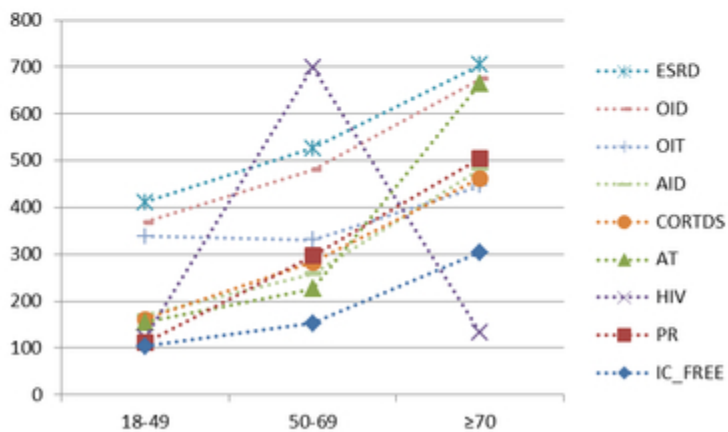


34x45mm (300 x 300 DPI)

Panel A



Panel B



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);

1
2
3 The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days
4 after HZ event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).
5
6

7 Additionally, main categories of resource utilization and cost tables were presented for the
8 following sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days
9 and 365 days post-initial HZ onset date:
10
11

- 12 • HZ only (i.e. no PHN and no HZ-related complication);
- 13
- 14 • HZ and PHN within 1 year of HZ event;
- 15
- 16 • HZ and other HZ-related complications but no PHN (overall and by complications
17 sub-categories):
 - 18 ○ Neurological;
 - 19
 - 20 ○ Ocular;
 - 21
 - 22 ○ Cutaneous;
 - 23
 - 24 ○ Other complications.
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31

32 A detailed mapping linking the exact event definition variables and criteria to the reference
33 unit cost was used. The unit costs for each type of resource were obtained from the following
34 reference sources:
35
36

- 37 • General practitioner (GP) prescribed medication costs: British National Formulary
38 (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the
39 prescription costs for each drug (prodcode) of interest. A detailed mapping was used
40 to link the exact cost of prodcode quantity and packtype for each drug;
41
42
- 43 • Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L,
44 Personal Social Services Research Unit. Unit costs of Health & Social Care 2014.
45 University of Kent, 2014);
46
- 47 • HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs
48 (National Schedule of Reference Costs, 2013/2014).
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

	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 Procodes 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

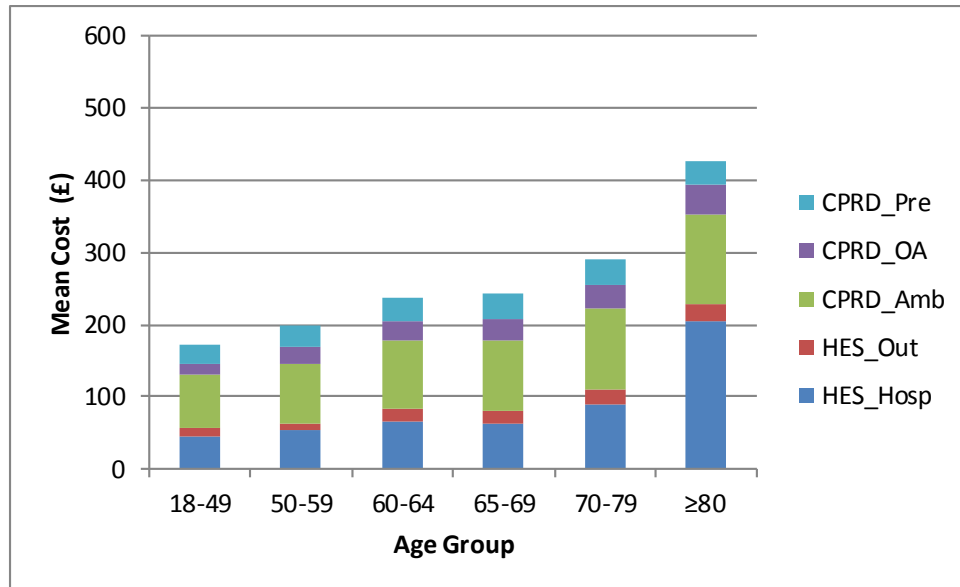
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
IC Population (≤90 days)						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD ambulatory visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD other ambulatory visits	16.1	22	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

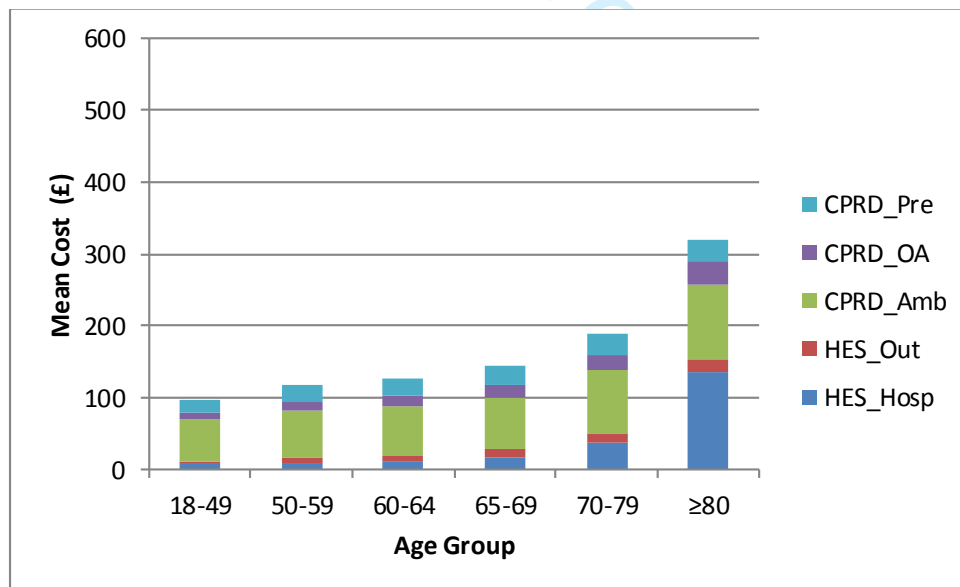
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

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



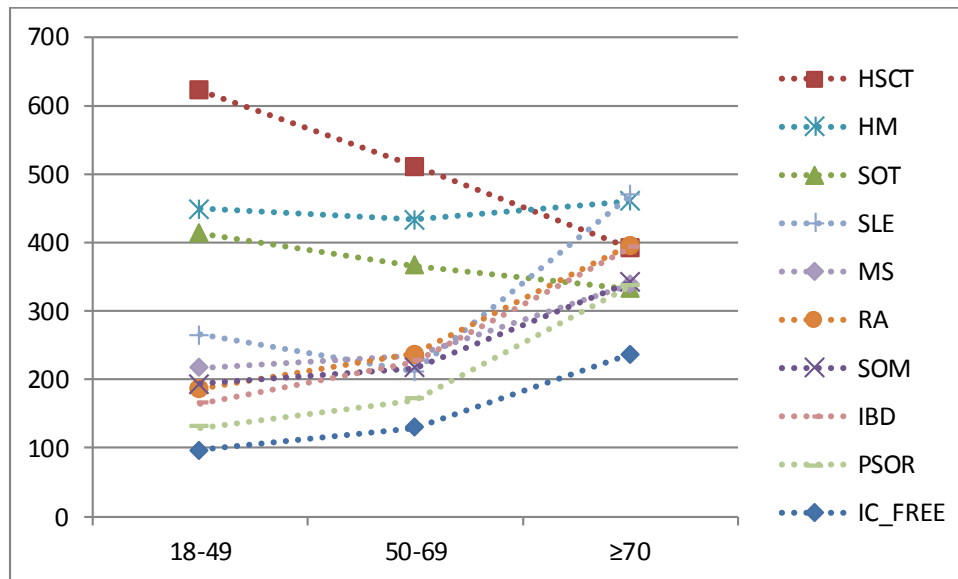
For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;

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

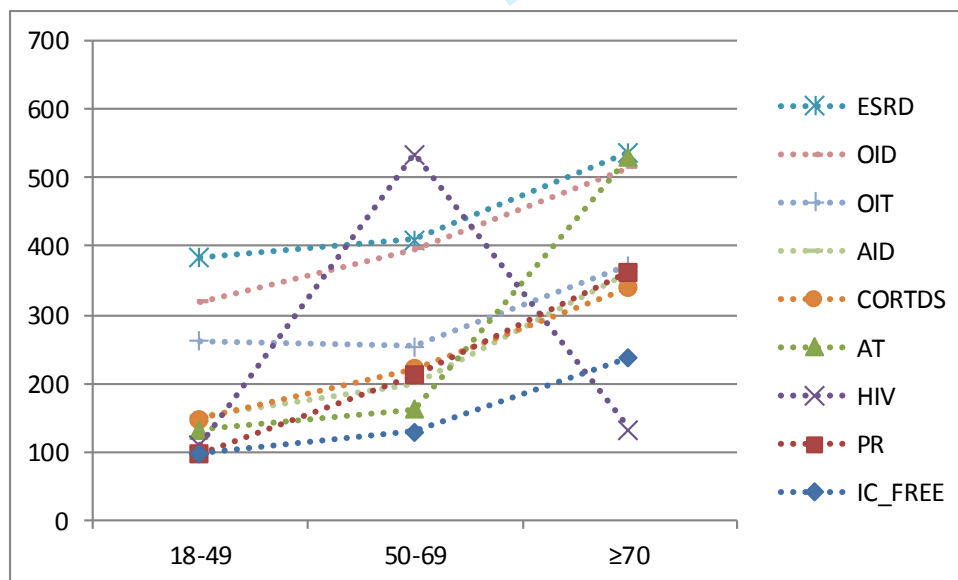
Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; CPRD, Clinical Practice Research Datalink; CPRD_Pre, CPRD Prescriptions; CPRD_OA, CPRD Other Ambulatory Visits; CPRD_Amb, CPRD Ambulatory Visits; HES_Out, HES Outpatient consultation; 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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 1 and 2,3 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Page 6
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	N/A

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Pages 9,10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023502.R2
Article Type:	Research
Date Submitted by the Author:	24-Jun-2019
Complete List of Authors:	Curran, Desmond; GlaxoSmithKline, Value Evidence Hunjan, Manjit; GlaxoSmithKline El Ghachi, Amale; Aixial France; Hoffmann-La Roche Ltd El-Hahi, Yassine; Valesta, Mechelen, Belgium c/o GSK; Accord Research Bianco, Veronique; GSK Vaccines, Research and Development Center Ferreira, Germano; P-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Herpes zoster, postherpetic neuralgia, immunocompromized, hospitalization, healthcare burden, herpes zoster treatment

SCHOLARONE™
Manuscripts

1
2
3
4 **1 TITLE PAGE**

5
6 **2 HERPES ZOSTER RELATED HEALTHCARE BURDEN AND COSTS IN**
7
8 **3 IMMUNOCOMPROMISED (IC) AND IC-FREE POPULATIONS IN ENGLAND: AN**
9
10 **4 OBSERVATIONAL RETROSPECTIVE DATABASE ANALYSIS**

11
12
13
14 **5 Desmond Curran^a, Manjit Hunjan^b, Amale El Ghachi^c, Yassine El Hahi^d, Veronique**
15
16 **6 Bianco^e, Germano Ferreira^f**

17
18
19 **7 Affiliations**

20
21
22 ^aGSK, Wavre, Belgium; desmond.x.curran@gsk.com

23
24 ^bGSK, Uxbridge, United Kingdom; manjit.k.hunjan@gsk.com

25
26
27 ^cAIXIAL, Boulogne-Billancourt, France c/o GSK, Wavre, Belgium; current affiliation F.

28
29
30 Hoffmann-La Roche Ltd., Basel, Switzerland ; amale.el_ghachi@roche.com

31
32 ^dValesta, Mechelen, Belgium c/o GSK, Wavre, Belgium; current affiliation Accord Research

33
34 s.r.o., Prague, Czech Republic ; yassineelhahi@gmail.com

35
36 ^eGSK, Rockville, Maryland, United States; veronique.x.bianco@gsk.com

37
38 ^fP-95 Epidemiology and pharmacovigilance services, Heverlee, Belgium; germano.ferreira@p-
39
40
41 95.com

42
43
44 **17 Corresponding author**

45
46
47 Desmond Curran

48
49 GSK, Avenue Fleming 20, 1300 Wavre, Belgium.

50
51
52 Email: desmond.x.curran@gsk.com

53
54
55
56
57
58
59
60

22 ABSTRACT

23 Objective

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

27 Methods

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

38 Results

39 The percentage of HZ cases requiring hospitalization was higher in IC individuals (2.7% *versus*
40 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and
41 IC-free individuals aged ≥ 80 YOA, respectively). Similarly, HZ-related mean treatment costs per
42 subject were higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49

1
2
3 43 YOA, respectively and £557 *versus* £401 in IC and IC-free individuals aged ≥ 80 YOA,
4
5 44 respectively). Costs varied considerably by IC condition.
6
7

8 45 **Conclusions**

9
10
11 46 Individuals with IC conditions, have a high burden of HZ, associated with an increased risk of HZ
12
13 and high HZ-related healthcare costs.
14
15
16 48

17 18 19 49 **Keywords**

20
21
22 50 Herpes zoster, post-herpetic neuralgia, immunocompromized, hospitalization, healthcare burden,
23
24 51 herpes zoster treatment.
25
26
27 52

53 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

1
2
3 **71 LIST OF ABBREVIATIONS**
4

5 72 £, 2014 UK pound sterling
6

7 73 A&E, Accident and Emergency
8

9 74 AID, autoimmune diseases
10

11 75 ARDI, age-related decline in immunity
12

13 76 AT, Autoimmune Thyroiditis
14

15 77 BNF, British National Formulary
16

17 78 CPRD, Clinical Practice Research Datalink
18

19 79 GP, General Practitioner
20

21 80 HCRU, healthcare resource utilization
22

23 81 HES, Hospital Episode Statistics
24

25 82 HIV, human immunodeficiency virus
26

27 83 HM, hematological malignancies
28

29 84 HSCT, hematopoietic stem cell transplantation
30

31 85 HZ, herpes zoster
32

33 86 HZ-Comp, HZ and complications with no PHN
34

35 87 IC, immunocompromized
36

37 88 ICD-10, International Classification of Diseases-10th revision
38

39 89 ISAC, Independent Scientific Advisory Committee
40

41 90 PHN, post-herpetic neuralgia
42

43 91 PSSRU, Personal Social Services Research Unit
44

45 92 PY, person-years
46

47 93 RA, rheumatoid arthritis
48

49 94 SLE, systemic lupus erythematosus
50

51 95 SOT, solid organ transplantations
52
53
54
55
56
57
58
59
60

- 1
2
3 96 UK, United Kingdom
4
5 97 US, United States
6
7 98 VZV-CMI, varicella zoster virus cell-mediated immunity
8
9 99 YOA, years of age
10
11
12 100 ZVL, zoster vaccine live
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

101 INTRODUCTION

102 Varicella zoster virus cell-mediated immunity (VZV-CMI) inhibits the development of herpes
103 zoster (HZ)¹. Therefore, if for any reason VZV-CMI declines, the risk of HZ increases. Reasons
104 for VZV-CMI decline can include, increasing age and immune suppression. VZV-CMI is not
105 optimal in individuals with immunocompromised (IC) conditions and the age-specific incidence
106 and severity of HZ greatly increases in IC patients due to underlying illness (e.g. human
107 immunodeficiency virus [HIV] infection) or immunosuppressive therapies for autoimmune
108 disease, malignancy, or organ transplantation².

109 The incidence and severity of HZ is marked with an increase in people ≥ 50 years of age (YOA)
110 due to an age-related decline in immunity (ARDI). In the United Kingdom (UK) the incidence of
111 HZ rises from 7.1 per 1000 person-years (PY) among 60-64 year olds to 12.2 per 1000 PY among
112 individuals aged ≥ 85 YOA³. Further to the impact of ARDI, a study by Forbes et al. in 2014
113 investigated the increased risk for HZ in the UK population, associated with autoimmune
114 conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); and chronic
115 conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney
116 disease, and asthma². In addition to the increased risk of HZ in the various IC conditions these
117 populations also experience increased severity of disease. In a study in Canada, Drolet et al.
118 reported that individuals with an impaired immune status had HZ severity of illness scores, as
119 measured by the Zoster Brief Pain Inventory, which were twice as high as individuals with normal
120 immune function^{4,5}. In a study in the United States (US), Yawn et al. reported that although 8% of
121 HZ cases were in individuals who were immunocompromised, these individuals represented 23.8%
122 of the total HZ-related costs⁶. The increase in healthcare costs was associated with higher rates of
123 post-herpetic neuralgia (PHN) and non-pain complications in this group of individuals⁶.

1
2
3 124 This study aims to estimate the healthcare resource utilization of HZ in selected IC populations and
4
5 125 in an IC-free (i.e., immunocompetent) population aged ≥ 18 YOA in England. The clinical burden
6
7 126 of disease epidemiological results of the study are reported elsewhere⁷, and may be summarized as
8
9
10 127 follows: the prevalence of IC conditions increased from 7.6% in individuals aged 18-44 YOA to
11
12 128 42.2% in individuals aged ≥ 80 YOA; the incidence rate of HZ in the IC cohort was 3.5/1000 PY
13
14 129 in individuals aged 18-49 YOA increasing to 12.6/1000 PY in individuals aged ≥ 80 YOA. In this
15
16 130 manuscript, we focus on the healthcare resource utilization and costs associated with HZ in both
17
18 131 IC and IC-free populations.

132 **METHODS**

133 The study was conducted as an observational retrospective descriptive study (e-track number:
134 201615), in a cohort of eligible matched IC and IC-free populations (aged ≥ 18 YOA). The IC
135 population included individuals who were registered in the Clinical Practice Research Datalink
136 (CPRD) from January 2000 to March 2012 with ≥ 12 -month follow-up before being diagnosed with
137 any of the selected 16 IC conditions (See Supplemental Material). The CPRD IC population cohort
138 was linked to the Hospital Episode Statistics (HES) database and matched, using a 1:1 ratio, to a
139 cohort of CPRD-HES linked IC-free population (N=621,588), by age, gender and practice
140 location⁸. Individuals with a missing date of IC diagnosis were excluded from the study population.
141 Clinical diagnoses were based on READ codes used in CPRD and with the International
142 Classifications of Diseases-10th revision (ICD-10) codes in the HES database.

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

1
2
3 146 requirements, with the Guidelines for Good Pharmacoepidemiology Practices⁹, all applicable
4
5 147 patient privacy requirements and the guiding principles of the Declaration of Helsinki.
6
7

8
9 148 The matched IC and IC-free cohorts were followed up from the index date until the earliest of the
10
11 149 following events: transfer out of the practice date, the last GP practice collections date, death date
12
13 150 or the end of the study⁷. Healthcare resource data associated with an incident HZ episode during
14
15 151 the study follow-up were extracted for IC and matched IC-free CPRD-HES-linked individuals.
16
17 152 Only reported records (resource utilization) with available event dates during the individuals'
18
19 153 eligibility period and those that occurred 7 days before the initial HZ onset date, up to 365 days
20
21 154 after the initial HZ onset date, were extracted. Consequently, individuals who recorded the first
22
23 155 PHN event date after 365 days post HZ event date were classified as not having PHN.
24
25
26
27

28 156 **Patient and Public Involvement**

29
30
31 157 This is a retrospective database analysis carried out following ethical committee approval. No
32
33 158 patient or the public was involved in the study design or in the recruitment or the conduct of this
34
35 159 study. No specific dissemination of study results to participants was done. However, we provided
36
37 160 a lay language summary contextualizing the results and potential clinical research relevance and
38
39 161 impact in Figure 1.
40
41
42
43

44 162 **Data sources**

45
46 163 Data were extracted from the following sources: (1) CPRD GOLD 2014Q3: Consultation, Clinical,
47
48 164 Therapy and Referral datasets; (2) HES Inpatient 2013Q3: HES_DIAGNOSIS_EPI dataset; (3)
49
50 165 HES Outpatient data (Set 9): Appointment and clinical datasets. Healthcare resource utilization
51
52 166 was defined as: HZ-treatment related prescribed medications; Consultations and care provided by
53
54
55
56
57
58
59
60

1
2
3 167 General Practitioners (GPs) or others in the GP practice); HES secondary care outpatient visits
4
5 168 (HES outpatient events); and HES inpatient hospitalizations (HES inpatient events).
6
7

8
9 169 For each patient, healthcare costs stratified by subcategory of interest (HES Inpatient
10
11 170 Hospitalizations; HES Outpatient consultations/visits; CPRD Ambulatory Visits; CPRD Other
12
13 171 Ambulatory Visits; CPRD Prescriptions) were computed by multiplying units of resource use by
14
15 172 their unit costs. These were then summed over all resource use categories to obtain a total cost for
16
17 173 each patient. Values were expressed in 2014 UK pound sterling (£).
18
19

20 21 174 **Healthcare resource costs** 22

23
24 175 For each patient, the cost of each prescription was calculated by merging the product code, package
25
26 176 type and prescribed quantity with the associated standard package size and unit cost. The unit cost
27
28 177 of a product in a prescription instance (i.e. one distinct record in the CPRD therapy) was calculated
29
30 178 using the cost described in the British National Formulary (BNF), 2015 (as listed price if included
31
32 179 or indicative price based on price in BNF).
33
34
35

36
37 180 Ambulatory visits included consultations with GPs and nurses in primary or community care. Visits
38
39 181 included consultations at the practice or at the home of the patient, during working hours and out
40
41 182 of hours. Consultations for which no clinical intervention was recorded were not included in the
42
43 183 cost estimate for GP practice related healthcare utilization, for example: information technology
44
45 184 data migration, administrative recording of received information. Administrative resource use in
46
47 185 primary care was considered, including time on the phone, writing reports, referrals, etc. A referral
48
49 186 to secondary care noted in a patient's record, *per se*, was not allocated the cost of the secondary
50
51 187 care appointment. The most conservative option for the cost per unit as included in the Personal
52
53 188 Social Services Research Unit (PSSRU) Costs of Health and Social Care, 2014 were applied e.g.
54
55
56
57
58
59
60

1
2
3 189 GP consultation costs excluded qualification, direct staff care and travel costs¹⁰. Where specific
4
5 190 costs for 2013/14 were not available, 2012/13 costs, were adjusted by applying the Hospital and
6
7 191 Community Health Services inflation index¹⁰. Administration costs were based on unit costs as
8
9
10 192 stated in the PSSRU, 2014.
11
12

13 193 Inpatient hospitalizations related to HZ were derived from HES data. Hospital Outpatient resource
14
15 194 utilization concerned HZ related referrals for non-inpatient hospital consultations, derived from the
16
17 195 HES Outpatient data. Additionally, visits to the Accident and Emergency (A&E) department in
18
19 196 hospitals were also recorded and costed. Inpatient hospitalization costs were based on the average
20
21 197 cost per episode using HES data for 2013/14 (calculated from the total average payment by result
22
23 198 spell cost and the average number of episodes per spell). Hospital outpatient costs were sourced
24
25 199 from National Tariff costs (2014) for specific consultant led outpatient consultations; conservative
26
27 200 costs were allocated i.e. wherever applicable costs for first attendance by a single professional
28
29 201 appointment were used¹¹. Costs allocated to A&E visits were based on the cost of a category 3
30
31 202 investigation with category 1-3 treatment¹¹. Only events related to HZ were costed out. Resources
32
33 203 related to HZ complications were considered using ICD-10 Code B020.
34
35
36
37
38

39 204 No costs were assigned to Referrals, Sick leave or Nursing home care/admission entries in CPRD.
40
41 205 Further details, including information on the IC populations included, ICD-10 codes for HZ and
42
43 206 PHN, and unit healthcare costs are provided in the Supplementary Material, specifically in
44
45 207 Supplementary Tables 1 to 4.
46
47
48
49

50 208 **RESULTS**

51
52 209 The CPRD-HES-linked matched IC and IC-free population cohorts (n=621,588 each) included
53
54 210 approximately 44% males and 56% females with a mean age of approximately 56 years. The age
55
56
57
58
59
60

1
2
3 211 distribution of matched cohorts was: 18-44 YOA (28.8%), 45-49 YOA (7.1%), 50-59 YOA
4
5 212 (17.2%), 60-64 YOA (9.9%), 65-69 YOA (9.4%), 70-79 YOA (16.6%), and ≥ 80 YOA (11.01%).
6
7

8
9 213 The proportion of inpatient hospital admissions by age group for the CPRD-HES-linked matched
10
11 214 IC and IC-free cohorts over the time periods of 7 days prior to 90 days post initial HZ onset (Panel
12
13 215 A) or 7 days prior to 365 days post initial HZ onset (Panel B) are presented in Figure 2. Hospital
14
15 216 admissions over the longer follow-up period of 7 days prior to 365 days post initial HZ onset (Panel
16
17 217 B) were similar to those of the shorter follow-up period (Panel A) over all age groups. The
18
19 218 percentage of HZ cases hospitalized were higher in IC individuals (e.g. in Panel B 2.7% *versus*
20
21 219 0.4% in IC and IC-free individuals aged 18-49 YOA, respectively and 9.5% *versus* 7.5% in IC and
22
23 220 IC-free individuals aged ≥ 80 YOA, respectively). Multiple HZ-related hospital visits were reported
24
25 221 for some individuals. As such, Table 1 presents the mean number of healthcare resources utilized
26
27 222 by IC Status, Age Group and Analysis period. The mean number of hospitalizations per HZ case
28
29 223 for the 365-day analysis was, 0.035 and 0.005 in IC and IC-free individuals aged 18-49 YOA,
30
31 224 respectively and 0.173 and 0.115 in IC and IC-free individuals aged ≥ 80 YOA, respectively. A
32
33 225 similar pattern of higher healthcare resource utilization with increasing age and in IC individuals
34
35 226 was observed for all resources for which costs were assigned. A similar mean number of sick leave
36
37 227 certificates were observed between the IC and the IC-free cohorts with the mean decreasing with
38
39 228 age. Nursing home care / admissions were only recorded for individuals aged ≥ 70 YOA in CPRD.
40
41
42
43
44
45

46 229 Figure 3 and Table 2 present the overall healthcare costs by CPRD-HES-linked matched IC cohort
47
48 230 and age group for the analysis period 7 days prior to 365 days post initial HZ onset. The costs
49
50 231 increase with age and are consistently higher in the IC cohort compared with the IC-free cohort.
51
52 232 Although the absolute cost difference between IC and IC-free individuals increases with age from
53
54 233 £85.5 in individuals aged 18-49 YOA to £156.1 in individuals aged ≥ 80 YOA the relative
55
56
57
58
59
60

1
2
3 234 difference is higher in younger individuals (i.e. 75.8%-99.2% in <70 YOA) compared with older
4
5 235 individuals (i.e. 38.9%-57.6% in ≥ 70 YOA). It is also noteworthy that the means are consistently
6
7 236 higher than medians, and as is common for healthcare cost data, the distribution is skewed to the
8
9
10 237 right. Supplementary Table 5 and Supplementary Figures 1 and 2 provide additional data on
11
12 238 healthcare Costs for the analysis period 7 days prior to 90 days post initial HZ onset.
13
14

15 239 Figure 4 presents the overall healthcare costs by each IC condition in the CPRD-HES-linked
16
17 240 matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post
18
19 241 initial HZ onset. For all IC conditions, the costs were higher than those for the IC-free group, in
20
21 242 particular for the hematopoietic stem cell transplantation (HSCT), hematological malignancies
22
23 243 (HM) and solid organ transplantations (SOT) conditions. In general, there was a similar trend of
24
25 244 increasing costs with increasing age-groups. A few outliers were observed due to small sample
26
27 245 sizes. For example, only 3 and 8 individuals aged ≥ 70 YOA were included in the HIV and HSCT
28
29 246 groups, respectively. Similarly, in total only 207 and 271 individuals with autoimmune thyroiditis
30
31 247 (AT) and SOT were included, respectively.
32
33
34
35
36

37 248 Table 3 presents the mean healthcare costs by IC status and HZ complication status. The mean
38
39 249 healthcare costs were approximately 4 to 5 times higher for individuals with PHN for the analysis
40
41 250 period 7 days prior to 365 days compared to individuals with HZ only. Similarly, mean healthcare
42
43 251 costs were approximately 2 to 4 times higher for individuals with HZ complications compared to
44
45 252 individuals with HZ only.
46
47
48
49

50 253 Supplementary Table 6 presents the non-HZ related hospital inpatient stay for the period 7 days to
51
52 254 365 days post initial-HZ onset. The mean number of non-HZ related hospitalizations were
53
54 255 consistently higher in IC patients compared to and IC-free patients and increased with age.
55
56
57
58
59
60

1
2
3 256
4
56 257 **DISCUSSION**

8 258 In this study, we presented the healthcare resource utilization and costs associated with HZ in both
9
10 259 IC and IC-free populations using large electronic health record databases in the UK. An important
11
12 260 feature of this study was that the design enabled the calculation of IC condition prevalence rates,
13
14 261 HZ incidence rates and occurrence of HZ-related healthcare utilization and costs at individual level
15
16 262 in the same pre-defined population(s), see Yanni et. al. for further detail on epidemiological
17
18 263 outcomes⁷. In this study, every effort was made to include only resources directly related to HZ.
19
20 264 For example, only hospitalized patients were included who had an ICD-10 HZ diagnosis identified
21
22 265 in the HES database. Similarly, only medications potentially related to HZ treatment were included
23
24 266 (see Supplementary Material Tables 2 and 4). HZ-related mean treatment costs per patient were
25
26 267 higher in IC individuals (£189 *versus* £104 in IC and IC-free individuals aged 18-49 YOA,
27
28 268 respectively increasing to £557 *versus* £401 in IC and IC-free individuals aged ≥ 80 YOA,
29
30 269 respectively).

31
32
33
34
35
36
37 270 Previous studies of healthcare costs of HZ in the UK, included a small study, which estimated the
38
39 271 mean healthcare costs per HZ patient, from a National Health Services perspective, of £85.6 and
40
41 272 £400.9 in individuals aged < 65 YOA and ≥ 65 YOA, respectively¹². A later UK study that used the
42
43 273 HES and the health improvement network databases, estimated the mean cost of treating a HZ
44
45 274 patient to be £65.5 in the first month of diagnosis, with patients aged ≥ 70 YOA having a mean cost
46
47 275 of £83 in the first month and £15.80 in months 2 and 3¹³. The costs of treating individuals with
48
49 276 PHN were much higher, i.e. mean cost per patient was estimated to be £921 in all individuals and
50
51 277 £909.60 in individuals aged ≥ 70 YOA¹³. Another study evaluated mean healthcare costs (excluding
52
53 278 hospitalization costs) to be £75.63 per HZ patient with mean direct costs for treating PHN episodes
54
55
56
57
58
59
60

1
2
3 279 (PHN pain occurring or persisting for 3 months) of £340.04¹⁴. These values augmented with
4
5 280 hospitalization costs were used as inputs in a cost-effectiveness model evaluating a HZ vaccine
6
7
8 281 using the population of England and Wales³. The costs estimated by van Hoek et al. are consistent
9
10 282 with the values estimated in our study for IC-free individuals by age group³.

11
12
13 283 In a previous study, mean prescription costs per HZ patient were reported to be £40.52¹⁴. In our
14
15 284 study, the mean prescription costs per HZ patient ranged from £19.7 to £40.8 depending on the age
16
17 285 group, IC status and analysis period included. Our study aimed to include only medications
18
19 286 considered to be directly related to HZ; i.e. excluded medications that may be linked to IC
20
21 287 conditions (e.g. aspirin, analgesic creams as they could be used primarily to reduce pain from other
22
23 288 conditions). This restriction and the introduction of generic versions of medications such as
24
25 289 acyclovir, gabapentin (and derivatives of gabapentin) which resulted in lower prices, contributed
26
27 290 to the reduced overall medication costs reported in this study.
28
29
30
31

32
33 291 Many studies on HCRU and costs include a number of days prior to diagnosis, e.g. 14 or 21 days,
34
35 292 as there may be a delay in diagnosis and HCRU may be utilized prior to diagnosis^{6,15}. In this
36
37 293 analysis, costs of HZ only cases were assessed during the period 7 days prior to 30 days post HZ
38
39 294 onset, although it is recognized that HZ episodes can last for longer. The costs of PHN were
40
41 295 analyzed over 2 time-periods, i.e. (1) 7 days prior to 90 days post HZ onset and (2) 7 days prior to
42
43 296 365 days post HZ onset. The rationale for the time periods studied was that using analysis period
44
45 297 1 alone could lead to an underestimation of PHN costs whereas using analysis period 2 only could
46
47 298 overestimate these costs. The most frequently used definition of PHN is: pain persisting or
48
49 299 appearing at least 90 days following rash onset. The median duration of PHN has been reported to
50
51 300 be 10.3 and 12.9 months in individuals aged ≤ 69 and ≥ 70 YOA respectively¹⁶, and is likely to be
52
53 301 longer in individuals who are immunocompromised⁵.
54
55
56
57
58
59
60

1
2
3 302 The healthcare costs associated with PHN and complications were higher than those for individuals
4
5 303 with HZ only. However, as reported elsewhere, when considering the overall cost of disease at a
6
7 304 population level, the overall healthcare-associated cost is higher for HZ only¹⁷. This is primarily a
8
9 305 result of the higher incidence rates of HZ only.

10
11
12
13 306 Few studies have investigated healthcare resource utilization and costs in IC individuals. Schroder
14
15 307 et al. carried out a study using the German Pharmacoepidemiological Research Database, which
16
17 308 consists of claims data from four statutory health insurances¹⁸. They reported that during the quarter
18
19 309 of the HZ diagnosis or during the two following quarters, 10% of all HZ patients with an IC
20
21 310 condition were hospitalized (with a HZ diagnosis), whereas among IC-free HZ patients, 4.2% were
22
23 311 hospitalized. White et al. reported that in their study using the US Market Scan Research Database,
24
25 312 direct medical costs were nearly twice as high in IC patients compared with IC-free patients¹⁹. Li
26
27 313 et al. carried out a study using the US Truven Health MarketScan Commercial and Medicare
28
29 314 Supplemental Insurance databases¹⁵. They concluded that patients with the studied IC conditions
30
31 315 (i.e. HIV, SOT, bone marrow or stem cell transplant, and cancer) had significantly higher
32
33 316 healthcare utilization and cost when developing HZ than their comparable matches without HZ.
34
35 317 Insurance databases include not only the healthcare resource utilization but also costs. In the CPRD
36
37 318 and HES Databases only the resource utilization is captured. As such the overall costs need to be
38
39 319 calculated by assigning unit costs to the resource utilization. There are advantages however of using
40
41 320 the CPRD and HES in that the databases offer more diversity than might be observed using
42
43 321 insurance databases, the latter of which may be somewhat limited by bias associated with factors
44
45 322 such as age, race, and income. A strength of the CPRD database is that it is considered to be broadly
46
47 323 representative of the characteristics of patients and GP practices in the UK^{20,21}.

1
2
3 324 This study has several limitations. Diagnoses were derived from administrative codes, which are
4
5 325 recognized to be subject to miscoding or under-coding and are not validated against medical
6
7 326 charts²². Increasing healthcare resource utilization and cost is likely to be related to increased
8
9
10 327 severity of IC conditions. In a study, Schroder et al. categorized individuals as low IC and high
11
12 328 IC¹⁸. However, insufficient details are recorded in the CPRD and HES databases to allow adequate
13
14 329 definition of patients' severity of immunosuppression e.g. laboratory parameters,
15
16 330 immunosuppressive medication details such as chemotherapy. In addition, many IC individuals
17
18
19 331 had prescriptions that included more than one immunosuppressing medicine. In this study we
20
21 332 selected 16 IC conditions in our definition of an IC population but perhaps other researchers would
22
23
24 333 select different IC conditions. As such our study is exploratory in nature and was not intended to
25
26 334 be definitive.

27
28
29 335
30
31 336 **CONCLUSION**
32
33 337 Immunosuppression is known to be associated with an increased risk of HZ in the UK^{2,7}. In this
34
35 338 descriptive analysis, involving a large representative national data source, the results suggest that
36
37 339 individuals with IC conditions were associated with higher HZ related healthcare utilization and
38
39
40 340 costs than IC-free individuals^{6,7,15}. The results from this study could be used in economic analyses
41
42 341 to evaluate the value of vaccination in reducing the burden of HZ in these populations.
43
44
45

46 342
47
48
49
50
51
52
53
54
55
56
57
58
59
60

343 **AUTHOR CONTRIBUTIONS**

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

353 **ACKNOWLEDGEMENTS**

354 The authors would like to thank Emmanuelle Espié, Yanni Emad, Morgane Guinnec, François
355 Haguinet for their contribution to the study. They would also like to thank the Business & Decision
356 Life Sciences platform for editorial assistance and coordination, on behalf of GSK. Gregory Collet
357 coordinated manuscript development and editorial support. Kathleen Daly provided editing
358 support. This study is based in part on data from the Clinical Practice Research Datalink obtained
359 under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the
360 interpretation and conclusions contained in this report are those of the authors alone.

361 **CONFLICTS OF INTEREST**

362 VB, MH and DC are employees of the GSK group of companies. DC and MH hold shares in the
363 GSK group of companies. AEG and YEH have nothing to disclose. GF was employed by the GSK
364 group of companies between 2012 and Feb 2015, during which the study was designed and
365 implemented. Later, as an employee of P-95 epidemiology and pharmacovigilance, GF provided

1
2
3 366 contracted consultancy services to the GSK group of companies for this and other GSK-sponsored
4
5 367 studies. P-95 provides contracted services to the GSK group of companies, beyond the scope of
6
7
8 368 this study.
9

10 11 369 **DATA SHARING STATEMENT**

12
13 370 All data used in this study are presented in the manuscript, references to the original material are
14
15 371 provided. Please contact the corresponding author shall you require any additional information
16
17

18 19 372 **ETHICAL APPROVAL**

20
21 373 Approval was obtained from the Clinical Practice Research Datalink Independent Scientific
22
23 374 Advisory Committee (14_222R).
24
25

26 27 375 **FUNDING**

28
29 376 GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK study
30
31 377 identifier: e-track number: 201615) activities and overall data management (collection, analysis
32
33 378 and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated with the
34
35 379 development and the publishing of the present manuscript. All authors had full access to the data
36
37 380 and the corresponding author was responsible for submission of the publication.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 381 **REFERENCES**
4

- 5 382 1. Oxman M. Zoster vaccine: current status and future prospects. *Clin Infect Dis* 2010;51(2):197-
6
7 383 213.
8
9
10
11 384 2. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster:
12
13 385 population based case-control study. *BMJ* 2014;348:g2911.
14
15
16 386 3. van Hoek AJ, Gay N, Melegaro A. Estimating the cost-effectiveness of vaccination against
17
18 387 herpes zoster in England and Wales. *Vaccine* 2009;27:1454-67.
19
20
21
22 388 4. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due
23
24 389 to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain
25
26 390 inventory. *J Pain* 2004;5(6):344-56.
27
28
29
30 391 5. Drolet M, Brisson M, Schmader K, et al. Predictors of postherpetic neuralgia among patients
31
32 392 with herpes zoster: a prospective study. *J Pain* 2010;11(11):1211-21.
33
34
35
36 393 6. Yawn BP, Itzler RF, Wollan PC, et al. Health care utilization and cost burden of herpes zoster
37
38 394 in a community population. *Mayo Clin Proc* 2009;84(9):787-94.
39
40
41 395 7. Yanni E, Ferreira G, El Hahi Y, et al. The burden of herpes zoster in 16 selected
42
43 396 immunocompromised populations in England: a cohort study in the Clinical Practice Research
44
45 397 Datalink 2000-2012. *BMJ Open* 2018;8:e020528.
46
47
48
49 398 8. Brazauskas R and Logan BR, Observational Studies: Matching or Regression? *Biol Blood*
50
51 399 *Marrow Transplant* 2016;22(3):557-563.
52
53
54
55
56
57
58
59
60

- 1
2
3 400 9. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology
4
5 401 Practices (GPP). Secondary Guidelines for Good Pharmacoepidemiology Practices (GPP) 2015.
6
7 402 https://www.pharmacoepi.org/resources/guidelines_08027.cfm.
8
9
10
11 403 10. Curtis LPSSRU. Unit costs of Health & Social Care 2014. Secondary Unit costs of Health &
12
13 404 Social Care 2014 2014. <http://www.pssru.ac.uk/project-pages/unit-costs/2014/>.
14
15
16 405 11. National Tariff Payment System. Annex 5A National Prices. Secondary Annex 5A National
17
18 406 Prices 2014/2015. [https://www.gov.uk/government/publications/national-tariff-payment-system-](https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015)
19
20 407 2014-to-2015.
21
22
23
24 408 12. Scott FT, Johnson RW, Leedham-Green M, et al. The burden of Herpes Zoster: a prospective
25
26 409 population based study. *Vaccine* 2006;24(9):1308-14.
27
28
29
30 410 13. Taieb V, Schwarzbard J, Butt T, et al. The Epidemiological and Cost Burden of Herpes
31
32 411 Zoster (Hz) and Post-Herpetic Neuralgia (Phn) in the UK. *Value Health* 2015;18(7):A589.
33
34
35
36 412 14. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-
37
38 413 herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;137(1):38-47.
39
40
41 414 15. Li A, Chen SY, Burstin SJ, et al. Cost of Herpes Zoster in Patients With Selected Immune-
42
43 415 Compromised Conditions in the United States. *Open Forum Infect Dis* 2016;3(2):ofw067.
44
45
46
47 416 16. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the
48
49 417 prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost Eff Resour Alloc*
50
51 418 2010;8:7.
52
53
54
55
56
57
58
59
60

- 1
2
3 419 17. Gater A, Uhart M, McCool R, et al. The humanistic, economic and societal burden of herpes
4
5 420 zoster in Europe: a critical review. *BMC Public Health* 2015;15:193.
6
7
8 421 18. Schröder C, Enders D, Schink T, et al. Incidence of herpes zoster amongst adults varies by
9
10 422 severity of immunosuppression. *J Infect* 2017;S0163-4453(17):30228-1.
11
12
13
14 423 19. White RR, Lenhart G, Singhal PK, et al. Incremental 1-Year Medical Resource Utilization
15
16 424 and Costs for Patients with Herpes Zoster from a Set of US Health Plans. *Pharmacoeconomics*
17
18 425 2009;27(9):781-92.
19
20
21
22 426 20. Campbell J, Dedman DJ, Eaton SC, et al. Is the CPRD GOLD population comparable to the
23
24 427 U.K. population? *Pharmacoepidemiol Drug Saf* 2013;22:280.
25
26
27
28 428 21. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice
29
30 429 Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827-36.
31
32
33 430 22. Pierik JG, Gumbs PD, Fortanier SA, et al. Epidemiological characteristics and societal burden
34
35 431 of varicella zoster virus in the Netherlands. *BMC Infect Dis* 2012;12:110.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

432 **TABLES**433 **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

1					
2					
3	60-64	0.545	0.885	0.251	0.360
4					
5	65-69	0.607	1.064	0.330	0.454
6					
7	70-79	0.686	1.251	0.417	0.722
8					
9	≥80	0.860	1.616	0.668	1.183
10					
11	CPRD Prescriptions (All treatments)				
12	18-49	1.247	1.363	0.890	0.931
13					
14	50-59	1.670	1.994	1.143	1.227
15					
16	60-64	1.969	2.602	1.379	1.489
17					
18	65-69	2.129	2.894	1.473	1.717
19					
20	70-79	2.310	3.295	1.814	2.347
21					
22	≥80	2.405	3.743	1.844	2.575
23					
24	CPRD Referrals*				
25	18-49	0.018	0.020	0.011	0.012
26					
27	50-59	0.021	0.026	0.018	0.022
28					
29	60-64	0.031	0.040	0.020	0.024
30					
31	65-69	0.031	0.044	0.015	0.023
32					
33	70-79	0.033	0.054	0.031	0.047
34					
35	≥80	0.040	0.065	0.029	0.048
36					
37	CPRD Sick leave*				
38	18-49	0.162	0.175	0.155	0.161
39					
40	50-59	0.156	0.178	0.173	0.182
41					
42	60-64	0.060	0.069	0.080	0.087
43					
44	65-69	0.017	0.017	0.008	0.008
45					
46	70-79	0.001	0.001	0.002	0.003
47					
48	≥80	0.000	0.000	0.000	0.000
49					
50	CPRD Nursing home care/admission*				
51	18-69	0.000	0.000	0.000	0.000
52					
53	70-79	0.001	0.001	0.001	0.001
54					
55					
56					
57					
58					
59					
60					

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

≥80	0.004	0.004	0.003	0.003
-----	-------	-------	-------	-------

434
435
436
437
438
439

* 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.

For peer review only

440 **Table 2: Mean cost (£) of healthcare resource utilization by IC status, age group and**
 441 **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

442
 443 * post initial HZ onset

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

445

446 **Table 3: Mean cost (£) of healthcare resource utilization by IC status, age group, analysis**
 447 **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, 158.46	341.0, 149.46

448

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

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

451 [†] Individuals with HZ and PHN: includes costs 7 days prior to 365 days post initial HZ onset452 [§] Individuals with HZ and complications but no PHN: includes only costs 7 days prior to 30 days post initial HZ onset

453 Abbreviations: £: 2014 UK pound sterling; IC, immunocompromized; HZ, herpes zoster; PHN, post-herpetic neuralgia; HZ-

454 Comp: HZ and complications with no PHN; SE: Standard Errors; YOA: years of age

455

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

456 **FIGURE**

457 **Figure 1: Lay Language Summary**

For peer review only

1
2
3 458 **Figure 2: Inpatient Hospital Admission by HES-linked matched IC or IC-free cohort over**
4
5 459 **the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to**
6
7 460 **365 days post initial HZ onset (Panel B)**
8
9

10 461
11
12
13 462 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
14 463 For HZ individuals with PHN: data from 7 days prior until the following time periods after HZ onset included - 90 days (Panel A)
15 464 and 365 days (Panel B).
16 465 Abbreviations: HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; PHN, post-herpetic neuralgia
17
18
19 466
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 467 **Figure 3 : Healthcare Costs for by HES-linked matched IC (Panel A) and IC-free cohort**
4
5 468 **(Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset**
6
7

8 469
9
10
11 470 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
12
13 471 For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
14 472 Abbreviations: £, 2014 UK pound sterling; CPRD, Clinical Practice Research Datalink; CPRD-Pre, CPRD Prescriptions; CPRD-
15 473 OA, CPRD Other Ambulatory Visits; CPRD-Amb, CPRD Ambulatory Visits; HES, Hospital Episode Statistics; HES-Out, HES
16 474 Outpatient consultation; HES-Hosp, HES Hospital admission; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic
17 475 neuralgia.
18
19 476
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 477 **Figure 4 : Healthcare Costs for each IC condition in the HES-linked matched IC and IC-**
4
5 478 **free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ**
6
7
8 479 **onset**
9

10 480
11
12
13 481 For HZ individuals without PHN: data from 7 days prior to 30 days post HZ onset included.
14 482 For HZ individuals with PHN: data from 7 days prior until 365 days after HZ onset.
15 483 Abbreviations: £, 2014 UK pound sterling; AID, autoimmune diseases; AT, autoimmune thyroiditis; CORTDS, corticosteroid
16 484 exposure; ESRD, end-stage renal disease; HES, Hospital Episode Statistics; HIV, human immunodeficiency virus; HM,
17 485 hematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IBD, inflammatory bowel
18 486 syndrome; IC, immunocompromised; MS, multiple sclerosis; PHN, post-herpetic neuralgia; RA, rheumatoid arthritis; SLE,
19 487 systemic lupus erythematosus; SOM, solid organ malignancies; SOT, solid organ transplantations; PSOR, psoriasis; OID, other
20 488 immunodeficiency; OIT, other immunosuppressive therapy; PR, polymyalgia rheumatica.
21
22
23
24 489

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

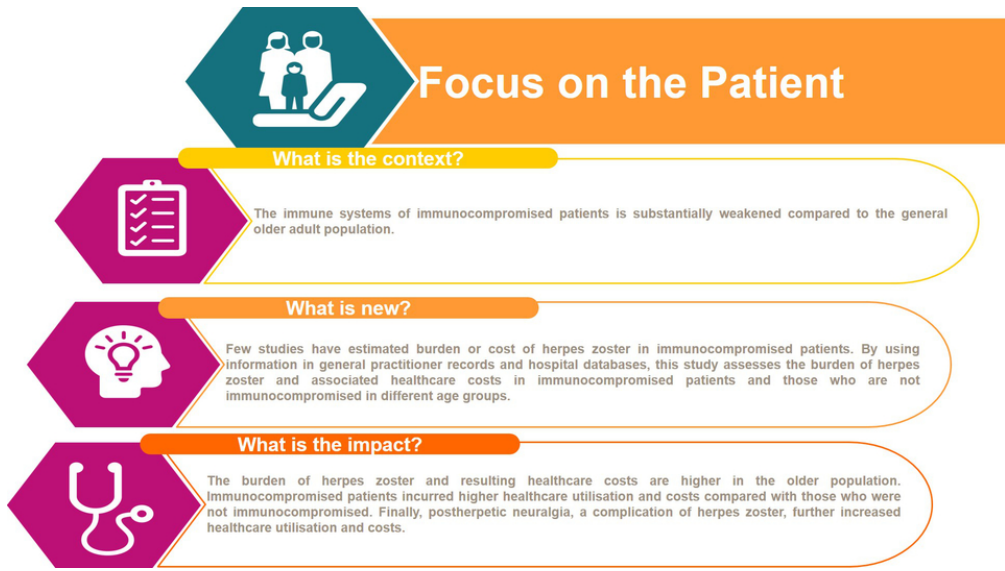


Figure 1: Lay Language Summary

81x45mm (300 x 300 DPI)

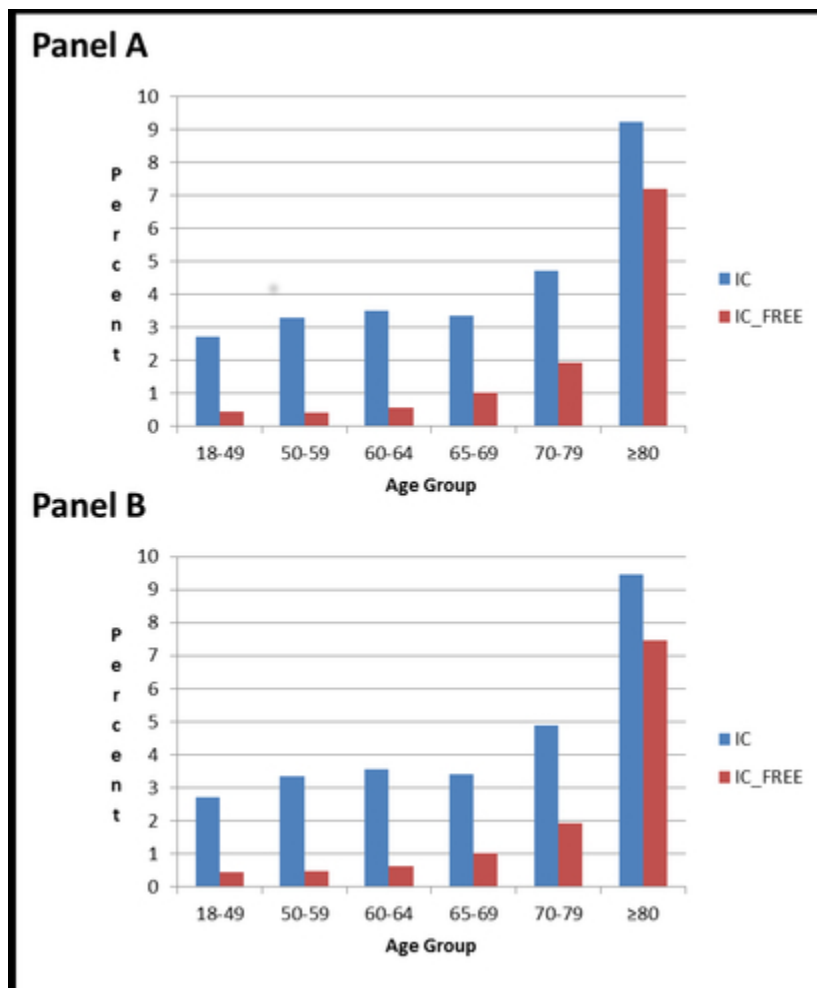
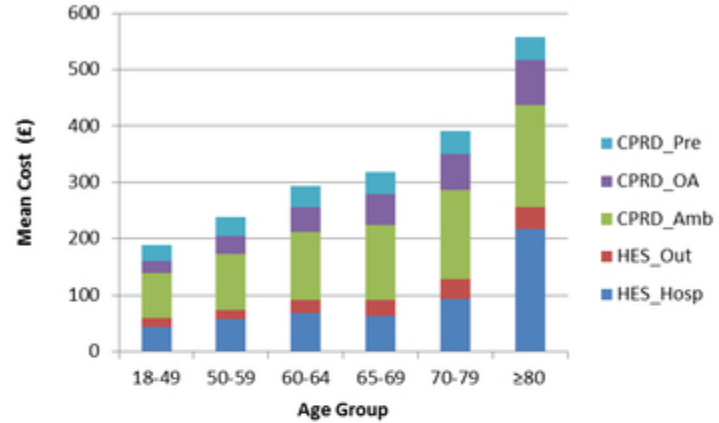


Figure 2: Inpatient Hospital Admission by HES-linked matched IC or IC-free cohort over the time periods: 7 days prior to 90 days post initial HZ onset (Panel A) and 7 days prior to 365 days post initial HZ onset (Panel B)

34x41mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Panel A



Panel B

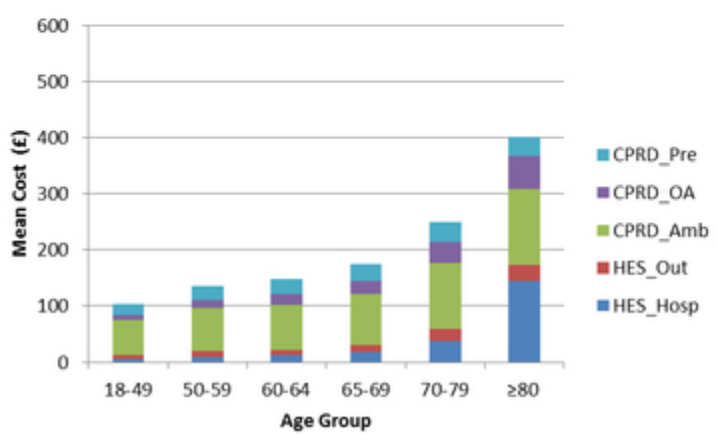


Figure 3 : Healthcare Costs for by HES-linked matched IC (Panel A) and IC-free cohort (Panel B) for the analysis period 7 days prior to 365 days post initial HZ onset

34x45mm (300 x 300 DPI)

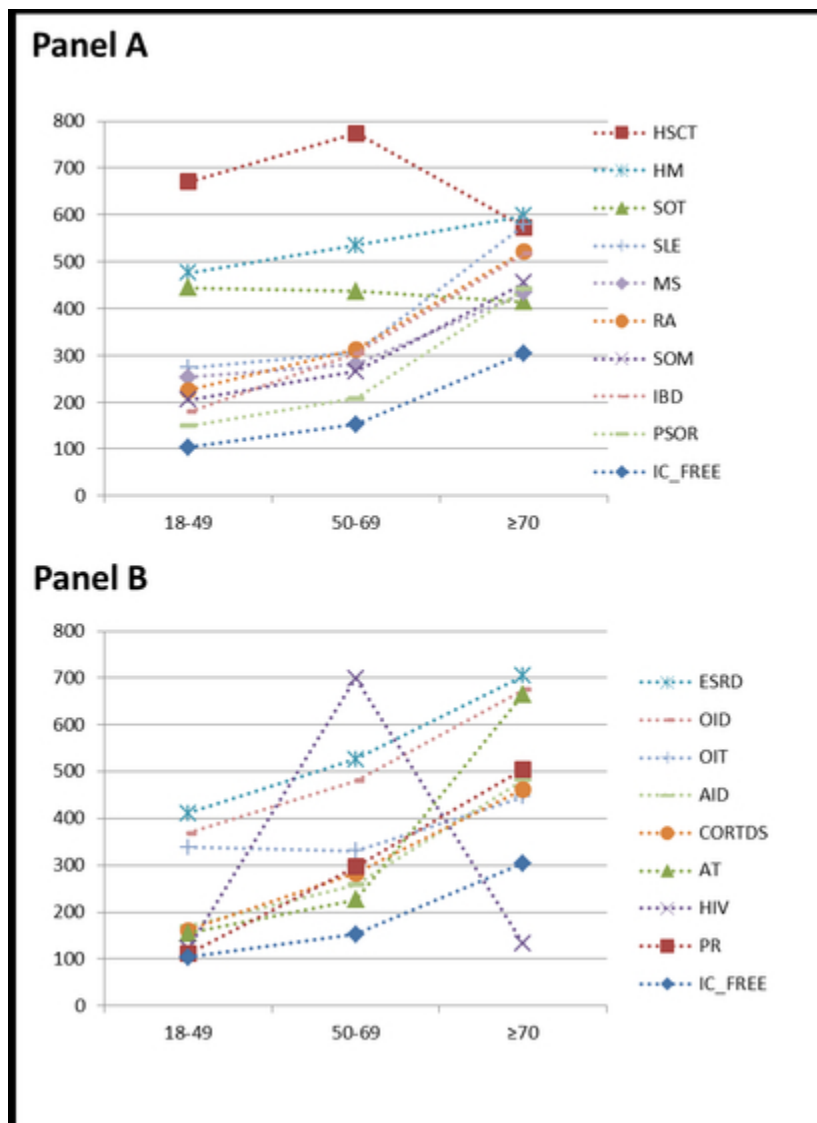


Figure 4 : Healthcare Costs for each IC condition in the HES-linked matched IC and IC-free cohort by age group for the analysis period 7 days prior to 365 days post initial HZ onset

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);

1
2
3 The analysis tables were generated for all HZ subjects from -7 days up to 90 and 365 days
4 after HZ event; i.e. HZ + PHN 90 Days: (a) + (b), HZ + PHN 365 Days: (a) + (c).
5
6

7 Additionally, main categories of resource utilization and cost tables were presented for the
8 following sub-populations for a 7-day period up to the case onset date up to 30 days, 90 days
9 and 365 days post-initial HZ onset date:
10
11

- 12 • HZ only (i.e. no PHN and no HZ-related complication);
- 13
- 14 • HZ and PHN within 1 year of HZ event;
- 15
- 16 • HZ and other HZ-related complications but no PHN (overall and by complications
17 sub-categories):
 - 18 ○ Neurological;
 - 19
 - 20 ○ Ocular;
 - 21
 - 22 ○ Cutaneous;
 - 23
 - 24 ○ Other complications.
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31

32 A detailed mapping linking the exact event definition variables and criteria to the reference
33 unit cost was used. The unit costs for each type of resource were obtained from the following
34 reference sources:
35
36

- 37 • General practitioner (GP) prescribed medication costs: British National Formulary
38 (BNF) 65 and 70. The quantity prescribed and pack type were used to estimate the
39 prescription costs for each drug (prodcode) of interest. A detailed mapping was used
40 to link the exact cost of prodcode quantity and packtype for each drug;
41
42
- 43 • Primary care costs: Personal Social Services Research Unit (PSSRU, Curtis L,
44 Personal Social Services Research Unit. Unit costs of Health & Social Care 2014.
45 University of Kent, 2014);
46
- 47 • HES inpatient hospitalisation and HES outpatient specialist costs: NHS Tariffs
48 (National Schedule of Reference Costs, 2013/2014).
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

	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).

1
2
3 The CPRD GOLD, referred to as CPRD, is a large computerised database of linked
4 anonymised longitudinal medical records from primary care in the UK, drawn from General
5 Practitioners' (GPs') computer systems used for clinical records in their practices. At the time
6 of data extraction, the CPRD included data from 15,436,637 subjects from 684 practices in
7 the UK. The population in the database matched the age and gender distribution of the UK
8 population as a whole. Mean follow-up of subjects was approximately 7 years (median 5.0
9 years).

10
11
12 Information in the CPRD includes records of clinical events (medical diagnoses), referrals to
13 secondary care and specialists, primary care prescriptions, immunisations and vaccinations,
14 diagnostic tests, lifestyle (smoking and alcohol status) as well as that related to other routine
15 General Practitioner (GP) medical services. More recently the CPRD was linked to certain
16 key secondary care data and mortality data from the ONS.

17
18
19 READ codes comprise coded clinical terms used by clinicians to record outputs of patient
20 assessments as well as health and social care procedures. Medical codes used in CPRD,
21 referred to as medcodes, are CPRD-generated numerical representations of alphanumeric
22 READ codes and are used to identify medical diagnoses in the database.

23 24 25 26 *The Hospital Episode Statistics*

27
28 HES inpatient Set 9 (2013Q3);

- 29 • Hospitalizations (HES Inpatient: HES_DIAGNOSIS_EPI dataset);

30
31 HES outpatient Set 9;

- 32 • Outpatient Visits (HESOP Clinical dataset);

33
34 At the time of data extraction, HES included information related to inpatient admissions,
35 outpatient and accident & emergency activity in NHS (National Health Service) hospitals that
36 were restricted to England only. Records are collated from over 125 million patients annually.
37 ICD-10 clinical coding is used to record diagnoses in HES.

38
39 Records for approximately 60% of patients registered in GP practices in CPRD are eligible
40 for linking with their HES records. Record linkage is dependent on agreement by the GP and
41 is limited to subjects in CPRD with a valid NHS number in England.

42
43 A combination of the subject's NHS number, gender, date of birth and postcode is used to
44 link patient records. This process is managed by an independent party to HES and CPRD.

45
46 A large proportion of subjects with IC conditions and HZ-related or potential complications
47 received care in a hospital setting at some point during their disease history. Although,
48 generally, communication from hospitals (e.g. via discharge letters) inform GPs about care
49 received by their patients, not all of these events are encoded by GPs in patients' notes and
50 therefore there are discrepancies between the CPRD and HES-linked data.
51
52
53
54
55
56
57
58
59
60

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

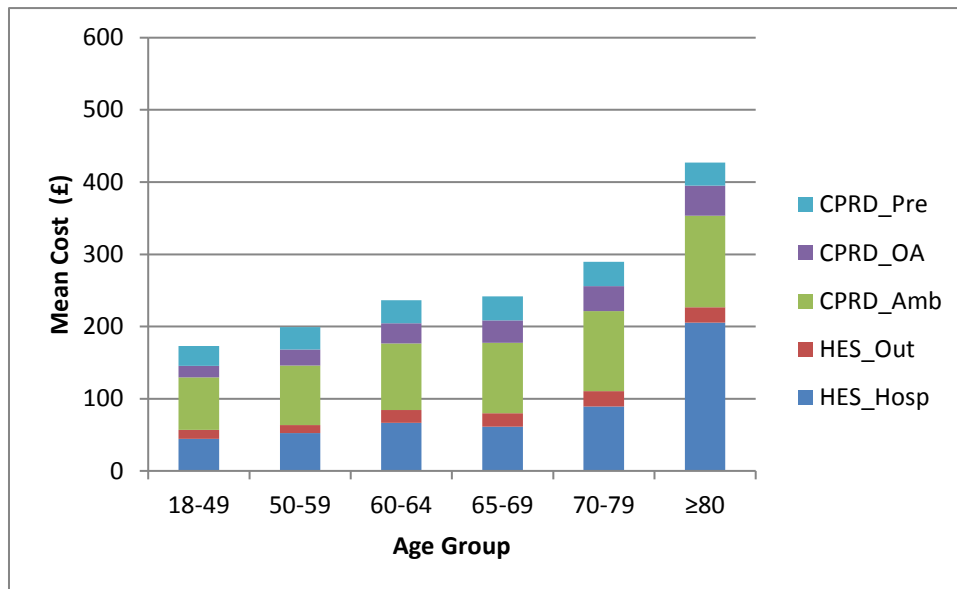
Category	18-49 YOA	50-59 YOA	60-64 YOA	65-69 YOA	70-79 YOA	≥80 YOA
IC Population (≤90 days)						
Hospitalizations	44.2	52.4	66.7	61.2	89.3	205.5
HES outpatient consultations/visits	12.4	11.2	17.8	18.6	21	21.3
CPRD ambulatory visits	72.9	82.3	92.1	97.5	110.8	126.5
CPRD other ambulatory visits	16.1	22	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

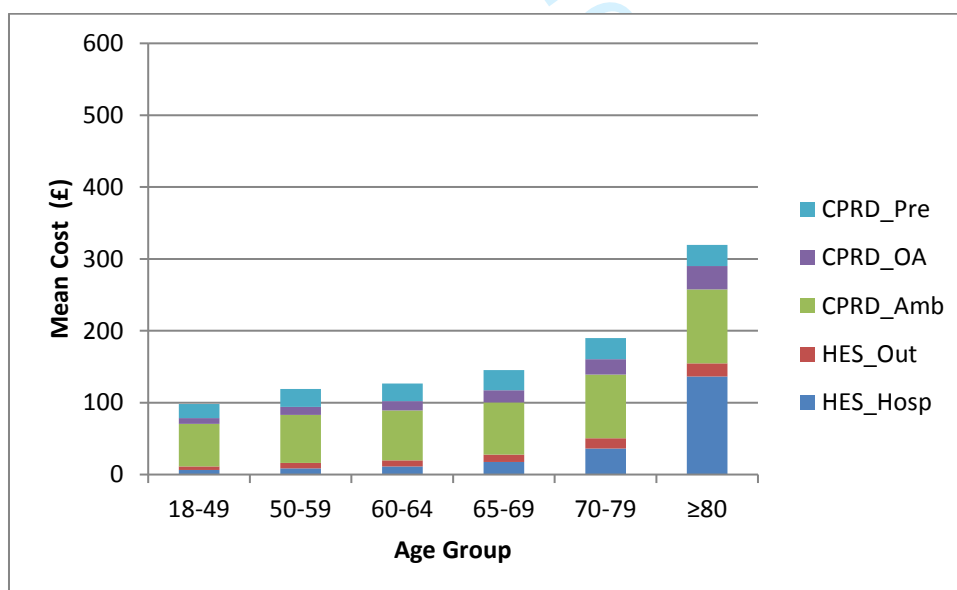
HES, Hospital Episode Statistics; IC, immunocompromised; CPRD, Clinical Practice Research Datalink; CPRD; YOA, years of age

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



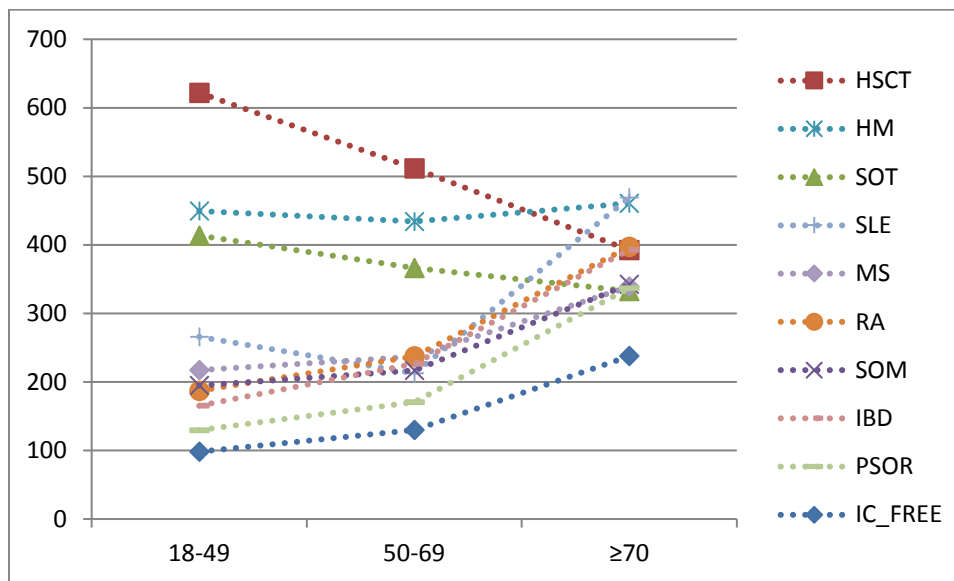
For HZ subjects without PHN: data from 7 days prior to 30 days post HZ onset included;

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

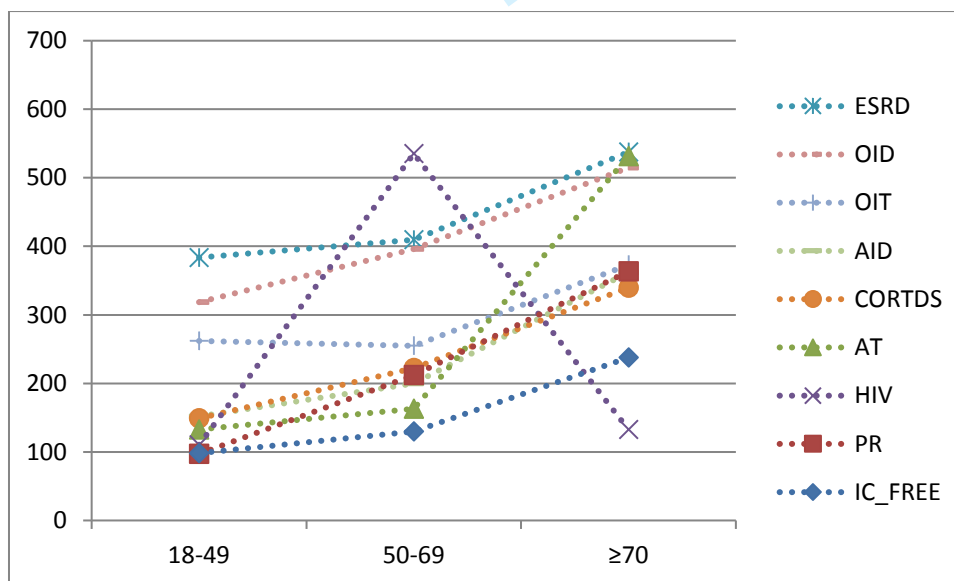
Abbreviations: HES, Hospital Episode Statistics; IC, immunocompromised; HZ, herpes zoster; PHN, post-herpetic neuralgia; CPRD, Clinical Practice Research Datalink; CPRD_Pre, CPRD Prescriptions; CPRD_OA, CPRD Other Ambulatory Visits; CPRD_Amb, CPRD Ambulatory Visits; HES_Out, HES Outpatient consultation; 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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 1 and 2,3 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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Page 6
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	N/A

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Pages 9,10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
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 (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	N/A
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.