

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 editorial.bmjopen@bmj.com

BMJ Open

Evaluation of the public health impact of introducing a novel Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025553
Article Type:	Research
Date Submitted by the Author:	30-Jul-2018
Complete List of Authors:	van Oorschot, Desiree; GSK Vaccines, Value Evidence Hunjan, Manjit; GlaxoSmithKline Bracke, Benjamin ; GSK Vaccines, Value Evidence Lorenc, Stephane; GSK Vaccines, Value Evidence Curran, Desmond; GlaxoSmithKline, Value Evidence Starkie-Camejo, Helen; GlaxoSmithKline
Keywords:	Shingles, Adult vaccination, herpes zoster, recombinant zoster vaccine, Public health < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

Peer Review Only

TITLE PAGE

TYPE OF MANUSCRIPT:

MANUSCRIPT TITLE:

Evaluation of the public health impact of introducing a novel Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme

AUTHOR(S): [ORDER UNDER DISCUSSION]

Van Oorschot Desirée¹, Hunjan Manjit², Bracke Benjamin¹, Lorenc Stéphane³, Curran Desmond¹, Starkie Camejo Helen²

AFFILIATIONS:

¹ GSK, Wavre, Belgium; ² GSK, Uxbridge, UK; ³ Freelance, on behalf of GSK, Wavre, Belgium

CORRESPONDING AUTHOR:

Name: Van Oorschot Desirée

Mailing Address: Avenue Fleming 20, 1300, Wavre, Belgium

Phone No: +3210855111

E-mail address: desiree.x.van-oorschot@gsk.com

ABSTRACT

OBJECTIVES

In 2013, the Herpes Zoster (HZ) immunisation programme was introduced in the UK for adults 70 years of age (YOA). The Joint Committee on Vaccination and Immunisation (JCVI) based their recommendations on the clinical profile of zoster vaccine live (ZVL), the only vaccine against HZ available at the time. The recently approved Adjuvanted Recombinant Zoster Vaccine (RZV) has a substantially different clinical profile that may offer additional benefits.

This study aimed to 1) assess the public health impact of introducing RZV in the UK compared to the current vaccination strategy and 2) explore via scenario analyses the optimal age-group of vaccination in terms of public health impact.

METHODS

A previously developed health economic model was adapted to the UK setting. The base-case analysis considered individuals 70 YOA, ZVL and first-dose RZV coverage of 48.3%, 70% compliance for the second-dose of RZV over a life-time horizon. Outcomes included reduction of HZ and postherpetic neuralgia (PHN) cases, complication rate and the use of health-care resources. The impact of coverage and second-dose compliance was also explored.

RESULTS

Compared to no revaccination, RZV would lead to a reduction of 30,262 HZ and 5,409 PHN cases while ZVL would lead to a reduction of 7,909 HZ and 3,567 PHN cases. The number needed to vaccinate to prevent 1 HZ case is 12 with RZV and 45 with ZVL. When RZV second-dose compliance is reduced to 60%, fewer HZ and PHN cases would be avoided, though still more than predicted for ZVL. The highest public health impact with RZV could be achieved in individuals 60 or 65 YOA.

CONCLUSION

Under the model assumptions, RZV is predicted to avert more HZ and PHN cases compared to ZVL. Results were robust under different scenario and sensitivity analyses.

KEYWORDS

Herpes Zoster vaccination; adjuvanted recombinant zoster vaccine; public health impact

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The most recent UK-specific data from published literature is included in the ZONA model.
- Model structure and inputs have been validated by external experts.
- Results of this analyses estimate the impact of an RZV program in the UK population in 2018.
- Further analyses have to be performed once data becomes available on the duration of protection of RZV.
- Assumptions regarding second dose compliance had to be made in absence of real-world data.

INTRODUCTION

The varicella zoster virus (VZV) usually affects children and leads to varicella, also known as chickenpox. The virus remains dormant life-long in patients' dorsal root ganglia.¹ Later in life, VZV specific T-cell-immunity decreases due to immunosenescence or immunosuppressing illnesses or medications. Reactivation of VZV results in herpes zoster (HZ), also called shingles.^{2 3} Over 95% of individuals will have acquired VZV during their childhood or early adulthood.^{4 5} Approximately one in three people will develop HZ during their life-time with the risk increasing sharply after the age of 50 years of age (YOA), leading to an estimated 5HZ episodes per 1,000 people in the UK, each year.⁶⁻⁸ Similar incidence rates were reported in other European countries and elsewhere.^{2 7} Furthermore, results from observational studies suggest that HZ incidence has risen during the past decade in various countries and is predicted to continue to rise as the average age of the population increases.^{2 9 10}

HZ tends to start with prodromal pain, followed by a dermatomal rash which is usually unilateral and develops typically over the trunk or face. Rash is often accompanied by severe pain. Skin lesions and pain usually disappear completely within 4–6 weeks. Postherpetic neuralgia (PHN), often defined as pain persisting or appearing 30 to 90 days after rash onset, is the most common complication which can last from several weeks to months.^{8 11} Even though mortality due to HZ infection is low, HZ greatly affects quality of life (QoL) in terms of physical and social functioning and the well-being of the patients.¹² Furthermore, severity of pain strongly correlates with the reported QoL.^{11 13} Current treatment options, which mainly rely on antivirals, analgesics and antidepressants, provide only partial symptomatic relief and limited protection against the development of PHN and other complications. Thus, the impact of the disease on patients QoL is not adequately managed with existing interventions.¹¹

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommended universal mass vaccination (UMV) for HZ using Zoster Vaccine Live (ZVL; *Zostavax*)¹⁴, the only vaccine available at the time the UMV programme was introduced in 2013. ZVL is a live-attenuated virus vaccine indicated for the prevention of HZ and, in Europe, of PHN in individuals ≥ 50 YOA.¹⁵ Vaccine efficacy (VE) against HZ (VE_{HZ}) of ZVL in the shingles prevention study (SPS) was 63.9% in individuals 60-69 YOA and 37.6% in individuals ≥ 70 YOA.^{15 16} Long-term clinical trial data and observational effectiveness studies showed that VE of ZVL decreased

1
2
3 substantially over time conferring no protection against HZ beyond 8 years after
4 vaccination.^{17 18}
5

6
7 Even though ZVL is indicated in individuals ≥ 50 YOA, the JCVI recommended
8 vaccination with ZVL at 70 YOA (and a catch-up vaccination for people 78 YOA),
9 based on clinical trial data and an economic model showing that vaccination at 70
10 YOA would be the most cost-effective option given that the burden of disease
11 increases with age, while VE of ZVL decreases in older individuals and over time.^{3 14} A
12 further limitation to the indicated use of ZVL in individuals ≥ 50 YOA is its
13 contraindication in primary or acquired immunodeficiency states due to blood
14 disorders or other types of cancer, infection with human immunodeficiency virus, or
15 due to high dose immunosuppressive therapy.^{15 19} A proportion of individuals would
16 therefore not be able to receive ZVL.²⁰
17
18
19
20
21

22 A novel Adjuvanted Recombinant Zoster Vaccine (RZV, *Shingrix*) has been granted
23 marketing authorisation by the European Medicines Agency (EMA) and is indicated
24 for use in individuals ≥ 50 YOA. RZV is a non-live vaccine consisting of the VZV
25 glycoprotein E (gE), a prominent antigen target of VZV-specific CD4+ T-cell immune
26 responses, and AS01_B adjuvant system, which boosts immunogenicity and duration
27 of the immune response.²¹ RZV is administered in two doses 2 to 6 months apart and
28 is not contraindicated in immunocompromised (IC) individuals as it is a non-live
29 vaccine.²² Two large, phase III trials, i.e. the Zoster Efficacy Studies in Adults 50 and
30 70 YOA or older [ZOE-50 (NCT01165177) and ZOE-70 (NCT01165229), respectively]
31 demonstrated high VE_{HZ} of RZV in all age-groups; VE_{HZ} was 97.2% in individuals ≥ 50
32 YOA included in the ZOE-50 study and 91.3% in individuals ≥ 70 YOA included in the
33 ZOE-50 and ZOE-70 studies.^{23 24} VE persisted over the four-year duration of the
34 clinical trial.²⁴
35
36
37
38
39
40

41 The objective of this study is to explore the public health impact of introducing the
42 RZV vaccine in the UK in the routine population 70 YOA. The effect of RZV and ZVL on
43 HZ and PHN incidence, complications and health resource utilisation is compared to
44 no vaccination. Different scenario analyses are carried out to assess the impact of
45 first-dose RZV coverage and second-dose RZV compliance and to determine the
46 optimal age for vaccination.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

METHODS

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were not involved as the analysis is based on mathematical modeling.

MODEL STRUCTURE

The ZOster economic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting. The economic model considers up to five various age cohorts that can transition between different health states, including no HZ, HZ, health states associated with complications of HZ (PHN and non-PHN complications) and death from HZ or natural causes.²⁵ Cycle length is set to one year and a life-long time horizon is assumed. The model allows evaluation of three different HZ vaccination strategies: vaccination with RZV, vaccination with ZVL and no vaccination, using single cohorts. Further details regarding the model structure are reported in Curran et al, 2017.²⁵

MODEL INPUT PARAMETERS

Wherever possible, UK-specific data were used. Efficacy data for RZV and ZVL were derived from pivotal clinical trials conducted for ZVL and RZV.^{16 23 24 26}

DEMOGRAPHICS

Populations in the model are projected to 2018 values. The base-case population consisted of the routine vaccination cohort 70 YOA. Based on projections by the Office of National Statistics (ONS)²⁷, the predicted population numbers in the routine cohort of 70 YOA is 722,616, in 2018. Different age cohorts were modelled for use in scenario analyses (Table 1).

All-cause mortality rates were derived from ONS data projected to the year 2018/2019 (Supplementary information [SI] Table 1).²⁷

EPIDEMIOLOGY

HZ INCIDENCE

HZ incidence was derived from a recent UK Clinical Practice Research Datalink (CPRD) study, which assessed the incidence of HZ in immunocompetent (IC-free) and IC individuals between 2000 and 2012²⁸ (SI Table 2). The CPRD database study presents the most recent real-world data on HZ incidence and was therefore considered the most appropriate source for this parameter. The IC-free and IC population were matched by age, gender and location of general practitioner (GP) and the proportion of IC individuals was adjusted in the whole population to account for an increase in immunodeficiencies in older individuals. In the age-group 70-79 YOA, 35% of individuals had primary or acquired immunodeficiency and a subgroup of this IC population is contraindicated to receive ZVL. Incidence numbers were converted to annual probabilities of developing HZ (**Error! Reference source not found.**). Lower and upper ranges of probabilities for HZ incidence in the whole population were obtained from published data since it was not possible to derive it from the split IC and IC-free data set analysed in the CPRD study³ (SI Table 3).

Incidence rate of recurrent HZ is assumed to be the same as the incidence of the initial event. This assumption is supported by published data which indicates that the incidence rates of initial and recurrent HZ events are similar.²⁹

PHN PROBABILITY

PHN is defined as pain appearing or persisting for more than 3 months after initiation of HZ. PHN incidence was derived from published data.^{8 30} Gauthier et al. derived PHN incidence from the CPRD in the population excluding patients with underlying IC conditions using prescription medication records on top of PHN codes to identify these episodes. Forbes et al reported odds ratios of developing PHN for people with human immunodeficiency virus and hematopoietic stem cell transplantation compared to IC-free population and these data were used in combination with data reported by Gauthier et al. to model the proportion of PHN cases following an episode of HZ in the general population (**Error! Reference source not found.**, SI Table 4). As for HZ, the model assumes that the incidence of recurrent PHN is the same as for first-time PHN.

HZ-RELATED MORTALITY

Values for HZ-associated mortality are based on published literature³¹ (SI Table 5). The study by Edmunds et al. was the only report including a granular breakdown of HZ case fatality rate by age-group in the UK and was therefore considered to be the most appropriate source for HZ-associated mortality. The published data are based on the population of England and Wales. However, increasing mortality with increasing age is consistent with observations from studies conducted in other countries³² and it is assumed that these rates apply to the entire UK population.

NON-PHN COMPLICATIONS

A wide range of complications other than PHN can occur in people experiencing an episode of HZ and could have a substantial impact on the burden of the disease. In the model, four main categories of complications were included, i.e., ocular, neurological, cutaneous and other non-pain complications. Probabilities of developing these complications after the initial HZ episodes were taken from published literature²⁹ (**Error! Reference source not found.**).

HOSPITALISATION AND GP VISITS DUE TO COMPLICATIONS

The CPRD study was used to derive the proportion of patients being hospitalised or visiting their GP due to HZ-related complications.²⁸ Hospitalisation rates were higher in the IC cohort for all age-groups. In addition, health-care resource use was higher in older adults (SI Tables 6 & 7).

VACCINE EFFICACY AND SAFETY

EFFICACY

Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the ZOE-50 and ZOE-70 trials for RZV^{16 23 24 26} (Table 1, SI Table 8). VE for RZV is based on a 2-dose schedule given 2 months apart. However, compliance with 2nd dose RZV is likely < 100% in practice. Therefore, efficacy data for 1-dose RZV were analysed post-hoc based on limited clinical data from individuals in the ZOE trials receiving only 1-dose RZV.²⁵

Waning for both vaccines was modelled by linear fitting, using data from the above-

1
2
3 mentioned trials as well as from the long-term persistence study (LTPS) for ZVL.²⁵ For
4 RZV, waning rates were assumed to be 1% (range: 0%, 2.6%) during the first 4 years
5 after vaccination and 2.3% (range: 0.7%, 4.6%) thereafter in individuals < 70 YOA. In
6 the population ≥ 70 YOA, waning rate was assumed to be constant over time at 3.6%
7 (range: 1.4%, 6.6%).²⁵ For ZVL, the model indicated a waning rate of 5.4% (range:
8 4.5%, 6.4%) during the first 4 years after vaccination and 5.1% (range: 4.1%, 6.0%)
9 thereafter in all age-groups^{17 25} (SI Table 9).
10
11
12
13

14 *COVERAGE AND COMPLIANCE*

15

16 In the base-case analysis, coverage is set at 48.3% in line with latest coverage
17 numbers for the UK.²⁰ The impact of different coverage rates was assessed in
18 sensitivity analyses. Compliance with the second-dose of RZV was set to 70%.
19
20
21

22 *OUTCOMES*

23

24 The model was used to estimate the avoidance of HZ and PHN cases, complications,
25 deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related
26 deaths and number of GP visits and hospitalisations for three different vaccination
27 strategies, i.e., vaccination with RZV, vaccination with ZVL and no vaccination. The
28 number needed to vaccinate (NNV) to avert one case of HZ and PHN was also
29 evaluated.
30
31
32
33

34 *SCENARIO ANALYSES*

35

36 Different scenario analyses were carried out where assumptions regarding
37 vaccination coverage and compliance and age at vaccination were changed.
38
39

40 In a first scenario analysis, the impact of increasing coverage of RZV to 70% was
41 explored. A higher coverage of 70% in the UK was deemed plausible considering that
42 a) the influenza vaccine uptake in people ≥ 65 YOA was 70.5% in 2016/2017³³ and b)
43 in the absence of a contraindication, vaccinators might not hesitate to administer
44 the vaccine in IC individuals.
45
46
47

48 In a second scenario analysis, the second-dose compliance was varied, assuming a
49 lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of
50 the clinical trial second-dose compliance.²⁵
51
52

53 Finally, the impact of changing the vaccination age on health outcomes was
54
55
56
57
58
59
60

1
2
3 explored. VE is in general higher in younger individuals favouring early vaccination.
4 On the other hand, duration of protection decreases over time and burden of
5 disease (severity and duration of HZ and PHN) is higher in older individuals, favouring
6 vaccination at an older age.³⁴ The relative balance of these factors may be different
7 in case of ZVL and RZV, leading to different conclusions regarding optimal
8 vaccination age.
9
10
11

12 *SENSITIVITY ANALYSES*

13
14
15 Deterministic sensitivity analyses (DSA) were conducted to test the robustness of the
16 results subject to changes in input parameters. To this aim, HZ and PHN incidence
17 rates, VE and waning rates for both vaccines, incidence rate of HZ-related
18 complications and vaccine-related adverse events, coverage and second-dose
19 compliance were varied in one-way sensitivity analyses according to pre-defined
20 ranges. Tornado diagrams were used to illustrate parameters that had the largest
21 impact on HZ cases avoided.
22
23
24
25

26 Probabilistic sensitivity analysis (PSA) was carried out to assess the variability of
27 results when changing parameters concomitantly using Monte Carlo simulation
28 (5,000 simulations). Each parameter could be attributed a value within its predefined
29 range and according to the assigned probability distribution. A beta-distribution was
30 used for all parameters except for vaccine coverage which followed a uniform
31 distribution. Age-specific incidence parameters which varied across age-groups were
32 assumed to be correlated using a correlation of 0.5. The results of the PSA are
33 presented using a histogram displaying the HZ cases avoided with RZV compared
34 with ZVL.
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

RESULTS

BASE-CASE ANALYSIS

In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a reduction of 7,909 HZ and 3,567 PHN cases (

For peer review only

1
2
3 Table 2). Vaccination with RZV reduced the number of HZ-related complications and
4 the health-resource use (
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 Table 2). There were few HZ-related deaths; compared to no vaccination, RZV
4 prevented 8 HZ-related deaths while ZVL prevented none. The NNV to prevent one
5 case of HZ was 12 with RZV and 45 with ZVL. The NNV to avoid one case of PHN was
6 65 with RZV and 98 with ZVL, respectively.
7
8
9

10 *SCENARIO ANALYSES*

11
12 In a first scenario analysis, we increased coverage from 48.3% to 70% for RZV. In this
13 scenario, an additional 13,596 HZ and 2,430 PHN cases would be prevented in the
14 routine vaccination cohort (70 YOA) (
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

1
2
3 Figure 1, light blue bar showing the additional proportion of HZ and PHN cases
4 avoided with RZV compared to no vaccination).
5
6

7 In a second scenario analysis, compliance with second-dose of RZV was set to lower
8 and upper limits of 60% and 89%. Compared to no vaccination, the numbers of HZ
9 cases avoided with RZV were 28,145 and 34,284 at the lower and upper limits for
10 compliance, respectively (Figure 2).
11
12

13 To determine the optimal age for vaccination, scenario analyses were carried out to
14 evaluate the public health impact in different age cohorts (50, 60, 65, 70 and 80
15 YOA) in terms of HZ and PHN cases avoided, resource utilisation and NNV per
16 100,000 people.
17
18

19 In case of RZV, the scenario that led to avoidance of the most HZ cases per 100,000
20 people would be vaccinating at 60 YOA, while slightly more PHN cases per 100,000
21 people could be avoided by vaccinating at 65 YOA. In case of ZVL, the number of HZ
22 cases avoided per 100,000 people would be highest in the 65 YOA cohort, but more
23 PHN cases per 100,000 people would be avoided in the 70 YOA cohort (Figure
24 **3Error! Reference source not found.**). In all age-groups, number of HZ and PHN
25 cases avoided per 100,000 people was higher for RZV compared to ZVL.
26 Complications avoided ranged from 689 with RZV and 250 with ZVL in the 65 YOA
27 cohort, to 434 with RZV and 46 with ZVL in the 80 YOA cohort.
28
29

30 Consistent with these results, for RZV, the NNV to avoid one case of HZ was lowest in
31 the 60 YOA (NNV = 9) and the NNV to avoid one case of PHN was lowest in the 65
32 YOA cohort (NNV = 54) (
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
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

Table 3).

The higher number of HZ and PHN cases avoided with RZV compared to ZVL across all age cohorts leads to an important reduction in the use of health care resources, which might be an indicator of a reduction in direct costs due to HZ (

For peer review only

1
2
3 Table 4). The number of GP visits per 100,000 people avoided is highest for the 60
4 YOA and 65 YOA cohorts for both vaccines, and consistently higher for RZV
5 compared to ZVL. The number of hospitalisations avoided increases with increasing
6 age for RZV, reflecting the increased risk of hospitalisation due to HZ in older
7 individuals.
8
9

10 11 *SENSITIVITY ANALYSES*

12
13 In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the
14 robustness of results was tested by changing input parameters to their lower and
15 upper estimated confidence ranges (SI Tables 3 – 5; SI Tables 8 – 9). In the base case
16 analyses, RZV prevented an additional 22,353 HZ cases as compared to ZVL. The
17 parameter with the highest impact on the relative advantage of RZV over ZVL was
18 annual waning of RZV (2 doses) VE_{HZ} in people ≥ 70 YOA, although the highest waning
19 for RZV would still lead to a reduction of over 13,000 HZ cases compared to ZVL.
20 Other parameters influencing the number of HZ cases avoided include initial VE_{HZ} in
21 people ≥ 70 YOA for ZVL and RZV single dose, HZ incidence, and RZV compliance to
22 second-dose (Figure 4).
23
24
25
26
27

28 During PSA, all parameters were varied simultaneously along their predefined
29 ranges. In all simulations ($n = 5,000$), RZV led to a reduction of HZ cases as compared
30 to ZVL. The distribution of the number of HZ cases avoided by RZV relative to ZVL is
31 shown in Figure 5. Overall, 83.1% of simulations predicted that RZV would prevent at
32 least 15,000 additional HZ cases compared with ZVL in the age-group 70 YOA.
33
34
35
36

37 **DISCUSSION**

38
39 UMV against HZ using ZVL was introduced in the UK in 2013 and observational
40 studies suggest that the programme has brought down HZ incidence by
41 approximately one third in the vaccinated cohorts.^{35 36} RZV has been approved by
42 the EMA in individuals ≥ 50 YOA, thereby offering an alternative option to vaccinate
43 people against HZ in addition to the existing ZVL. The aim of this study was to
44 evaluate the public health impact of RZV in terms of HZ prevention compared to ZVL
45 or no vaccination in the UK setting.
46
47
48
49

50 In the base-case considering the current vaccination cohort of people 70 YOA, RZV
51 reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no
52 vaccination. In comparison, ZVL prevented 7,909 HZ and 3,567 PHN cases as
53
54
55
56
57

1
2
3 compared to no vaccination. NNV to prevent one episode of HZ was almost four
4 times lower with RZV compared to ZVL, i.e., 12 with RZV vs 45 with ZVL. In addition,
5 the estimated number of hospitalisations and GP visits due to HZ and PHN were
6 substantially lower with RZV compared with ZVL. HZ-related mortality is in general
7 low; nevertheless, our simulations predicted that 8 deaths could be prevented with
8 an RZV vaccination strategy while no HZ-related deaths were prevented adopting a
9 ZVL vaccination strategy.
10
11
12

13
14 Results were robust under deterministic and probabilistic sensitivity analyses. Annual
15 waning of RZV VE in people ≥ 70 YOA had the greatest impact on the number of HZ
16 avoided relative to ZVL, but even assuming an extreme assumption on waning, with
17 an annual waning rate of 6.6%, RZV would prevent an additional 15,704 HZ cases as
18 compared to ZVL. Other parameters to which the relative vaccination strategies
19 proved sensitive included annual HZ incidence and VE_{HZ} of RZV and ZVL. Probabilistic
20 sensitivity analyses were always in favour of the RZV vaccination strategy with 83.1%
21 of simulations showing a reduction of at least $\geq 15,000$ HZ cases with respect to ZVL.
22 We also tested different scenarios in which coverage and compliance were varied,
23 assuming that the public health impact would increase as a greater proportion of
24 individuals would be vaccinated. Increasing the coverage estimate of the first-dose
25 of RZV from 48.3% to 70% would further reduce HZ and PHN incidence thereby
26 leading to a greater reduction in healthcare resources used. We hypothesise that the
27 coverage with RZV might be higher because a proportion of the eligible individuals
28 are currently not receiving the vaccine with ZVL. Even though the proportion of
29 individuals with a true contraindication to ZVL is estimated to be small (2.8%²⁰) HZ
30 vaccination with ZVL might be withheld even in those IC individuals who are not
31 contraindicated as vaccinators may have been risk averse. Reducing RZV compliance
32 to 60%, RZV would still prevent approximately three times more HZ cases compared
33 to ZVL. This is in line with a recent public health impact study carried out for the
34 German setting where a compliance rate of 50% would still lead to an improvement
35 of 200% over ZVL in terms of HZ prevention.²⁵
36
37
38
39
40
41
42
43
44
45

46 The recommended vaccination strategy was based on the clinical profile of ZVL, the
47 only vaccine available at the time. In its recommendation, the JCVI noted that ZVL VE
48 decreases with increasing age and over time; hence, the current age cohort eligible
49 for vaccination, i.e., individuals 70 YOA, is a compromise to optimise limited efficacy
50 and duration of protection against HZ. The JCVI also stated that optimal age at
51 vaccination would depend on the characteristics of any given vaccine.³⁷ Therefore,
52
53
54
55
56
57
58
59
60

1
2
3 the impact of vaccination age on HZ and PHN incidence was explored through
4 scenario analyses including different age-cohorts (50, 60, 65, 70 and 80 YOA). The
5 number of HZ and PHN cases avoided per 100,000 people was higher with RZV than
6 with ZVL across all age cohorts. In case of RZV, most HZ cases were avoided in the 60
7 YOA cohort, while PHN case avoidance was highest in the 65 YOA cohort. This
8 observation is consistent with a higher probability of developing PHN at an increased
9 age. On the other hand, the projected number of PHN cases avoided with ZVL was
10 highest in the 70 YOA. This finding is due to a top-up efficacy seen with ZVL against
11 PHN in the population ≥ 70 YOA: vaccinated individuals with breakthrough HZ are at
12 a lower risk of developing PHN as compared to unvaccinated individuals with HZ. In
13 the individuals < 70 YOA, no additional protection against PHN was observed in
14 clinical studies with ZVL. For RZV no additional top-up efficacy could be calculated
15 based on the limited number of breakthrough cases, and thus VE_{HZ} and VE_{PHN} were
16 assumed to be the same. As a result, for RZV, the NNV to avoid one case of HZ and
17 PHN was lowest for the 60 YOA and 65 YOA cohorts. NNV increased in the 70 YOA
18 and more so in the 80 YOA, where a proportion of the simulated cohort died due to
19 natural causes before any health benefit of vaccination occurred.
20
21
22
23
24
25
26

27
28 From a health care utilisation perspective, RZV reduced the number of GP visits by
29 more than 13,000 compared to ZVL in all age-groups. The highest reduction in GP
30 visits was predicted in the 65 YOA cohort, while the largest impact on
31 hospitalisations was predicted for the 80 YOA cohort. The latter might be explained
32 by the higher risk of hospitalisation inherent to older individuals due to a higher
33 degree of frailty. Nevertheless, it should be noted that the reduction in
34 hospitalisations was predicted to be several-fold higher with RZV compared to ZVL in
35 all age-cohorts. Reduction in the use of health care resources is a good indicator of
36 potential decrease in direct costs of new health care interventions; however, this
37 requires further investigation in a cost-effectiveness analysis with RZV in the UK
38 context.
39
40
41
42
43

44 The potential public health impact of RZV in the UK setting has previously been
45 studied by our group.³⁸ The study showed a substantial reduction in HZ and PHN
46 cases compared to no vaccination; however, no comparison was made to ZVL. A
47 number of studies have evaluated the impact of ZVL on disease burden and
48 associated cost-effectiveness in the UK setting. Van Hoek et al. analysed cost-
49 effectiveness of ZVL in different age-groups with the base-case considering a cohort
50 of immunocompetent 65-year-old individuals in the UK. This cohort was modelled
51
52
53
54
55
56
57
58
59
60

1
2
3 over a life-time and a vaccine coverage of 73.5%.³ Waning rates might have been
4 underestimated in this model since long-term data from the LTPS study for
5 persistence of efficacy of the ZVL vaccination were not yet taken into account.²⁵ The
6 LTPS study showed that VE_{HZ} of ZVL decreases significantly over time with no
7 statistically significant protection observed after 8 years of vaccination.^{17 18} In the
8 economic model published by Moore et al., the NNV of ZVL to prevent one case of
9 ZVL was 15, and hence lower than that found in our simulations. However, the
10 authors assumed a waning rate of 0%.¹⁰

11
12
13
14
15 The public health impact of RZV was also evaluated for other settings, including
16 Germany, US, Canada and Australia. These studies used a wide range of assumptions
17 regarding coverage, compliance and duration of vaccine protection for both RZV and
18 ZVL.^{28 39-41} Despite differences in these assumptions, all studies showed a consistent
19 improvement in the reduction of HZ cases and its complications compared to no
20 vaccination or vaccination with ZVL. In a recent independent cost-effectiveness study
21 for the US setting, employing conservative assumptions regarding RZV waning rate,
22 coverage and compliance, the authors concluded that RZV was more effective
23 compared to ZVL under the vast majority of assumptions evaluated.³⁹

24
25
26
27
28
29 As with every model, there are strengths and limitations associated with the
30 modelling strategy employed. For RZV, most recent UK-specific data available at the
31 time we conducted this study were used; for HZ incidence the CPRD database, a
32 large UK-specific database, was analysed and values for both IC and non-IC cohorts
33 were combined.²⁸ For PHN incidence, published data from two reports were used to
34 estimate the PHN probability in the total population including individuals with
35 immunodeficient states. The estimates of PHN cases prevented are close to real
36 values, validating our approach. Demographic data projected to the year 2018 were
37 used based on numbers reported by the ONS.²⁷ The limitations in this study are
38 related to assumptions that had to be made in the absence of real-world data,
39 including coverage with RZV, compliance and long-term waning for RZV. Coverage
40 and compliance were set to values observed in comparable vaccination programs
41 and these parameters were varied in scenario and one-way sensitivity analyses.
42 Results from long-term studies with RZV are still outstanding and follow-up data is
43 currently limited to 4 years. However, the model has been developed such that it can
44 be updated once additional data becomes available. For ZVL waning rates, we
45 included both data from the SPS and the LTPS study²⁵; however, data from a recent
46 observational study evaluating effectiveness of ZVL in the UK were not included as
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 they were not available at the time of modelling.³⁶ Finally, the rate of HZ-associated
4 complications was assumed to be the same in all individuals with HZ regardless of
5 their vaccination status. This assumption ignores the potential benefit vaccination
6 might have by lowering the severity and duration of break-through HZ cases. Clinical
7 trial data suggest that VE_{HZ} and VE_{PHN} are similar and there is some evidence that
8 duration and severity of HZ/PHN pain is lower in individuals having received RZV as
9 compared to unvaccinated individuals.⁴²
10
11
12

13
14 Future research might be directed towards assessing severity and duration of HZ and
15 PHN cases depending on vaccination status, identifying subgroups of the population
16 that may have enhanced benefit from the vaccine and evaluating cost-effectiveness
17 in the current UMV cohort and across different age-cohorts.
18
19

20 A lay language summary contextualizing the outcomes and potential impact of this
21 study for healthcare providers is displayed in Figure 6.
22
23
24
25
26

27 **CONCLUSION**

28
29 Within the model assumptions, RZV has the greater public health impact in terms of
30 HZ and PHN case avoidance and reduction in health care utilisation. When the UMV
31 was introduced in 2013, vaccinating people at 70 YOA was the best option based on
32 the vaccine characteristics of ZVL. With the approval of RZV in the US, Canada, Japan
33 and Europe in adults ≥ 50 YOA and given the different clinical profile of the two
34 available vaccines, the optimal HZ prevention strategy needs to be re-evaluated.
35 Varying the age at vaccination in the model, we demonstrated that the different
36 clinical profile of RZV shows a different optimal vaccination strategy compared to
37 ZVL with the optimal vaccination age being 60 YOA or 65 YOA cohorts while being
38 superior to ZVL in all age cohorts studied.
39
40
41
42
43
44

45 **ACKNOWLEDGEMENTS**

46
47 Authors would like to Lijoy Varghese for this contribution to the study. They also
48 want to thank Business & Decision Life Sciences platform for editorial assistance and
49 publications coordination, on behalf of GSK. Stephanie Garcia coordinated
50 manuscript development and editorial support. Katrin Spiegel provided writing
51 support.
52
53
54
55
56
57
58
59
60

REFERENCES

1. Mueller NH, Gilden DH, Cohrs RJ, et al. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. *Neurol Clin* 2008;**26**(3):675-97. doi:10.1016/j.ncl.2008.03.011.
2. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* 2014;**4**:e004833. doi:10.1136/bmjopen-2014-004833
3. van Hoek AJ, Gay N, Melegaro A, et al. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. *Vaccine* 2009;**27**(9):1454-67. doi:10.1016/j.vaccine.2008.12.024
4. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Therapeutic Advances in Vaccines* 2015;**3**(4):109-20. doi:10.1177/2051013615599151
5. Bollaerts K, Riera-Montes M, Heining U, et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: Deriving incidence from seroprevalence data. *Epidemiol Infect* 2017;**145**(13):2666-77. doi:10.1017/S0950268817001546
6. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect* 2001;**127**:305-14. doi:10.1017/S0950268801005921
7. Pinchinat S, Cebrián-Cuenca AM, Bricout H, et al. Similar herpes zoster incidence across Europe: Results from a systematic literature review. *BMC Infect Dis* 2013;**13**:170. doi:10.1186/1471-2334-13-170
8. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;**137**(1):38-47. doi:10.1017/S0950268808000678
9. Varghese L, Standaert B, Olivieri A, et al. The temporal impact of aging on the burden of herpes zoster. *BMC Geriatr* 2017;**17**:30. doi:10.1186/s12877-017-0420-9
10. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost effectiveness and resource allocation : C/E* 2010;**8**:7-7. doi:10.1186/1478-7547-8-7
11. Gater A, Abetz-Webb L, Carroll S, et al. Burden of herpes zoster in the UK: Findings from the zoster quality of life (ZQOL) study. *BMC Infect Dis* 2014;**14**:402. doi:10.1186/1471-2334-14-402
12. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: A prospective study. *CMAJ* 2010;**182**(16):1731-36. doi:10.1503/cmaj.091711
13. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *The Clinical journal of pain* 2007;**23**(6):490-6. doi:10.1097/AJP.0b013e318065b6c9

14. Joint Committee on Vaccination and Immunisation. Joint Committee on Vaccination and Immunisation Statement on varicella and herpes zoster vaccines. available from: http://webarchive.nationalarchives.gov.uk/20120907151317/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf [accessed June 26, 2018].
15. Merck Sharp Dohme Ltd. Zostavax Summary of Product Characteristics (SmPC). available from: <https://www.medicines.org.uk/emc/product/6101/smpc> [accessed June 26, 2018].
16. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *NEnglJMed* 2012;**366**(20):1859-69. doi:10.1056/NEJMoa1208410
17. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 2015;**60**(6):900-09. doi:10.1093/cid/ciu918
18. Tseng HF, Harpaz R, Luo Y, et al. Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged ≥ 60 Years. *J Infect Dis* 2016;**213**(12):1872-75. doi:10.1093/infdis/jiw047
19. Public Health England. Shingles (herpes zoster), 2016:Chapter 28a-Chapter 28a.
20. Public Health England. Herpes zoster (shingles) immunisation programme : September 2016 to August 2017 Report for England. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667636/Annual_shingles_report_2016-2017.pdf [accessed June 26, 2018].
21. Chlibek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. *Vaccine* 2016;**34**(6):863-68. doi:10.1016/j.vaccine.2015.09.073
22. GlaxoSmithKline Biologicals SA. Shingrix Summary of Product Characteristics (SmPC). available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004336/WC500246550.pdf [accessed June 26, 2018].
23. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med* 2015;**372**(22):2087-96. doi:10.1056/NEJMoa1501184
24. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med* 2016;**375**(11):1019-32. doi:10.1056/NEJMoa1603800
25. Curran D, Van Oorschot D, Varghese L, et al. Assessment of the potential public health impact of Herpes Zoster vaccination in Germany. *Hum Vaccin Immunother* 2017;**13**(10):2213-21. doi:10.1080/21645515.2017.1345399
26. Schmader KE, Levin MJ, Gnann JW, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis* 2012;**54**(7):922-28. doi:10.1093/cid/cir970
27. Office of National Statistics. 2014 based National population projections. available from:

- <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
28. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The United Kingdom. *Value Health* 2017;**20**(9):A786. doi:10.1016/j.jval.2017.08.2296
29. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;**82**(11):1341-9.
30. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;**157**(1):30-54. doi:10.1097/j.pain.0000000000000307
31. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine* 2001;**19**(23-24):3076-90. doi:10.1016/S0264-410X(01)00044-5
32. Bricout H, Haugh M, Olatunde O, et al. Herpes zoster-associated mortality in Europe: A systematic review. *BMC Public Health* 2015;**15**(1):466. doi:10.1186/s12889-015-1753-y
33. Public Health England. Influenza: the green book, chapter 19. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/663694/Greenbook_chapter_19_Influenza_.pdf [accessed June 29, 2018].
34. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (Shingles) and postherpetic neuralgia. *Mayo Clin Proc* 2009;**84**(3):274-80. doi:10.4065/84.3.274
35. Amirthalingam GA, Nick. Keel, Philip. Mullett, David. Correa, Ana. de Lusignan, Simon. Ramsay, Mary. Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study. *Lancet Public Health* 2018;**3**:e82-90. doi:10.1016/S2468-2667(17)30234-7
36. Walker JL, Andrews NJ, Amirthalingam G, et al. Effectiveness of herpes zoster vaccination in an older United Kingdom population. *Vaccine* 2018;**36**(17):2371-77. doi:10.1016/j.vaccine.2018.02.021
37. Joint Committee on Vaccination Immunisation. Minute of the meeting on 4 October 2017. available from: https://www.iostrust.org.uk/sites/default/files/minute_2017_10_draft.pdf <https://www.bmj.com/content/bmj/345/bmj.e6879.full.pdf> [accessed June 26, 2018].
38. Van Oorschot D, Hunjan M, Varghese L, et al. The public health perspective of an investigational herpes zoster vaccine in the united kingdom (UK). *Value Health* 2016;**19**(7):A400-A00. doi:10.1016/j.jval.2016.09.309
39. Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. *JAMA Internal Medicine* 2018;**178**(2):248-58. doi:10.1001/jamainternmed.2017.7431

- 1
2
3 40. Varghese L, Nissen M, Olivieri A, et al. Public health perspective of phase III
4 results of an investigational Herpes Zoster vaccine. Public Health Association
5 of Australia. *Public Health Association of Australia - Communicable Disease*
6 *Control Conference*, Brisbane 2015:42.
7 <https://www.phaa.net.au/documents/item/581> (accessed June 26, 2018).
8
9 41. Varghese L, Curran D, Yan S, et al. Estimating the Potential Public Health Impact
10 of Introducing the HZ/su Vaccine in the US Population Aged ≥ 50 Years. *Open*
11 *Forum Infectious Diseases* 2015;**2**(suppl_1). doi:10.1093/ofid/ofv133.1477
12
13 42. Curran D, Athan E, Diez-Domingo J, et al. Quality-of-Life Impact of an
14 Investigational Subunit-Adjuvanted Herpes Zoster Vaccine in Adults ≥ 50 Years
15 of Age. *Open Forum Infectious Diseases* 2016;**3**(suppl_1).
16 doi:10.1093/ofid/ofw194.77
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

FOOTNOTES

TRADEMARK

Shingrix is a trademark of the GSK group of companies.

Zostavax is a trademark from Merck Sharp & Dohme Corp.

AUTHORS' CONTRIBUTION

DVO, DC, SL, BB participated to the conception and design of the analysis; DVO, DC, MH developed and adapted the model; DVO, DC, MH, HSC, BB were involved in the collection, analysis and/or interpretation of the data. All authors had full access to the data and approved the final version of the paper for submission.

CONFLICTS OF INTEREST

DVO, MH, BB, DC and HSC are employees of the GSK group of companies. MH, DC, and HSC hold shares in the GSK group of companies. SL is a freelance consultant working on behalf of the GSK group of companies.

DATA SHARING STATEMENT

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

ETHICAL APPROVAL

Ethical approval is not applicable for modelling analysis.

FUNDING SECTION

GlaxoSmithKline Biologicals SA funded this study (GSK study identifier: HO-17-18511) and was involved in all stages of study conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also covered all costs associated with the development and publication of this manuscript.

TABLES AND FIGURES

Table 1: Demographic, epidemiological and efficacy data according to age group

Age		50 YOA	60 YOA	65 YOA	70 YOA	80 YOA
Number of people in-age group in 2018		908,255	783,067	686,215	722,616	389,107
HZ incidence per 1,000 individuals	IC	6.85	8.80	9.93	11.32	12.61
	IC-Free	4.9	6.92	8.62	11.04	11.02
Proportion developing PHN (%)		11.42	13.89	15.71	17.12	20.42
Non-PHN complications incidence (%)	Ocular	2.87	3.82	3.82	4.14	5.41
	Neurological	2.46	3.17	3.17	5.99	4.23
	Cutaneous	1.74	1.05	1.05	2.09	2.44
	Other	2.03	1.63	1.63	2.44	2.85
HZ - Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95-100)	98.4 (95-100)	98.4 (95-100)	97.8 (94.1-100)	97.8 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (54.1-80.6)	63.9 (56.0-71.0)	63.9 (56.0-71.0)	40.85 (28.0-52.0)	18.25 (0-48.0)
PHN Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95.0-100)	98.4 (95.0-100)	98.4 (95.0-100)	97.84 (94.1-100)	97.84 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (30.8-89.6)	65.69 (25.4-84.2)	65.69 (25.4-84.2)	73.38 (51.6-85.8)	39.51 (0-73.8)

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

Table 2: Health outcomes and health resource utilisation in the vaccination cohort 70 YOA - base-case analysis, N=722,616

	RZV	ZVL	No vaccination	RZV vs no vaccination	ZVL vs no vaccination
HZ cases, n	88,643	110,996	118,905	30,262	7,909
PHN cases, n	16,570	18,411	21,979	5,409	3,567
HZ-related complications					
Total, n	13,109	16,405	17,565	4,455	1,160
Ocular, n	4,207	5,221	5,548	1,341	327
Neurological, n	4,565	5,782	6,255	1,691	474
Cutaneous, n	2,001	2,492	2,658	657	165
Other non-pain, n	2,336	2,910	3,103	767	193
Deaths					
HZ-related deaths, n	56	64	64	8	0
Resource utilisation					
Hospitalisation, n	7,827	9,463	9,820	1,993	357
GP visits, n	438,328	546,691	583,612	145,284	36,921

GP: general practitioner; HZ: herpes zoster; PHN: postherpetic neuralgia; n: number of cases; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

Table 3 NNV to avoid one case of HZ or PHN according to age at vaccination

Age cohort	NNV HZ		NNV PHN	
	RZV	ZVL	RZV	ZVL
50 YOA	10	39	69	328
60 YOA	9	27	55	171
65 YOA	10	23	54	134
70 YOA	12	45	65	98
80 YOA	17	156	82	258

RZV: adjuvanted recombinant zoster vaccine; HZ: herpes zoster ; YOA: years of age; ZVL: zoster vaccine live; NNV: number needed to vaccinate

For peer review only

Table 4 Reduction on resource utilisation per 100,000 people

	GP visits avoided		Hospitalisations avoided	
	RZV	ZVL	RZV	ZVL
50 YOA	17,481	3,652	126	17
60 YOA	22,078	6,375	216	42
65 YOA	23,447	8,702	266	69
70 YOA	20,105	5,109	276	49
80 YOA	15,243	1,629	394	42

GP: general practitioner; HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

For peer review only

1
2
3 **Figure 1 Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light**
4 **blue bars) comparing RZV vs no vaccination in people 70 YOA**

5 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; PHN: postherpetic neuralgia; YOA: years of age

6
7 **Figure 2 Impact of second-dose RZV compliance on HZ incidence**

8 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live

9
10 **Figure 3 Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for**
11 **different vaccination cohorts.**

12
13 HZ: herpes zoster; no vac: no vaccination; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster
14 vaccine; YOA: years of age; ZVL: zoster vaccine live

15
16 **Figure 4 Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70**
17 **YOA; coverage 48.3%; compliance 70%)**

18 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

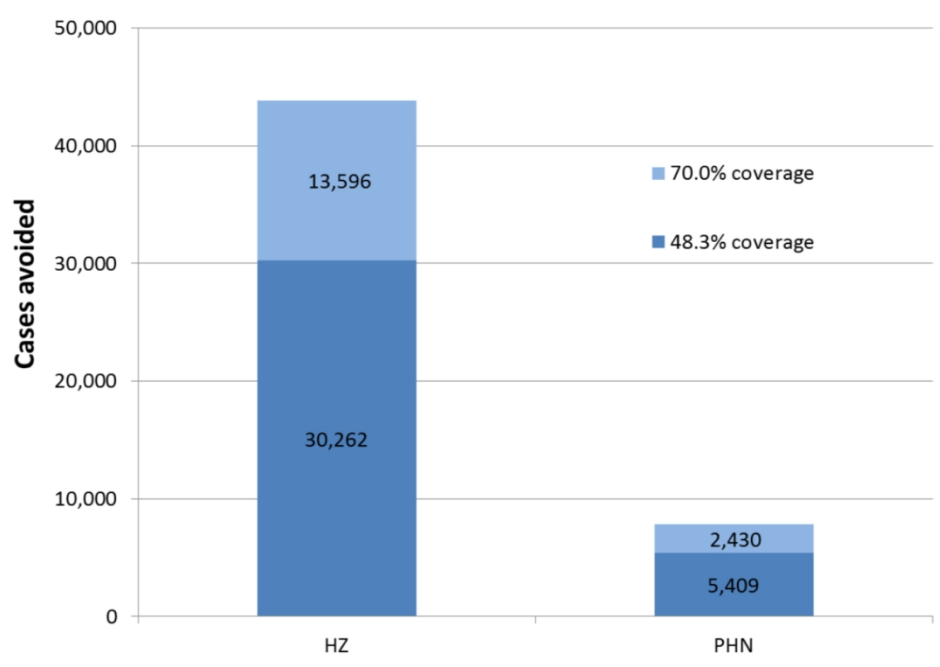
19
20 **Figure 5 Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL**

21 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live

22
23 The orange line shows the percentage of simulations averting at least the number of HZ cases shown on the x-
24 axis.

25
26 **Figure 6 Lay language summary of the study**

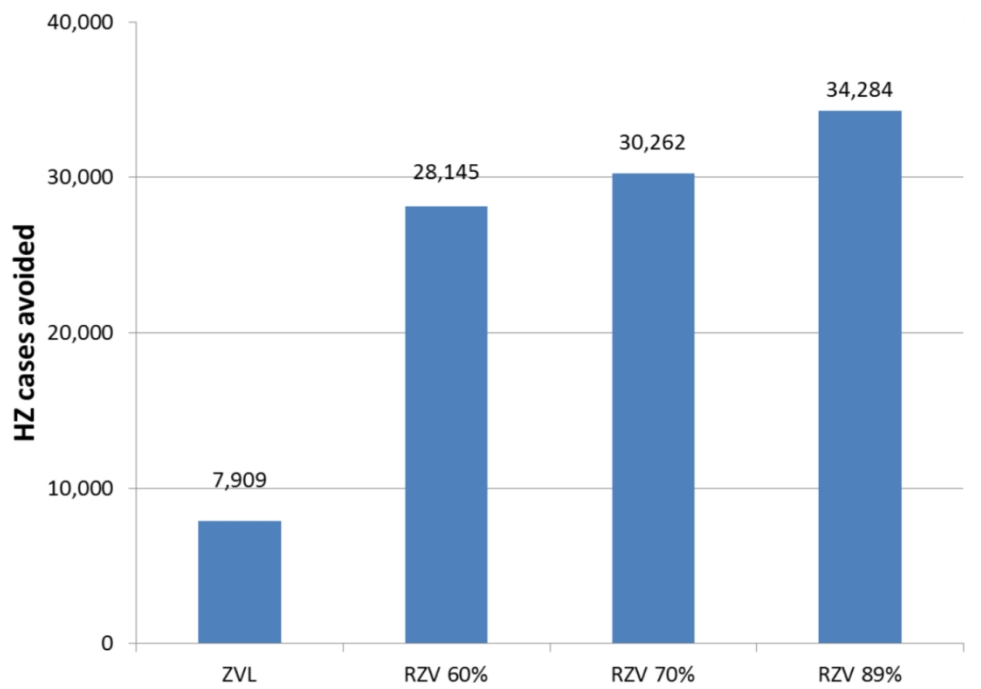
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light blue bars) comparing RZV vs no vaccination in people 70 YOA

131x90mm (300 x 300 DPI)

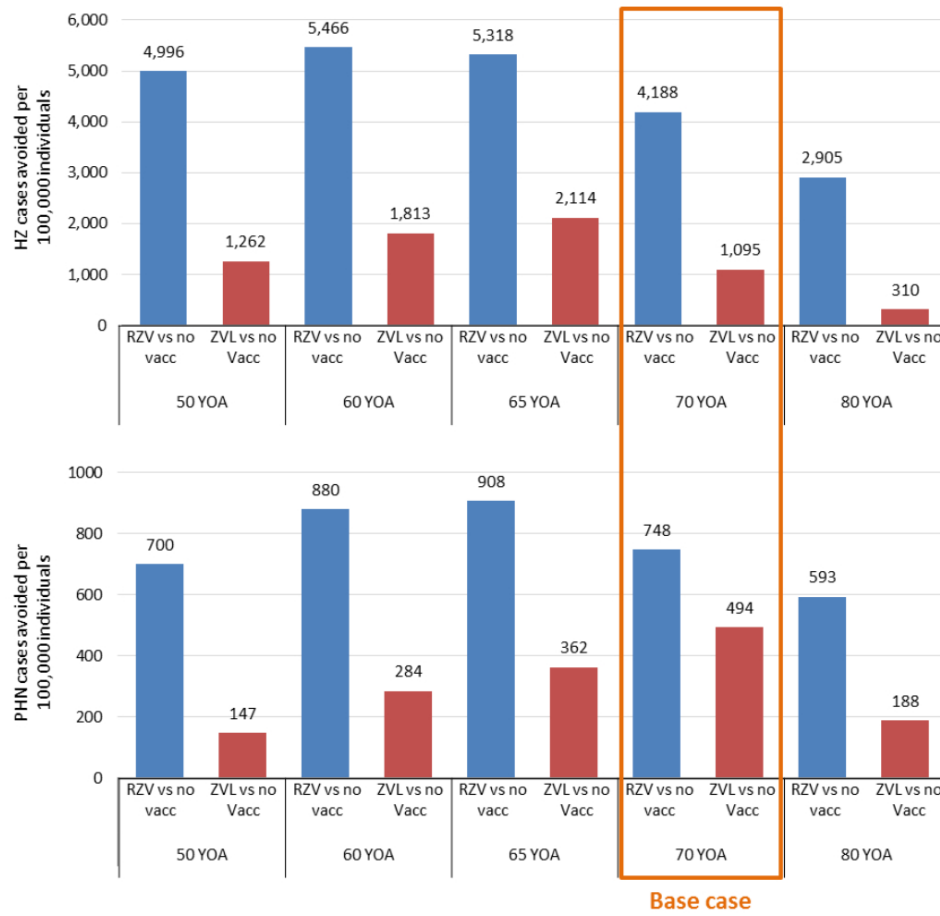
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Impact of second-dose RZV compliance on HZ incidence

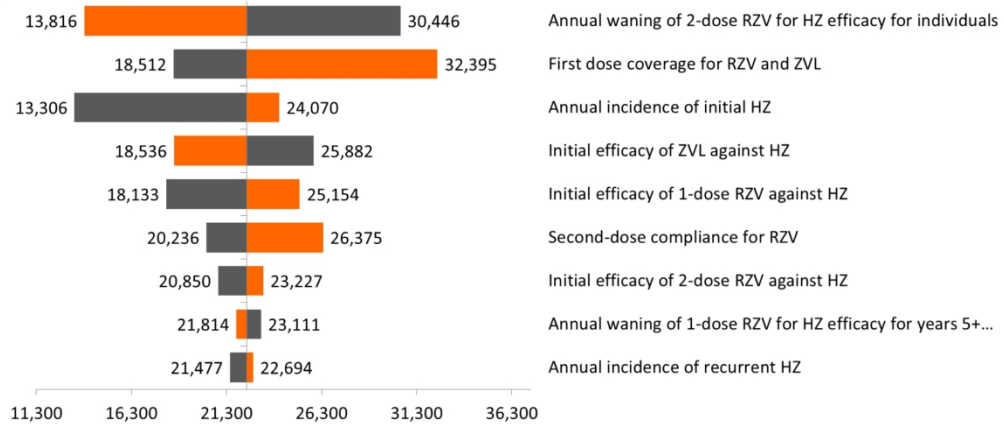
128x90mm (300 x 300 DPI)

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



Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

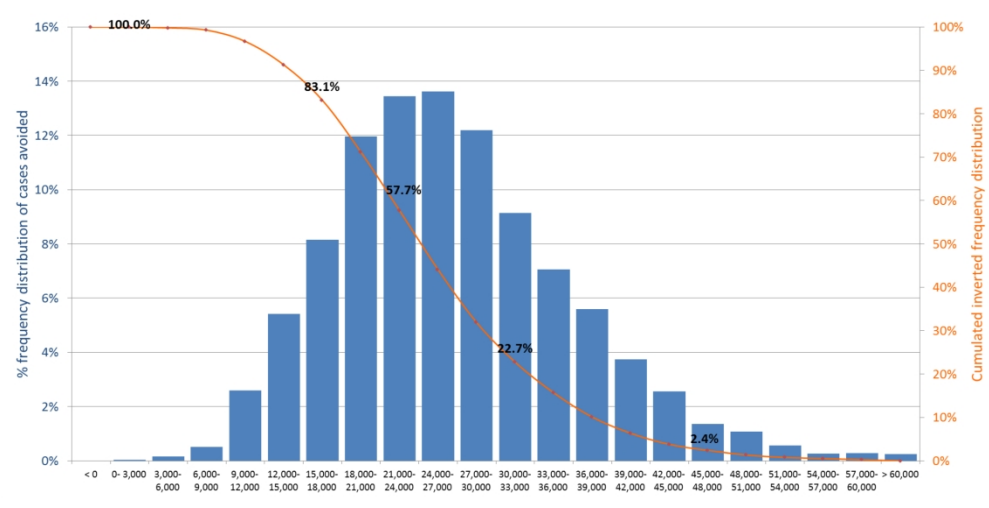
91x90mm (300 x 300 DPI)



Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

179x77mm (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



Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

186x90mm (300 x 300 DPI)



Focus on the Patient

What is the context?

Herpes zoster (shingles) is a painful rash that lasts for several weeks and which can lead to prolonged pain even after the initial rash has cleared. Herpes zoster arises when varicella zoster virus, acquired during varicella, reactivates. This happens especially in older people with a weakened immune system. Herpes zoster has a detrimental impact on the quality of life and current treatment options provide only partial symptom relief.

What is new?

In the UK, a universal mass vaccination programme against herpes zoster has been introduced in 2013. The programme recommends vaccination of people aged 70 or 78 years with a zoster vaccine live, the only vaccine available at that time. In 2018, a new recombinant zoster vaccine against herpes zoster has become available. The goal of this study was to explore the impact of different vaccination strategies using a mathematical model.

What is the impact?

The model predicts that the recombinant zoster vaccine would lead to a greater reduction in the number of herpes zoster episodes compared to the zoster vaccine live. Furthermore, the model suggests that the duration of protection with the recombinant zoster vaccine lasts longer. If adopting a vaccination strategy with the recombinant zoster vaccine, the optimal age at vaccination would be 60 or 65 years old.

Lay language summary of the study

162x92mm (300 x 300 DPI)

Supplementary Material

Evaluation of the public health impact of
introducing a novel Adjuvanted Recombinant
Zoster Vaccine into the UK universal mass
vaccination programme

Van Oorschot Desirée, Hunjan Manjit, Bracke Benjamin, Lorenc
Stéphane, Curran Desmond, Starkie Camejo Helen

BMJ Open

SI Table 1: Mortality in the general UK population in 2018/2019

Age (YOA)	Number of deaths	Annual probability of death
50-54	15,903	0.00342
55-59	22,590	0.00544
60-64	29,886	0.008366
65-69	45,562	0.013091
70-74	65,747	0.021570
75-79	78,692	0.036493
80-84	104,536	0.065713
85-89	114,461	0.117689
90-94	82,948	0.198093
95-99	33,361	0.304037
≥ 100	5,496	0.436439

YOA: years of age.

Projected numbers using data reported by the Office of National Statistics based on observed numbers of the UK population in 2014.¹

The immunocompromised (IC) population was identified as individuals presenting one of the following conditions: Hematopoietic stem cell transplantation, solid organ transplantation, solid organ malignancies, haematological malignancies, human immunodeficiency virus, end-stage renal disease, corticosteroid exposure, other immunosuppressive therapy, other immunodeficiency conditions and autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, multiple sclerosis, polymyalgia rheumatica and autoimmune thyroiditis).

Herpes Zoster (HZ) incidence for the whole (IC and IC-free) population was calculated by applying a weighting for IC proportion by age group.² A unitary weight across the populations was not deemed to be appropriate or robust as prevalence of herpes zoster varies between the age groups; rising with increasing age. This is because applying IC incidence, accounting for the overall proportion of IC (16.2%) irrespective of age group would underestimate the incidence in older people and overestimate it in younger people.

SI Table 2: Weighting CPRD population for IC proportion by age

Age Group (YOA)	Prevalence of IC (%)	IC weighting	IC-free weighting
50-59	16.13	0.161	0.839
60-64	22.26	0.223	0.777
65-69	27.56	0.276	0.724
70-79	34.88	0.349	0.651
≥ 80	42.16	0.422	0.578

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 3: Incidence and probability of HZ in the whole population

Age (YOA)	Incidence rate/1,000 patient years		Probability	Range	
	IC	IC-Free		Lower limit	Upper limit
50-59	6.85	4.9	0.0052	0.00375	0.00791
60-64	8.8	6.92	0.0073	0.004392	0.009001
65-69	9.93	8.62	0.0089	0.005108	0.010147
70-79	11.32	11.04	0.0111	0.005975	0.011605
≥ 80	12.61	11.02	0.0116	0.007363	0.013955

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 4: Proportion of PHN (after 3 months)

Age (YOA)	Proportion (%)	Lower limit (%)	Upper limit (%)
50-59	11.418	8.91	14.13
60-64	13.894	12.03	15.88
65-69	15.705	13.95	17.57
70-79	17.116	13.53	20.94
≥ 80	20.418	17.08	23.82

PHN: postherpetic neuralgia; YOA: years of age

SI Table 5 HZ-associated mortality

Age (YOA)	Probability	Lower limit	Upper limit
50-54	0.00001	0.0000063	0.000012
55-59	0.00001	0.0000063	0.000012
60-64	0.00003	0.0000189	0.000035
65-69	0.00003	0.0000189	0.000035
70-74	0.00004	0.0000245	0.000046
75-79	0.00009	0.0000644	0.000120
80-84	0.00049	0.0003409	0.000633
85-89	0.00202	0.0014126	0.002623
90-94	0.00202	0.0014126	0.002623
95-99	0.00202	0.0014126	0.002623
≥ 100	0.00202	0.0014126	0.002623

HZ: herpes zoster; YOA: years of age

SI Table 6: Hospitalisation rates in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	0.044	0.007	0.012622
60-64	0.054	0.009	0.019245
65-69	0.050	0.014	0.023713
70-79	0.074	0.030	0.045143
≥ 80	0.168	0.115	0.135529

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age; IC-free: immunocompetent

*Weighted averages calculated using IC proportions in the CPRD study.

SI Table 7 GP visits in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	3.75	2.69	2.86
60-64	4.41	2.86	3.20
65-69	5.05	3.19	3.70
70-79	5.75	4.09	4.67
≥ 80	6.15	4.59	5.25

*Weighted averages calculated using IC proportions in the CPRD study.

CPRD: Clinical Practice Research Datalink; GP: general practitioner; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 8: Vaccine Efficacy against HZ and PHN

Age (YOA)	ZVL			RZV – 2-dose			RZV – 1-dose		
	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit
HZ									
50-59	0.698	0.5410	0.8060	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.4085	0.2800	0.5200	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.1825	0.0000	0.4800	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
PHN									
50-59	0.698	0.3080	0.8960	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.7338	0.5160	0.8580	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.3951	0.0000	0.7380	0.9784	0.9410	1.0000	0.695	0.2490	0.8910

HZ: herpes zoster; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

SI Table 9: Vaccine Waning

Vaccine	Age group (YOA)/years after vaccination	Value	5% CI	95% CI
ZVL – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600
RZV – 2-dose	< 70 YOA/Years 1-4	0.010	0.0000	0.0260
	< 70 YOA/Years 4+	0.0230	0.0070	0.0460
	≥70 YOA/ all years after vaccination	0.0360	0.0140	0.0660
RZV – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600

CI: confidence interval; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

REFERENCES

1. Office of National Statistics. 2014 based National population projections. available from: <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
2. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The United Kingdom. *Value Health* 2017;**20**(9):A786. doi:10.1016/j.jval.2017.08.2296

For peer review only

Section/Item	Item no	Recommendation	Reported on page no/line no	Comment
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared	p 1	Strictly speaking, this is not an economic evaluation but public health impact study, as stated in the title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P 4/5	
Introduction				
Background and Objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	p. 7 p. 8	Context provided in first paragraph (epidemiology and rise of HZ episodes during past decades) “The objective of this study is to explore the public health impact of introducing the RZV vaccine in the UK in the routine population 70 YOA.”
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen	p. 8 p. 8/p. 12	See sentence above for base-case scenario (routine population 70 YOA). “Different scenario analyses are carried out to assess the impact of first dose RZV coverage and second dose RZV compliance and to determine the optimal age for vaccination.” Base-case was chosen because representing the current routine vaccination cohort in the UK. Scenario analyses chosen to test uncertainties in coverage and potential

				differences in optimal vaccination age between RZV and ZVL as explained on page 12.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	p. 8 p. 9	UK setting where there is UMV currently in place. “The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting”
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	NA	Public health impact study, not cost-effectiveness study.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	p. 9 p. 8	Vaccination with RZV, with ZVL and no vaccination UK setting with current UMV with ZVL And a small portion of patients contraindicated to ZVL (no vaccination)
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	p. 10	“Cycle length is set to one year and a life-long time horizon is assumed.”
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	NA	Public health impact study, not cost-effectiveness study.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	p. 12	“The model was used to estimate the avoidance of HZ and PHN cases, complications, deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related deaths and number of GP visits and hospitalisations for three different vaccination strategies...”
Measurements of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study	NA	

		was a sufficient source of clinical effectiveness data		
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	p. 11	“Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the ZOE-50 and ZOE-70 trials for RZV (Table 1, SI Table 8).” And following paragraphs for efficacy/waning
Measurement of valuation based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	NA	Public health impact study, not cost-effectiveness study.
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	NA	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	P. 11	“The CPRD study was used to derive the proportion of patients being hospitalised or visiting their GP due to HZ-related complications. Hospitalisation rates were higher in the IC cohort for all age-groups. In addition, health-care resource use was higher in older adults (SI Tables 6 & 7).” No unit costs, since PHI study
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe	NA	

		methods for converting costs into a common currency base and the exchange rate		
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	p. 9	“The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting.” Reference is made to Curran et al, 2017 which shows Figure and additional details regarding model structure
Assumptions	16	Describe all structural or other assumptions underpinning the decision analytical model	p. 9 p. 12	First paragraph (Model structure) and Curran et al, 2017 Coverage and compliance assumptions: “In the base-case analysis, coverage is set at 48.3% in line with latest coverage numbers for the UK. The impact of different coverage rates was assessed in sensitivity analyses. Compliance with the second-dose of RZV was set to 70%.”
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	p. 12 p. 13	“Different scenario analyses were carried out where assumptions regarding vaccination coverage and compliance and age at vaccination were changed” And rest of paragraph Sensitivity analyses (DSA and PSA) described
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to	p. 15 SI Tables 3 – 5 and Tables 8 - 11	“In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the robustness of results was tested by changing input parameters to their lower and upper estimated confidence ranges (SI Tables 3 – 5;

		show the input values is strongly recommended		SI Tables 8 - 11)"
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	p. 14 Table 2	"In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a reduction of 7,909 HZ and 3,567 PHN cases (Error! Reference source not found.)"
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	NA	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	p. 13/14 Figure 1-3 Table 3 p. 15 Figure 4	Scenario analyses Sensitivity analyses
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	p. 14 Figure 3	Subgroup analyses according to age cohorts
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	p. 15	"In the base-case considering the current vaccination cohort of people 70 YOA, RZV reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no vaccination..." and subsequent paragraphs

			p. 18	“As with every model, there are strengths and limitations associated with the modelling strategy employed....”
			p. 17/18	Comparison to existing PHI and CE studies.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	p. 20	Funding
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	p. 20	Conflict of interest

BMJ Open

Public health impact model estimating the impact of introducing an Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025553.R1
Article Type:	Research
Date Submitted by the Author:	31-Oct-2018
Complete List of Authors:	van Oorschot, Desiree; GlaxoSmithKline Hunjan, Manjit; GlaxoSmithKline Bracke, Benjamin ; GlaxoSmitKline Lorenc, Stephane; GlaxoSmithKline, Freelance on behalf of GSK Curran, Desmond; GlaxoSmithKline Starkie-Camejo, Helen; GlaxoSmithKline
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Infectious diseases
Keywords:	Shingles, Adult vaccination, herpes zoster, recombinant zoster vaccine, Public health < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3
4
5 **TITLE PAGE**
6
7

8 **TYPE OF MANUSCRIPT:**
9

10
11 **MANUSCRIPT TITLE:**
12

13 *Public health impact model estimating the impact of introducing an Adjuvanted*
14 *Recombinant Zoster Vaccine into the UK universal mass vaccination programme*
15

16
17 **AUTHOR(S):**
18

19 Van Oorschot Desirée¹, Hunjan Manjit², Bracke Benjamin¹, Lorenc Stéphane³, Curran
20 Desmond¹, Starkie Camejo Helen²
21
22

23
24 **AFFILIATIONS:**
25

26 ¹ GSK, Wavre, Belgium; ² GSK, Uxbridge, UK; ³ Freelance, on behalf of GSK, Wavre,
27 Belgium
28
29

30
31 **CORRESPONDING AUTHOR:**
32

33 Name: Van Oorschot Desirée

34 Mailing Address: Avenue Fleming 20, 1300, Wavre, Belgium

35 Phone No: +3210855111

36 E-mail address: desiree.x.van-oorschot@gsk.com
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

OBJECTIVES

In 2013, the Herpes Zoster (HZ) immunisation programme was introduced in the UK, recommending vaccination of adults 70 years of age (YOA) with the zoster vaccine live (ZVL), the only vaccine available at the time. The recently approved Adjuvanted Recombinant Zoster Vaccine (RZV) has a substantially different clinical profile that may offer additional benefits.

This study aimed to 1) assess the public health impact (PHI) of introducing RZV in the UK compared to the current vaccination strategy and 2) explore via scenario analyses the optimal age-group of vaccination in terms of PHI.

DESIGN

A previously developed health economic model was adapted to the UK setting.

SETTING

Calculations were based on efficacy data from pivotal clinical trials, HZ incidence and PHN probability from a UK study, and HZ-associated complication rates from published literature.

POPULATION

The base-case population considered a 2018-projected UK vaccination cohort of individuals 70 YOA.

INTERVENTIONS

Vaccination with ZVL or RZV, assuming a first-dose coverage of 48.3% for both vaccines and 70% compliance for the second-dose of RZV.

OUTCOME MEASURES

Outcomes included reduction of HZ and postherpetic neuralgia (PHN) cases, complications and the use of health-care resources over a life-time horizon. The impact of coverage and second-dose compliance was also explored.

RESULTS

Compared to no vaccination, RZV would lead to a reduction of 30,262 HZ and 5,409 PHN cases while ZVL would lead to a reduction of 7,909 HZ and 3,567 PHN cases. The number needed to vaccinate to prevent 1 HZ case is 12 with RZV and 45 with ZVL. The highest PHI with RZV could be achieved in individuals 60 or 65 YOA.

CONCLUSION

Under the model assumptions, RZV is predicted to avert more HZ and PHN cases compared to ZVL. Results were robust under different scenario and sensitivity analyses.

KEYWORDS

Herpes Zoster vaccination; adjuvanted recombinant zoster vaccine; public health impact

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The most recent UK-specific data from published literature is included in the ZONA model.
- Model structure and inputs have been validated by external experts.
- Results of this analyses estimate the impact of an RZV program in the UK population in 2018.
- Further analyses have to be performed once long term effectiveness data becomes available on the duration of protection of RZV.
- Assumptions regarding second dose compliance had to be made in absence of real-world data.

INTRODUCTION

The varicella zoster virus (VZV) usually affects children and leads to varicella, also known as chickenpox. The virus remains dormant life-long in patients' dorsal root ganglia.¹ Later in life, VZV specific T-cell-immunity decreases due to immunosenescence or immunosuppressing illnesses or medications. Reactivation of VZV results in herpes zoster (HZ), also called shingles.^{2 3} Over 95% of individuals will have acquired VZV during their childhood or early adulthood.^{4 5} Approximately one in three people will develop HZ during their life-time with the risk increasing sharply after the age of 50 years of age (YOA), leading to an estimated 5 HZ episodes per 1,000 people in the UK, each year.⁶⁻⁸ Similar incidence rates were reported in other European countries and elsewhere.^{2 7} Furthermore, results from observational studies suggest that HZ incidence has risen during the past decade in various countries and is predicted to continue to rise as the average age of the population increases.^{2 9 10}

HZ tends to start with prodromal pain, followed by a dermatomal rash which is usually unilateral and develops typically over the trunk or face. Rash is often accompanied by severe pain. Skin lesions and pain usually disappear completely within 4–6 weeks. Postherpetic neuralgia (PHN), often defined as pain persisting or appearing 30 to 90 days after rash onset, is the most common complication which can last from several weeks to months.^{8 11} Even though mortality due to HZ infection is low, HZ greatly affects quality of life (QoL) in terms of physical and social functioning and the well-being of the patients.¹² Furthermore, severity of pain strongly correlates with the reported QoL.^{11 13} Current treatment options, which mainly rely on antivirals, analgesics and antidepressants, provide only partial symptomatic relief and limited protection against the development of PHN and other complications. Thus, the impact of the disease on patients QoL is not adequately managed with existing interventions.¹¹

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommended universal mass vaccination (UMV) for HZ using Zoster Vaccine Live (ZVL; *Zostavax*)¹⁴, the only vaccine available at the time the UMV programme was introduced in 2013. ZVL is a live-attenuated virus vaccine indicated for the prevention of HZ and, in Europe, of PHN in individuals ≥ 50 YOA.¹⁵ Vaccine efficacy (VE) against HZ (VE_{HZ}) of ZVL in the shingles prevention study (SPS) was 63.9% in individuals 60-69 YOA and 37.6% in individuals ≥ 70 YOA.^{15 16} Long-term clinical trial data and observational effectiveness studies showed that VE of ZVL decreased substantially over time conferring little or no protection against HZ beyond 8 years after vaccination.^{17 18}

1
2
3
4 Even though ZVL is indicated in individuals ≥ 50 YOA, the JCVI recommended
5 vaccination with ZVL at 70 YOA (and a catch-up vaccination for people 78 YOA), based
6 on clinical trial data and an economic model showing that vaccination at 70 YOA would
7 be the most cost-effective option given that the burden of disease increases with age,
8 while VE of ZVL decreases in older individuals and over time.^{3,14} A further limitation to
9 the indicated use of ZVL in individuals ≥ 50 YOA is its contraindication in primary or
10 acquired immunodeficiency states due to blood disorders or other types of cancer,
11 infection with human immunodeficiency virus, or due to high dose
12 immunosuppressive therapy.¹⁵⁻¹⁹ A proportion of individuals would therefore not be
13 able to receive ZVL.²⁰

14
15
16
17
18
19
20 A novel Adjuvanted Recombinant Zoster Vaccine (RZV, *Shingrix*) has been granted
21 marketing authorisation by the European Medicines Agency (EMA) and is indicated for
22 use in individuals ≥ 50 YOA. RZV is a non-live vaccine consisting of the VZV glycoprotein
23 E (gE), a prominent antigen target of VZV-specific CD4+ T-cell immune responses, and
24 AS01_B adjuvant system, which boosts immunogenicity and duration of the immune
25 response.²¹ RZV is administered in two doses 2 to 6 months apart and is not
26 contraindicated in immunocompromised (IC) individuals as it is a non-live vaccine. As
27 with other vaccines, the administration of Shingrix to immunocompromised subjects
28 should be based on careful consideration of potential benefits and risks.²² Two large,
29 phase III trials, i.e. the Zoster Efficacy Studies in Adults 50 and 70 YOA or older [ZOE-50
30 (NCT01165177) and ZOE-70 (NCT01165229), respectively] demonstrated high VE_{HZ} of
31 RZV in all age-groups; VE_{HZ} was 97.2% in individuals ≥ 50 YOA included in the ZOE-50
32 study and 91.3% in individuals ≥ 70 YOA included in the ZOE-50 and ZOE-70 studies.²³
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
24 VE persisted over the four-year duration of the clinical trial.²⁴

61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

The objective of this study is to explore the public health impact of introducing the RZV vaccine in the UK in the routine population 70 YOA. The effect of RZV and ZVL on HZ and PHN incidence, complications and health resource utilisation is compared to no vaccination. Different scenario analyses are carried out to assess the impact of first-dose RZV coverage and second-dose RZV compliance and to determine the optimal age for vaccination.

METHODS

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were not involved as the analysis is based on mathematical modeling.

MODEL STRUCTURE

The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting. The economic model considers up to five various age cohorts that can transition between different health states, including no HZ, HZ, health states associated with complications of HZ (PHN and non-PHN complications) and death from HZ or natural causes.²⁵ Cycle length is set to one year and follows all subjects from the year of intervention over their remaining life-time. The model has three different arms, having the same yearly model structure: No vaccination, vaccination with RZV and vaccination with ZVL. Within the vaccine strategy, individuals can be fully compliant with the vaccine dosing schedule, only partially or not vaccinated at all (depending on the compliance rate). Further details regarding the model structure are reported in Curran et al, 2017.²⁵

MODEL INPUT PARAMETERS

Wherever possible, UK-specific data were used. Efficacy data for RZV and ZVL were derived from pivotal clinical trials conducted for ZVL and RZV.^{16 23 24 26} Both model structure and global inputs such as VE and waning were validated with an external expert panel (epidemiologists, clinicians and health economists with a background in HZ) in September 2016.

DEMOGRAPHICS

Populations in the model are projected to 2018 values. The base-case population consisted of the routine vaccination cohort 70 YOA. Based on projections by the Office of National Statistics (ONS)²⁷, the predicted population numbers in the routine cohort of 70 YOA is 722,616, in 2018. Different age cohorts were modelled for use in scenario analyses (Table 1).

All-cause mortality rates were derived from ONS data projected to the year 2018/2019 (Supplementary information [SI] Table 1).²⁷

EPIDEMIOLOGY

HZ INCIDENCE

HZ incidence was derived from a recent UK Clinical Practice Research Datalink (CPRD) study, which assessed the incidence of HZ in immunocompetent (IC-free) and IC individuals between 2000 and 2012²⁸ (SI Table 2). The CPRD database study presents the most recent real-world data on HZ incidence and was therefore considered the most appropriate source for this parameter. The IC-free and IC population were matched by age, gender and location of general practitioner (GP) and the proportion of IC individuals was adjusted in the whole population to account for an increase in immunodeficiencies in older individuals. In the age-group 70-79 YOA, 35% of individuals had primary or acquired immunodeficiency and a subgroup of this IC population is contraindicated to receive ZVL. Incidence numbers were converted to annual probabilities of developing HZ (Table 1). Lower and upper ranges of probabilities for HZ incidence in the whole population were obtained from published data since it was not possible to derive it from the split IC and IC-free data set analysed in the CPRD study³ (SI Table 3).

Incidence rate of recurrent HZ is assumed to be the same as the incidence of the initial event. This assumption is supported by published data which indicates that the incidence rates of initial and recurrent HZ events are similar.^{29 30}

PHN PROBABILITY

PHN is defined as pain appearing or persisting for more than 3 months after initiation of HZ. PHN incidence was derived from published data.^{8 31} Gauthier et al. derived PHN incidence from the CPRD in the population excluding patients with underlying IC conditions using prescription medication records on top of PHN codes to identify these episodes. Forbes et al reported odds ratios of developing PHN for people with human immunodeficiency virus and hematopoietic stem cell transplantation compared to IC-free population and these data were used in combination with data reported by Gauthier et al. to model the proportion of PHN cases following an episode of HZ in the general population (Table 1, SI Table 4). As for HZ, the model assumes that the incidence of recurrent PHN is the same as for first-time PHN.

HZ-RELATED MORTALITY

Values for HZ-associated mortality are based on published literature³² (SI Table 5). The

1
2
3
4 study by Edmunds et al. was the only report including a granular breakdown of HZ
5 case fatality rate by age-group in the UK and was therefore considered to be the most
6 appropriate source for HZ-associated mortality. The published data are based on the
7 population of England and Wales. However, increasing mortality with increasing age
8 is consistent with observations from studies conducted in other countries³³ and it is
9 assumed that these rates apply to the entire UK population.
10
11
12

13 *NON-PHN COMPLICATIONS*

14
15
16 A wide range of complications other than PHN can occur in people experiencing an
17 episode of HZ and could have a substantial impact on the burden of the disease. In the
18 model, four main categories of complications were included, i.e., ocular, neurological,
19 cutaneous and other non-pain complications. Probabilities of developing these
20 complications after the initial HZ episodes were taken from published literature²⁹
21 (Table 1).
22
23
24

25 *HOSPITALISATION AND GP VISITS DUE TO COMPLICATIONS*

26
27
28 The CPRD study was used to derive the proportion of patients being hospitalised or
29 visiting their GP due to HZ-related complications.²⁸ Hospitalisation rates were higher
30 in the IC cohort for all age-groups. In addition, health-care resource use was higher in
31 older adults (SI Tables 6 & 7).
32
33
34

35 *VACCINE EFFICACY AND SAFETY*

36 *EFFICACY*

37
38
39 Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from
40 the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the
41 ZOE-50 and ZOE-70 trials for RZV^{16 23 24 26} (Table 1, SI Table 8). VE for RZV is based on a
42 2-dose schedule given 2 months apart. However, compliance with 2nd dose RZV is likely
43 to be lower than 100%, as such there is a cohort of individuals who are only vaccinated
44 with one dose. Therefore, efficacy data for 1-dose RZV were analysed post-hoc based
45 on limited clinical data from individuals in the ZOE trials receiving only 1-dose RZV.²⁵
46
47
48
49
50
51

52
53 Waning for both vaccines was modelled by linear fitting, using data from the above-
54 mentioned trials as well as from the long-term persistence study (LTPS) for ZVL.²⁵ For
55 RZV, waning rates were assumed to be 1% (range: 0%, 2.6%) during the first 4 years
56 after vaccination and 2.3% (range: 0.7%, 4.6%) thereafter in individuals < 70 YOA. In
57
58
59
60

1
2
3
4 the population ≥ 70 YOA, waning rate was assumed to be constant over time at 3.6%
5 (range: 1.4%, 6.6%).²⁵ For ZVL, the model indicated a waning rate of 5.4% (range: 4.5%,
6 6.4%) during the first 4 years after vaccination and 5.1% (range: 4.1%, 6.0%) thereafter
7 in all age-groups^{17 25} (SI Table 9).
8
9

10 *COVERAGE AND COMPLIANCE*

11
12
13 In the base-case analysis, coverage is set at 48.3% in line with latest coverage numbers
14 for the UK.²⁰ The impact of different coverage rates was assessed in sensitivity
15 analyses. Compliance with the second-dose of RZV was set to 70%.
16
17

18 *OUTCOMES*

19
20
21 The model was used to estimate the avoidance of HZ and PHN cases, complications,
22 deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related
23 deaths and number of GP visits and hospitalisations for three different vaccination
24 strategies, i.e., vaccination with RZV, vaccination with ZVL and no vaccination.
25
26

27
28 The number needed to vaccinate (NNV) to avert one case of HZ and PHN was also
29 evaluated by applying the following calculation:
30
31

$$32 \quad NNV = \frac{1}{\left(\frac{\text{control cases}}{\text{vaccinated persons}} \right) - \left(\frac{\text{vaccinated cases}}{\text{vaccinated persons}} \right)}$$

33 *SCENARIO ANALYSES*

34
35
36 Different scenario analyses were carried out where assumptions regarding vaccination
37 coverage and compliance and age at vaccination were changed.
38
39

40
41 In a first scenario analysis, the impact of increasing coverage of RZV to 70% was
42 explored. A higher coverage of 70% in the UK was deemed plausible considering that
43 a) the influenza vaccine uptake in people ≥ 65 YOA was 70.5% in 2016/2017³⁴ and b)
44 in the absence of a contraindication, vaccinators might not hesitate to administer the
45 vaccine in IC individuals.
46
47

48
49 In a second scenario analysis, the second-dose compliance was varied, assuming a
50 lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of
51 the clinical trial second-dose compliance.²⁵
52
53
54
55
56
57
58
59
60

1
2
3
4 Finally, the impact of changing the vaccination age on health outcomes was explored.
5 VE is in general higher in younger individuals favouring early vaccination. On the other
6 hand, duration of protection decreases over time and burden of disease (severity and
7 duration of HZ and PHN) is higher in older individuals, favouring vaccination at an older
8 age.³⁵ The relative balance of these factors may be different in case of ZVL and RZV,
9 leading to different conclusions regarding optimal vaccination age.
10
11
12

13 *SENSITIVITY ANALYSES*

14
15
16 Deterministic sensitivity analyses (DSA) were conducted to test the robustness of the
17 results subject to changes in input parameters. To this aim, HZ and PHN incidence
18 rates, VE and waning rates for both vaccines, incidence rate of HZ-related
19 complications and vaccine-related adverse events, coverage and second-dose
20 compliance were varied in one-way sensitivity analyses according to pre-defined
21 ranges. Tornado diagrams were used to illustrate parameters that had the largest
22 impact on HZ cases avoided.
23
24
25
26

27
28 Probabilistic sensitivity analysis (PSA) was carried out to assess the variability of results
29 when changing parameters concomitantly using Monte Carlo simulation (5,000
30 simulations). Each parameter could be attributed a value within its predefined range
31 and according to the assigned probability distribution. A beta-distribution was used
32 for all parameters except for vaccine coverage which followed a uniform distribution.
33 Age-specific incidence parameters which varied across age-groups were assumed to
34 be correlated using a correlation of 0.5. The results of the PSA are presented using a
35 histogram displaying the HZ cases avoided with RZV compared with ZVL.
36
37
38
39
40

41 *RESULTS*

42 *BASE-CASE ANALYSIS*

43
44 In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN
45 cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a
46 reduction of 7,909 HZ and 3,567 PHN cases (Table 2). Vaccination with RZV reduced
47 the number of HZ-related complications and the health-resource use (Table 2). There
48 were few HZ-related deaths; compared to no vaccination, RZV prevented 8 HZ-related
49 deaths while ZVL prevented none. The NNV to prevent one case of HZ was 12 with RZV
50 and 45 with ZVL. The NNV to avoid one case of PHN was 65 with RZV and 98 with ZVL,
51 respectively.
52
53
54
55
56
57
58
59
60

SCENARIO ANALYSES

In a first scenario analysis, we increased coverage from 48.3% to 70% for RZV. In this scenario, an additional 13,596 HZ and 2,430 PHN cases would be prevented in the routine vaccination cohort (70 YOA) (Figure 1, light blue bar showing the additional proportion of HZ and PHN cases avoided with RZV compared to no vaccination).

In a second scenario analysis, compliance with second-dose of RZV was set to lower and upper limits of 60% and 89%. Compared to no vaccination, the numbers of HZ cases avoided with RZV were 28,145 and 34,284 at the lower and upper limits for compliance, respectively (Figure 2).

To determine the optimal age for vaccination, scenario analyses were carried out to evaluate the public health impact in different age cohorts (50, 60, 65, 70 and 80 YOA) in terms of NNV, HZ and PHN cases avoided and resource utilisation per 100,000 people.

In case of RZV, the scenario that led to avoidance of the most HZ cases per 100,000 people would be vaccinating at 60 YOA, while slightly more PHN cases per 100,000 people could be avoided by vaccinating at 65 YOA. In case of ZVL, the number of HZ cases avoided per 100,000 people would be highest in the 65 YOA cohort, but more PHN cases per 100,000 people would be avoided in the 70 YOA cohort (Figure 3). In all age-groups, number of HZ and PHN cases avoided per 100,000 people was higher for RZV compared to ZVL. Complications avoided ranged from 689 with RZV and 250 with ZVL in the 65 YOA cohort, to 434 with RZV and 46 with ZVL in the 80 YOA cohort.

Consistent with these results, for RZV, the NNV to avoid one case of HZ was lowest in the 60 YOA (NNV = 9) and the NNV to avoid one case of PHN was lowest in the 65 YOA cohort (NNV = 54) (Table 3).

The higher number of HZ and PHN cases avoided with RZV compared to ZVL across all age cohorts leads to an important reduction in the use of health care resources, which might be an indicator of a reduction in direct costs due to HZ (Table 4). The number of GP visits per 100,000 people avoided is highest for the 60 YOA and 65 YOA cohorts for both vaccines, and consistently higher for RZV compared to ZVL. The number of hospitalisations avoided increases with increasing age for RZV, reflecting the increased risk of hospitalisation due to HZ in older individuals.

SENSITIVITY ANALYSES

In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the robustness of results was tested by changing input parameters to their lower and upper estimated confidence ranges (SI Tables 3 – 5; SI Tables 8 – 9). In the base case analyses, RZV prevented an additional 22,353 HZ cases as compared to ZVL. The parameter with the highest impact on the relative advantage of RZV over ZVL was annual waning of RZV (2 doses) VE_{HZ} in people ≥ 70 YOA, although the highest waning for RZV would still lead to a reduction of over 13,000 HZ cases compared to ZVL. Other parameters influencing the number of HZ cases avoided include initial VE_{HZ} in people ≥ 70 YOA for ZVL and RZV single dose, HZ incidence, and RZV compliance to second-dose (Figure 4).

During PSA, all parameters were varied simultaneously along their predefined ranges. In all simulations ($n = 5,000$), RZV led to a reduction of HZ cases as compared to ZVL. The distribution of the number of HZ cases avoided by RZV relative to ZVL is shown in Figure 5. Overall, 83.1% of simulations predicted that RZV would prevent at least 15,000 additional HZ cases compared with ZVL in the age-group 70 YOA.

DISCUSSION

UMV against HZ using ZVL was introduced in the UK in 2013 and observational studies suggest that the programme has brought down HZ incidence by approximately one third in the vaccinated cohorts.^{36 37} RZV has been approved by the EMA in individuals ≥ 50 YOA, thereby offering an alternative option to vaccinate people against HZ in addition to the existing ZVL. The aim of this study was to evaluate the public health impact of RZV in terms of HZ prevention compared to ZVL or no vaccination in the UK setting.

In the base-case considering the current vaccination cohort of people 70 YOA, RZV reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no vaccination. In comparison, ZVL prevented 7,909 HZ and 3,567 PHN cases as compared to no vaccination. NNV to prevent one episode of HZ was almost four times lower with RZV compared to ZVL, i.e., 12 with RZV vs 45 with ZVL. In addition, the estimated number of hospitalisations and GP visits due to HZ and PHN were substantially lower with RZV compared with ZVL. HZ-related mortality is in general low; nevertheless, our simulations predicted that 8 deaths could be prevented with an RZV vaccination strategy while no HZ-related deaths were prevented adopting a ZVL vaccination

1
2
3
4 strategy.

5
6 Results were robust under deterministic and probabilistic sensitivity analyses. Annual
7 waning of RZV VE in people ≥ 70 YOA had the greatest impact on the number of HZ
8 avoided relative to ZVL, but even assuming an extreme assumption on waning, with
9 an annual waning rate of 6.6%, RZV would prevent an additional 13,816 HZ cases as
10 compared to ZVL. Other parameters to which the relative vaccination strategies
11 proved sensitive included annual HZ incidence and VE_{HZ} of RZV and ZVL. Probabilistic
12 sensitivity analyses were always in favour of the RZV vaccination strategy with 83.1%
13 of simulations showing a reduction of at least $\geq 15,000$ HZ cases with respect to ZVL.
14 We also tested different scenarios in which coverage and compliance were varied,
15 assuming that the public health impact would increase as a greater proportion of
16 individuals would be vaccinated. Increasing the coverage estimate of the first-dose of
17 RZV from 48.3% to 70% would further reduce HZ and PHN incidence thereby leading
18 to a greater reduction in healthcare resources used. We hypothesise that the coverage
19 with RZV might be higher because a proportion of the eligible individuals are currently
20 not receiving the vaccine with ZVL. Even though the proportion of individuals with a
21 true contraindication to ZVL is estimated to be small (2.8%²⁰) HZ vaccination with ZVL
22 might be withheld even in those IC individuals who have no contraindications as
23 vaccinators may have been risk averse. Reducing RZV compliance to 60%, RZV would
24 still prevent approximately three times more HZ cases compared to ZVL. This is in line
25 with a recent public health impact study carried out for the German setting where a
26 compliance rate of 50% would still lead to an improvement of 200% over ZVL in terms
27 of HZ prevention.²⁵ Although results are in line with the German study, this UK model
28 adaptation has some different methodological considerations that are of importance
29 to potential decision-making bodies. Firstly, this manuscript also assesses single year
30 cohorts versus multiple year cohorts. This was chosen to reflect the current HZ
31 vaccination programme in the UK where people get vaccinated with ZVL at 70 YOA
32 and 79 YOA within the catch-up programme. Secondly, the HZ incidence is calculated
33 based upon a weighting method of IC-free and IC populations using the prevalence of
34 IC in the different age groups. This is important to estimate the actual HZ incidence in
35 the general population.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 The recommended vaccination strategy was based on the clinical profile of ZVL, the
53 only vaccine available at the time. In its recommendation, the JCVI noted that ZVL VE
54 decreases with increasing age and over time; hence, the current age cohort eligible
55 for vaccination, i.e., individuals 70 YOA, is a compromise to optimise limited efficacy
56
57
58
59
60

1
2
3
4 and duration of protection against HZ. The JCVI also stated that optimal age at
5 vaccination would depend on the characteristics of any given vaccine.³⁸ Therefore, the
6 impact of vaccination age on HZ and PHN incidence was explored through scenario
7 analyses including different age-cohorts (50, 60, 65, 70 and 80 YOA). The number of
8 HZ and PHN cases avoided per 100,000 people was higher with RZV than with ZVL
9 across all age cohorts. In case of RZV, most HZ cases were avoided in the 60 YOA
10 cohort, while PHN case avoidance was highest in the 65 YOA cohort. This observation
11 is consistent with a higher probability of developing PHN at an increased age. On the
12 other hand, the projected number of PHN cases avoided with ZVL was highest in the
13 70 YOA. This finding is due to a top-up efficacy seen with ZVL against PHN in the
14 population ≥ 70 YOA: vaccinated individuals with breakthrough HZ are at a lower risk
15 of developing PHN as compared to unvaccinated individuals with HZ. In the individuals
16 < 70 YOA, no additional protection against PHN was observed in clinical studies with
17 ZVL. For RZV no additional top-up efficacy could be calculated based on the limited
18 number of breakthrough cases, and thus VE_{HZ} and VE_{PHN} were assumed to be the
19 same. As a result, for RZV, the NNV to avoid one case of HZ and PHN was lowest for
20 the 60 YOA and 65 YOA cohorts. NNV increased in the 70 YOA and more so in the 80
21 YOA, where a proportion of the simulated cohort died due to natural causes before
22 any health benefit of vaccination occurred.

23
24
25
26
27
28
29
30
31
32
33 From a health care utilisation perspective, RZV reduced the number of GP visits by
34 more than 13,000 compared to ZVL in all age-groups. The highest reduction in GP visits
35 was predicted in the 65 YOA cohort, while the largest impact on hospitalisations was
36 predicted for the 80 YOA cohort. The latter might be explained by the higher risk of
37 hospitalisation inherent to older individuals due to a higher degree of frailty.
38 Nevertheless, it should be noted that the reduction in hospitalisations was predicted
39 to be several-fold higher with RZV compared to ZVL in all age-cohorts. Reduction in
40 the use of health care resources is a good indicator of potential decrease in direct
41 costs of new health care interventions; however, this requires further investigation in
42 a cost-effectiveness analysis with RZV in the UK context.

43
44
45
46
47
48
49 The potential public health impact of RZV in the UK setting has previously been studied
50 by our group.³⁹ The study showed a substantial reduction in HZ and PHN cases
51 compared to no vaccination; however, no comparison was made to ZVL. A number of
52 studies have evaluated the impact of ZVL on disease burden and associated cost-
53 effectiveness in the UK setting. Van Hoek et al. analysed cost-effectiveness of ZVL in
54 different age-groups with the base-case considering a cohort of immunocompetent
55
56
57
58
59
60

1
2
3
4 65-year-old individuals in the UK. This cohort was modelled over a life-time and a
5 vaccine coverage of 73.5%.³ Waning rates might have been underestimated in this
6 model since long-term data from the LTPS study for persistence of efficacy of the ZVL
7 vaccination were not yet taken into account.²⁵ The LTPS study showed that VE_{HZ} of ZVL
8 decreases significantly over time with no statistically significant protection observed
9 after 8 years of vaccination.^{17 18} In the economic model published by Moore et al., the
10 NNV of ZVL to prevent one case of HZ was 15, and hence lower than that found in our
11 simulations. However, the authors assumed a waning rate of 0%.¹⁰
12
13
14
15

16 The public health impact of RZV was also evaluated for other settings, including
17 Germany, US, Canada and Australia. These studies used a wide range of assumptions
18 regarding coverage, compliance and duration of vaccine protection for both RZV and
19 ZVL.^{28 40-42} Despite differences in these assumptions, all studies showed a consistent
20 improvement in the reduction of HZ cases and its complications compared to no
21 vaccination or vaccination with ZVL. In a recent independent cost-effectiveness study
22 for the US setting, employing conservative assumptions regarding RZV waning rate,
23 coverage and compliance, the authors concluded that RZV was more effective
24 compared to ZVL under the vast majority of assumptions evaluated.⁴⁰
25
26
27
28
29
30

31 As with every model, there are strengths and limitations associated with the modelling
32 strategy employed. For RZV, most recent UK-specific data available at the time we
33 conducted this study were used; for HZ incidence the CPRD database, a large UK-
34 specific database, was analysed and values for both IC and non-IC cohorts were
35 combined.^{28 43} For PHN incidence, published data from two reports were used to
36 estimate the PHN probability in the total population including individuals with
37 immunodeficient states. The estimates of PHN cases prevented are close to real
38 values, validating our approach. Demographic data projected to the year 2018 were
39 used based on numbers reported by the ONS.²⁷ The limitations in this study are related
40 to assumptions that had to be made in the absence of real-world data, including
41 coverage with RZV, compliance and long-term waning for RZV. Coverage and
42 compliance were set to values observed in comparable vaccination programs and
43 these parameters were varied in scenario and one-way sensitivity analyses. Results
44 from long-term studies with RZV are still outstanding and follow-up data is currently
45 limited to 4 years. However, the model has been developed such that it can be
46 updated once additional data becomes available. For ZVL waning rates, we included
47 both data from the SPS and the LTPS study²⁵ to ensure that we could compare ZVL
48 and RZV in the ZONA model. Recent observational studies looking into the vaccine
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 effectiveness of ZVL show that the vaccine wanes rapidly and has little to no protection
5 left beyond year 8 after vaccination.^{18 37} Finally, the rate of HZ-associated
6 complications was assumed to be the same in all individuals with HZ regardless of their
7 vaccination status. This assumption ignores the potential benefit vaccination might
8 have by lowering the severity and duration of break-through HZ cases. Clinical trial
9 data suggest that VE_{HZ} and VE_{PHN} are similar and there is some evidence that duration
10 and severity of HZ/PHN pain is lower in individuals having received RZV as compared
11 to unvaccinated individuals.⁴⁴
12
13
14
15

16 Future research might be directed towards assessing severity and duration of HZ and
17 PHN cases depending on vaccination status, identifying subgroups of the population
18 that may have enhanced benefit from the vaccine and evaluating cost-effectiveness
19 in the current UMV cohort and across different age-cohorts.
20
21
22

23 A lay language summary contextualizing the outcomes and potential impact of this
24 study for healthcare providers is displayed in Figure 6.
25
26
27
28
29

30 **CONCLUSION**

31
32
33 Within the model assumptions, RZV has the greater public health impact in terms of
34 HZ and PHN case avoidance and reduction in health care utilisation. When the UMV
35 was introduced in 2013, vaccinating people at 70 YOA was the best option based on
36 the vaccine characteristics of ZVL. With the approval of RZV in the US, Canada, Japan
37 and Europe in adults ≥ 50 YOA the optimal HZ prevention strategy needs to be re-
38 evaluated. The model projects for RZV a longer duration of protection and the VE
39 remains high in older age groups compared to ZVL. Therefore, the results of this model
40 show that the difference in clinical profile of RZV leads to a different optimal age of
41 vaccination. Vaccinating the UK population with RZV at 60 YOA or 65 YOA is the
42 optimal vaccination strategy in terms of public health impact, while being superior to
43 ZVL in all age cohorts studied.
44
45
46
47
48
49
50

51 **ACKNOWLEDGEMENTS**

52
53
54 Authors would like to Lijoy Varghese for this contribution to the study. They also want
55 to thank Business & Decision Life Sciences platform for editorial assistance and
56 publications coordination, on behalf of GSK. Stephanie Garcia coordinated manuscript
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

development and editorial support. Katrin Spiegel provided writing support.

REFERENCES

1. Mueller NH, Gilden DH, Cohrs RJ, et al. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. *Neurol Clin* 2008;**26**(3):675-97. doi:10.1016/j.ncl.2008.03.011.
2. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* 2014;**4**:e004833. doi:10.1136/bmjopen-2014-004833
3. van Hoek AJ, Gay N, Melegaro A, et al. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. *Vaccine* 2009;**27**(9):1454-67. doi:10.1016/j.vaccine.2008.12.024
4. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Therapeutic Advances in Vaccines* 2015;**3**(4):109-20. doi:10.1177/2051013615599151
5. Bollaerts K, Riera-Montes M, Heininger U, et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: deriving incidence from seroprevalence data. *Epidemiol Infect* 2017;**145**(13):2666-77. doi:10.1017/S0950268817001546
6. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect* 2001;**127**:305-14. doi:10.1017/S0950268801005921
7. Pinchinat S, Cebrián-Cuenca AM, Bricout H, et al. Similar herpes zoster incidence across Europe: Results from a systematic literature review. *BMC Infect Dis* 2013;**13**:170. doi:10.1186/1471-2334-13-170
8. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;**137**(1):38-47. doi:10.1017/S0950268808000678
9. Varghese L, Standaert B, Olivieri A, et al. The temporal impact of aging on the burden of herpes zoster. *BMC Geriatr* 2017;**17**:30. doi:10.1186/s12877-017-0420-9
10. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost effectiveness and resource allocation : C/E* 2010;**8**:7-7. doi:10.1186/1478-7547-8-7
11. Gater A, Abetz-Webb L, Carroll S, et al. Burden of herpes zoster in the UK: Findings from the zoster quality of life (ZQOL) study. *BMC Infect Dis* 2014;**14**:402. doi:10.1186/1471-2334-14-402
12. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: A prospective study. *CMAJ* 2010;**182**(16):1731-36. doi:10.1503/cmaj.091711
13. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *The Clinical journal of pain* 2007;**23**(6):490-6. doi:10.1097/AJP.0b013e318065b6c9
14. Joint Committee on Vaccination and Immunisation. Joint Committee on Vaccination and Immunisation Statement on varicella and herpes zoster vaccines. available from: <http://webarchive.nationalarchives.gov.uk/20120907151317/http://www.dh.gov>

- v.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf [accessed June 26, 2018].
15. Merck Sharp Dohme Ltd. Zostavax Summary of Product Characteristics (SmPC). available from: <https://www.medicines.org.uk/emc/product/6101/smcp> [accessed June 26, 2018].
 16. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *NEnglJMed* 2012;**366**(20):1859-69. doi:10.1056/NEJMoA1208410
 17. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 2015;**60**(6):900-09. doi:10.1093/cid/ciu918
 18. Tseng HF, Harpaz R, Luo Y, et al. Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged ≥ 60 Years. *J Infect Dis* 2016;**213**(12):1872-75. doi:10.1093/infdis/jiw047
 19. Public Health England. Shingles (herpes zoster), 2016:Chapter 28a.
 20. Public Health England. Herpes zoster (shingles) immunisation programme : September 2016 to August 2017 Report for England. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667636/Annual_shingles_report_2016-2017_.pdf [accessed June 26, 2018].
 21. Chlibek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. *Vaccine* 2016;**34**(6):863-68. doi:10.1016/j.vaccine.2015.09.073
 22. GlaxoSmithKline Biologicals SA. Shingrix Summary of Product Characteristics (SmPC). available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004336/WC500246550.pdf [accessed June 26, 2018].
 23. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med* 2015;**372**(22):2087-96. doi:10.1056/NEJMoA1501184
 24. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med* 2016;**375**(11):1019-32. doi:10.1056/NEJMoA1603800
 25. Curran D, Van Oorschot D, Varghese L, et al. Assessment of the potential public health impact of Herpes Zoster vaccination in Germany. *Hum Vaccin Immunother* 2017;**13**(10):2213-21. doi:10.1080/21645515.2017.1345399
 26. Schmader KE, Levin MJ, Gnann JW, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis* 2012;**54**(7):922-28. doi:10.1093/cid/cir970
 27. Office of National Statistics. 2014 based National population projections. available from: <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
 28. Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012. *BMJ Open* 2018;**8**(6). doi:10.1136/bmjopen-2017-020528

- 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
29. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;**82**(11):1341-9.
30. Yawn BP, Wollan PC, Kurland MJ, et al. Herpes Zoster Recurrences More Frequent Than Previously Reported. *Mayo Clin Proc* 2011;**86**(2):88-93. doi:10.4065/mcp.2010.0618
31. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;**157**(1):30-54. doi:10.1097/j.pain.0000000000000307
32. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine* 2001;**19**(23-24):3076-90. doi:10.1016/S0264-410X(01)00044-5
33. Bricout H, Haugh M, Olatunde O, et al. Herpes zoster-associated mortality in Europe: A systematic review. *BMC Public Health* 2015;**15**(1):466. doi:10.1186/s12889-015-1753-y
34. Public Health England. Influenza: the green book, chapter 19. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/663694/Greenbook_chapter_19_Influenza_.pdf [accessed June 29, 2018].
35. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (Shingles) and postherpetic neuralgia. *Mayo Clin Proc* 2009;**84**(3):274-80. doi:10.4065/84.3.274
36. Amirhalingam GA, Nick. Keel, Philip. Mullett, David. Correa, Ana. de Lusignan, Simon. Ramsay, Mary. Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study. *Lancet Public Health* 2018;**3**:e82-90. doi:10.1016/S2468-2667(17)30234-7
37. Walker JL, Andrews NJ, Amirhalingam G, et al. Effectiveness of herpes zoster vaccination in an older United Kingdom population. *Vaccine* 2018;**36**(17):2371-77. doi:10.1016/j.vaccine.2018.02.021
38. Joint Committee on Vaccination Immunisation. Minute of the meeting on 4 October 2017. available from: https://www.jostrust.org.uk/sites/default/files/minute_2017_10_draft.pdf <https://www.bmj.com/content/bmj/345/bmj.e6879.full.pdf> [accessed June 26, 2018].
39. Van Oorschoot D, Hunjan M, Varghese L, et al. The public health perspective of an investigational herpes zoster vaccine in the united kingdom (UK). *Value Health* 2016;**19**(7):A400-A00. doi:10.1016/j.jval.2016.09.309
40. Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. *JAMA Internal Medicine* 2018;**178**(2):248-58. doi:10.1001/jamainternmed.2017.7431
41. Varghese L, Curran D, Yan S, et al. Estimating the Potential Public Health Impact of Introducing the HZ/su Vaccine in the US Population Aged ≥ 50 Years. *Open Forum Infectious Diseases* 2015;**2**(suppl_1). doi:10.1093/ofid/ofv133.1477
42. Varghese L, Nissen M, Olivieri A, et al. Public health perspective of phase III results of an investigational Herpes Zoster vaccine. Public Health Association of Australia. *Public Health Association of Australia - Communicable Disease Control Conference*, Brisbane 2015:42. <https://www.phaa.net.au/documents/item/581> (accessed June 26, 2018).
43. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The

- 1
2
3 United Kingdom. *Value Health* 2017;**20**(9):A786.
4 doi:10.1016/j.jval.2017.08.2296
5
6 44. Curran D, Athan E, Diez-Domingo J, et al. Quality-of-Life Impact of an
7 Investigational Subunit-Adjuvanted Herpes Zoster Vaccine in Adults ≥ 50 Years
8 of Age. *Open Forum Infectious Diseases* 2016;**3**(suppl_1).
9 doi:10.1093/ofid/ofw194.77
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

FOOTNOTES

TRADEMARK

Shingrix is a trademark of the GSK group of companies.

Zostavax is a trademark from Merck Sharp & Dohme Corp.

AUTHORS' CONTRIBUTION

DVO, DC, SL, BB participated to the conception and design of the analysis; DVO, DC, MH developed and adapted the model; DVO, DC, MH, HSC, BB were involved in the collection, analysis and/or interpretation of the data. All authors had full access to the data and approved the final version of the paper for submission.

CONFLICTS OF INTEREST

DVO, MH, BB, DC and HSC are employees of the GSK group of companies. MH, DC, and HSC hold shares in the GSK group of companies. SL is a freelance consultant working on behalf of the GSK group of companies.

DATA SHARING STATEMENT

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

ETHICAL APPROVAL

Ethical approval is not applicable for this public health impact modelling analysis.

FUNDING SECTION

GlaxoSmithKline Biologicals SA funded this study (GSK study identifier: HO-17-18511) and was involved in all stages of study conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also covered all costs associated with the development and publication of this manuscript.

TABLES AND FIGURES

Table 1: Demographic, epidemiological and efficacy data according to age group

Age		50 YOA	60 YOA	65 YOA	70 YOA	80 YOA
Number of people in-age group in 2018		908,255	783,067	686,215	722,616	389,107
HZ incidence per 1,000 individuals	IC	6.85	8.80	9.93	11.32	12.61
	IC-Free	4.9	6.92	8.62	11.04	11.02
Proportion developing PHN (%)		11.42	13.89	15.71	17.12	20.42
Non-PHN complications incidence (%)	Ocular	2.87	3.82	3.82	4.14	5.41
	Neurological	2.46	3.17	3.17	5.99	4.23
	Cutaneous	1.74	1.05	1.05	2.09	2.44
	Other	2.03	1.63	1.63	2.44	2.85
HZ - Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95-100)	98.4 (95-100)	98.4 (95-100)	97.8 (94.1-100)	97.8 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (54.1-80.6)	63.9 (56.0-71.0)	63.9 (56.0-71.0)	40.85 (28.0-52.0)	18.25 (0-48.0)
PHN Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95.0-100)	98.4 (95.0-100)	98.4 (95.0-100)	97.84 (94.1-100)	97.84 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (30.8-89.6)	65.69 (25.4-84.2)	65.69 (25.4-84.2)	73.38 (51.6-85.8)	39.51 (0-73.8)

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

Table 2: Health outcomes and health resource utilisation in the vaccination cohort 70 YOA - base-case analysis, N=722,616

	RZV	ZVL	No vaccination	RZV vs no vaccination	ZVL vs no vaccination
HZ cases, n	88,643	110,996	118,905	30,262	7,909
PHN cases, n	16,570	18,411	21,979	5,409	3,567
HZ-related complications					
Total, n	13,109	16,405	17,565	4,455	1,160
Ocular, n	4,207	5,221	5,548	1,341	327
Neurological, n	4,565	5,782	6,255	1,691	474
Cutaneous, n	2,001	2,492	2,658	657	165
Other non-pain, n	2,336	2,910	3,103	767	193
Deaths					
HZ-related deaths, n	56	64	64	8	0
Resource utilisation					
Hospitalisation, n	7,827	9,463	9,820	1,993	357
GP visits, n	438,328	546,691	583,612	145,284	36,921

GP: general practitioner; HZ: herpes zoster; PHN: postherpetic neuralgia; n: number of cases; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

Table 3 NNV to avoid one case of HZ or PHN according to age at vaccination

Age cohort	NNV HZ		NNV PHN	
	RZV	ZVL	RZV	ZVL
50 YOA	10	39	69	328
60 YOA	9	27	55	171
65 YOA	10	23	54	134
70 YOA	12	45	65	98
80 YOA	17	156	82	258

RZV: adjuvanted recombinant zoster vaccine; HZ: herpes zoster ; YOA: years of age; ZVL: zoster vaccine live; NNV: number needed to vaccinate

Table 4 Reduction on resource utilisation per 100,000 people

	GP visits avoided		Hospitalisations avoided	
	RZV	ZVL	RZV	ZVL
50 YOA	17,481	3,652	126	17
60 YOA	22,078	6,375	216	42
65 YOA	23,447	8,702	266	69
70 YOA	20,105	5,109	276	49
80 YOA	15,243	1,629	394	42

GP: general practitioner; HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

1
2
3 **Figure 1 Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light blue**
4 **bars) comparing RZV vs no vaccination in people 70 YOA**
5

6 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; PHN: postherpetic neuralgia; YOA: years of age
7

8 **Figure 2 Impact of second-dose RZV compliance on HZ incidence**
9

10 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live
11

12 **Figure 3 Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for**
13 **different vaccination cohorts.**
14

15 HZ: herpes zoster; no vac: no vaccination; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster
16 vaccine; YOA: years of age; ZVL: zoster vaccine live
17

18 **Figure 4 Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70**
19 **YOA; coverage 48.3%; compliance 70%)**
20

21 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live
22

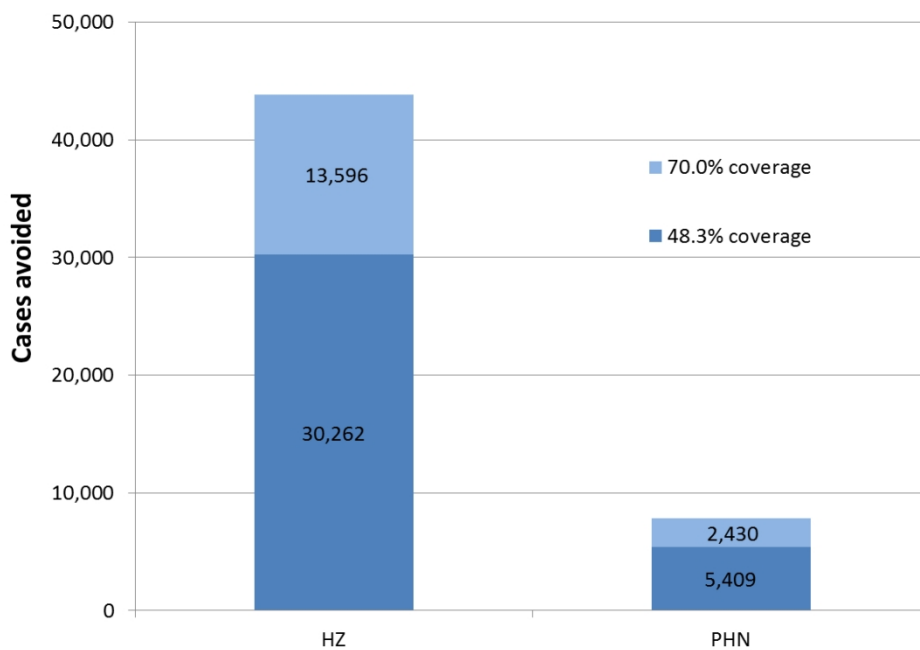
23 Lower values are in orange and upper values are in grey
24

25 **Figure 5 Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL**
26

27 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live
28

29 The orange line shows the percentage of simulations averting at least the number of HZ cases shown on the x-axis.
30

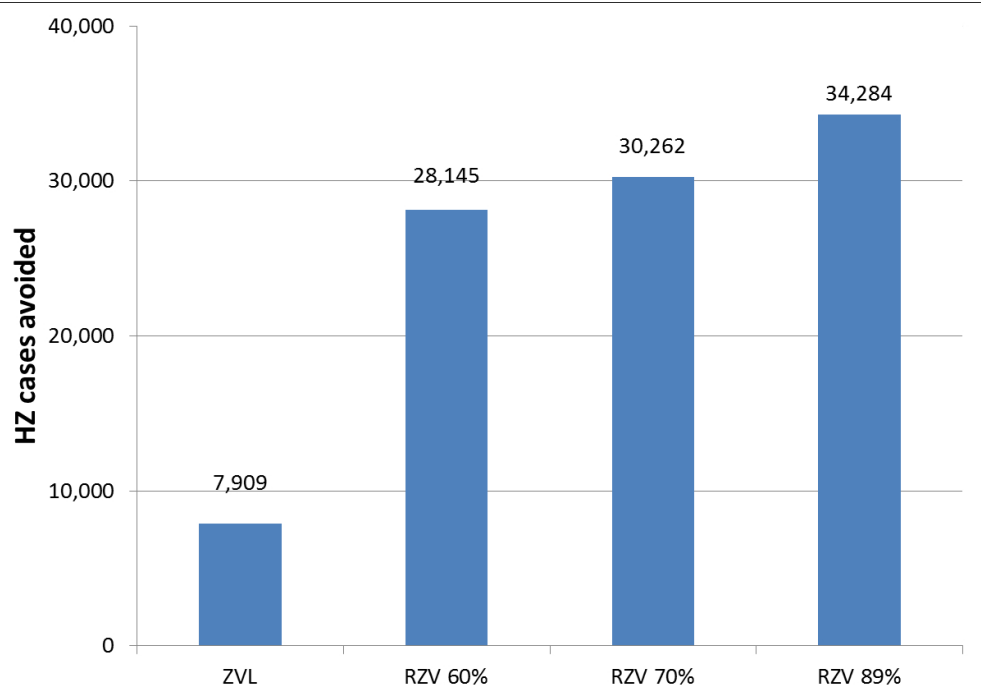
31 **Figure 6 Lay language summary of the study**
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light blue bars) comparing RZV vs no vaccination in people 70 YOA

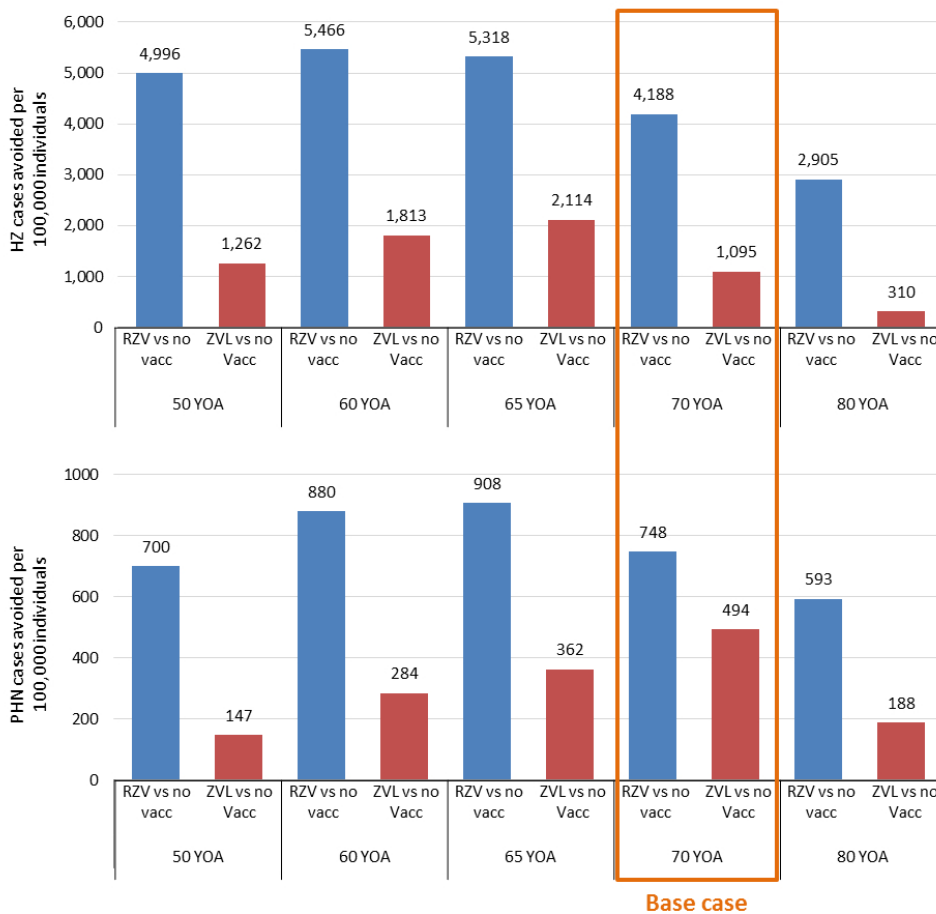
109x75mm (300 x 300 DPI)

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



Impact of second-dose RZV compliance on HZ incidence

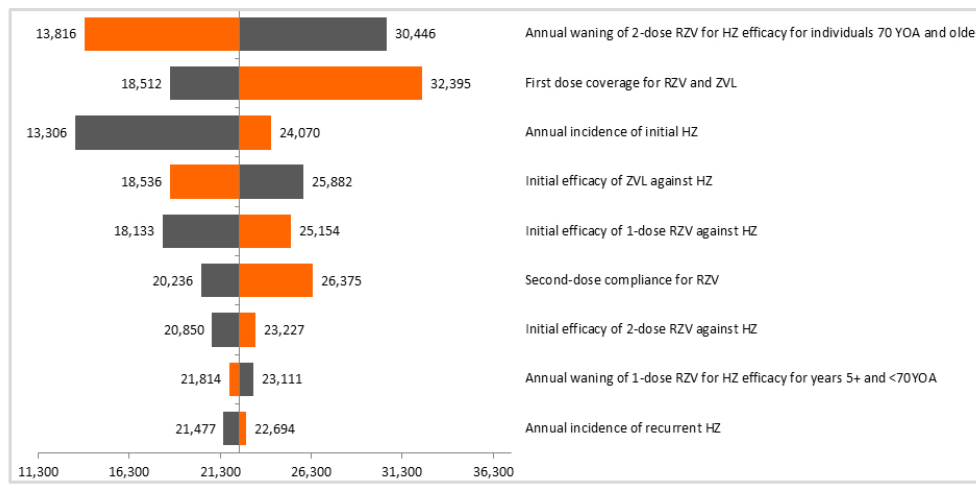
103x72mm (300 x 300 DPI)



Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

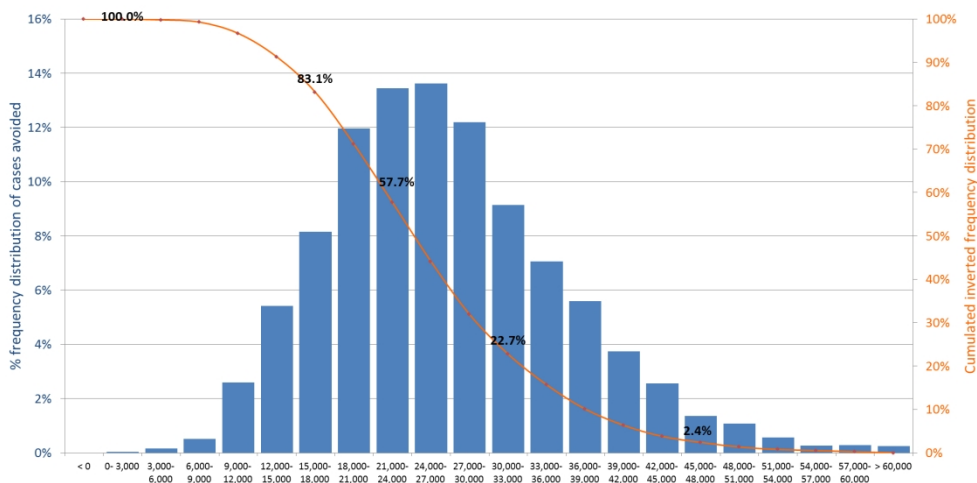
81x80mm (300 x 300 DPI)

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



Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

81x60mm (300 x 300 DPI)



Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

177x86mm (300 x 300 DPI)



Focus on the Patient

What is the context?

Herpes zoster (shingles) is a painful rash that lasts for several weeks and which can lead to prolonged pain even after the initial rash has cleared. Herpes zoster arises when varicella zoster virus, acquired during varicella, reactivates. This happens especially in older people with a weakened immune system. Herpes zoster has a detrimental impact on the quality of life and current treatment options provide only partial symptom relief.

What is new?

In the UK, a universal mass vaccination programme against herpes zoster has been introduced in 2013. The programme recommends vaccination of people aged 70 or 78 years with *Zostavax*, the only vaccine available at that time. In 2018, a new vaccine against herpes zoster, *Shingrix*, has become available. The goal of this study was to explore the impact of different vaccination strategies using a mathematical model.

What is the impact?

The model predicts that *Shingrix* would lead to a greater reduction in the number of herpes zoster episodes compared to *Zostavax*. If adopting a vaccination strategy with *Shingrix*, the optimal age at vaccination would be 60 or 65 years old.

Lay language summary of the study

108x60mm (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

Evaluation of the public health impact of introducing a novel Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme

Van Oorschot Desirée, Hunjan Manjit, Bracke Benjamin, Lorenc Stéphane, Curran Desmond, Starkie Camejo Helen

BMJ Open

SI Table 1: Mortality in the general UK population in 2018/2019

Age (YOA)	Number of deaths	Annual probability of death
50-54	15,903	0.00342
55-59	22,590	0.00544
60-64	29,886	0.008366
65-69	45,562	0.013091
70-74	65,747	0.021570
75-79	78,692	0.036493
80-84	104,536	0.065713
85-89	114,461	0.117689
90-94	82,948	0.198093
95-99	33,361	0.304037
≥ 100	5,496	0.436439

YOA: years of age.

Projected numbers using data reported by the Office of National Statistics based on observed numbers of the UK population in 2014.¹

The immunocompromised (IC) population was identified as individuals presenting one of the following conditions: Hematopoietic stem cell transplantation, solid organ transplantation, solid organ malignancies, haematological malignancies, human immunodeficiency virus, end-stage renal disease, corticosteroid exposure, other immunosuppressive therapy, other immunodeficiency conditions and autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, multiple sclerosis, polymyalgia rheumatica and autoimmune thyroiditis).²

Herpes Zoster (HZ) incidence for the whole (IC and IC-free) population was calculated by applying a weighting for IC proportion by age group.³ A unitary weight across the populations was not deemed to be appropriate or robust as prevalence of herpes zoster varies between the age groups; rising with increasing age. This is because applying IC incidence, accounting for the overall proportion of IC (16.2%) irrespective of age group would underestimate the incidence in older people and overestimate it in younger people.

SI Table 2: Weighting CPRD population for IC proportion by age

Age Group (YOA)	Prevalence of IC (%)	IC weighting	IC-free weighting
50-59	16.13	0.161	0.839
60-64	22.26	0.223	0.777
65-69	27.56	0.276	0.724
70-79	34.88	0.349	0.651
≥ 80	42.16	0.422	0.578

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 3: Incidence and probability of HZ in the whole population

Age (YOA)	Incidence rate/1,000 patient years		Probability	Range	
	IC	IC-Free		Lower limit	Upper limit
50-59	6.85	4.9	0.0052	0.00375	0.00791
60-64	8.8	6.92	0.0073	0.004392	0.009001
65-69	9.93	8.62	0.0089	0.005108	0.010147
70-79	11.32	11.04	0.0111	0.005975	0.011605
≥ 80	12.61	11.02	0.0116	0.007363	0.013955

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 4: Proportion of PHN (after 3 months)

Age (YOA)	Proportion (%)	Lower limit (%)	Upper limit (%)
50-59	11.418	8.91	14.13
60-64	13.894	12.03	15.88
65-69	15.705	13.95	17.57
70-79	17.116	13.53	20.94
≥ 80	20.418	17.08	23.82

PHN: postherpetic neuralgia; YOA: years of age

SI Table 5 HZ-associated mortality

Age (YOA)	Probability	Lower limit	Upper limit
50-54	0.00001	0.0000063	0.000012
55-59	0.00001	0.0000063	0.000012
60-64	0.00003	0.0000189	0.000035
65-69	0.00003	0.0000189	0.000035
70-74	0.00004	0.0000245	0.000046
75-79	0.00009	0.0000644	0.000120
80-84	0.00049	0.0003409	0.000633
85-89	0.00202	0.0014126	0.002623
90-94	0.00202	0.0014126	0.002623
95-99	0.00202	0.0014126	0.002623
≥ 100	0.00202	0.0014126	0.002623

HZ: herpes zoster; YOA: years of age

SI Table 6: Hospitalisation rates in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	0.044	0.007	0.012622
60-64	0.054	0.009	0.019245
65-69	0.050	0.014	0.023713
70-79	0.074	0.030	0.045143
≥ 80	0.168	0.115	0.135529

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age; IC-free: immunocompetent

*Weighted averages calculated using IC proportions in the CPRD study.

SI Table 7 GP visits in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	3.75	2.69	2.86
60-64	4.41	2.86	3.20
65-69	5.05	3.19	3.70
70-79	5.75	4.09	4.67
≥ 80	6.15	4.59	5.25

*Weighted averages calculated using IC proportions in the CPRD study.

CPRD: Clinical Practice Research Datalink; GP: general practitioner; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 8: Vaccine Efficacy against HZ and PHN

Age (YOA)	ZVL			RZV – 2-dose			RZV – 1-dose		
	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit
HZ									
50-59	0.698	0.5410	0.8060	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.4085	0.2800	0.5200	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.1825	0.0000	0.4800	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
PHN									
50-59	0.698	0.3080	0.8960	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.7338	0.5160	0.8580	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.3951	0.0000	0.7380	0.9784	0.9410	1.0000	0.695	0.2490	0.8910

HZ: herpes zoster; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

SI Table 9: Vaccine Waning

Vaccine	Age group (YOA)/years after vaccination	Value	5% CI	95% CI
ZVL – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600
RZV – 2-dose	< 70 YOA/Years 1-4	0.010	0.0000	0.0260
	< 70 YOA/Years 4+	0.0230	0.0070	0.0460
	≥70 YOA/ all years after vaccination	0.0360	0.0140	0.0660
RZV – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600

CI: confidence interval; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

REFERENCES

1. Office of National Statistics. 2014 based National population projections. available from: <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
2. Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012. *BMJ Open* 2018;**8**(6). doi:10.1136/bmjopen-2017-020528
3. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The United Kingdom. *Value Health* 2017;**20**(9):A786. doi:10.1016/j.jval.2017.08.2296

For peer review only

Section/Item	Item no	Recommendation	Reported on page no/line no	Comment
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared	p 1	Strictly speaking, this is not an economic evaluation but public health impact study, as stated in the title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P 4/5	
Introduction				
Background and Objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	p. 7 p. 8	Context provided in first paragraph (epidemiology and rise of HZ episodes during past decades) “The objective of this study is to explore the public health impact of introducing the RZV vaccine in the UK in the routine population 70 YOA.”
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen	p. 8 p. 8/p. 12	See sentence above for base-case scenario (routine population 70 YOA). “Different scenario analyses are carried out to assess the impact of first dose RZV coverage and second dose RZV compliance and to determine the optimal age for vaccination.” Base-case was chosen because representing the current routine vaccination cohort in the UK. Scenario analyses chosen to test uncertainties in coverage and potential

				differences in optimal vaccination age between RZV and ZVL as explained on page 12.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	p. 8 p. 9	UK setting where there is UMV currently in place. “The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting”
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	NA	Public health impact study, not cost-effectiveness study.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	p. 9 p. 8	Vaccination with RZV, with ZVL and no vaccination UK setting with current UMV with ZVL And a small portion of patients contraindicated to ZVL (no vaccination)
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	p. 10	“Cycle length is set to one year and a life-long time horizon is assumed.”
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	NA	Public health impact study, not cost-effectiveness study.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	p. 12	“The model was used to estimate the avoidance of HZ and PHN cases, complications, deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related deaths and number of GP visits and hospitalisations for three different vaccination strategies...”
Measurements of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study	NA	

		was a sufficient source of clinical effectiveness data		
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	p. 11	“Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the ZOE-50 and ZOE-70 trials for RZV (Table 1, SI Table 8).” And following paragraphs for efficacy/waning
Measurement of valuation based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	NA	Public health impact study, not cost-effectiveness study.
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	NA	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	P. 11	“The CPRD study was used to derive the proportion of patients being hospitalised or visiting their GP due to HZ-related complications. Hospitalisation rates were higher in the IC cohort for all age-groups. In addition, health-care resource use was higher in older adults (SI Tables 6 & 7).” No unit costs, since PHI study
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe	NA	

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

		methods for converting costs into a common currency base and the exchange rate		
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	p. 9	“The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting.” Reference is made to Curran et al, 2017 which shows Figure and additional details regarding model structure
Assumptions	16	Describe all structural or other assumptions underpinning the decision analytical model	p. 9 p. 12	First paragraph (Model structure) and Curran et al, 2017 Coverage and compliance assumptions: “In the base-case analysis, coverage is set at 48.3% in line with latest coverage numbers for the UK. The impact of different coverage rates was assessed in sensitivity analyses. Compliance with the second-dose of RZV was set to 70%.”
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	p. 12 p. 13	“Different scenario analyses were carried out where assumptions regarding vaccination coverage and compliance and age at vaccination were changed” And rest of paragraph Sensitivity analyses (DSA and PSA) described
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to	p. 15 SI Tables 3 – 5 and Tables 8 - 11	“In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the robustness of results was tested by changing input parameters to their lower and upper estimated confidence ranges (SI Tables 3 – 5;

		show the input values is strongly recommended		SI Tables 8 - 11)"
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	p. 14 Table 2	"In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a reduction of 7,909 HZ and 3,567 PHN cases (Error! Reference source not found.)"
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	NA	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	p. 13/14 Figure 1-3 Table 3 p. 15 Figure 4	Scenario analyses Sensitivity analyses
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	p. 14 Figure 3	Subgroup analyses according to age cohorts
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	p. 15	"In the base-case considering the current vaccination cohort of people 70 YOA, RZV reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no vaccination..." and subsequent paragraphs

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

			p. 18 p. 17/18	“As with every model, there are strengths and limitations associated with the modelling strategy employed....” Comparison to existing PHI and CE studies.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	p. 20	Funding
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	p. 20	Conflict of interest

Review only

BMJ Open

Public health impact model estimating the impact of introducing an Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025553.R2
Article Type:	Research
Date Submitted by the Author:	15-Jan-2019
Complete List of Authors:	van Oorschot, Desiree; GlaxoSmithKline Hunjan, Manjit; GlaxoSmithKline Bracke, Benjamin ; GlaxoSmitKline Lorenc, Stephane; GlaxoSmithKline, Freelance on behalf of GSK Curran, Desmond; GlaxoSmithKline Starkie-Camejo, Helen; GlaxoSmithKline
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Infectious diseases
Keywords:	Shingles, Adult vaccination, herpes zoster, recombinant zoster vaccine, Public health < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3
4
5 **TITLE PAGE**
6
7

8 **TYPE OF MANUSCRIPT:**
9

10
11 **MANUSCRIPT TITLE:**
12

13 *Public health impact model estimating the impact of introducing an Adjuvanted*
14 *Recombinant Zoster Vaccine into the UK universal mass vaccination programme*
15

16
17 **AUTHOR(S):**
18

19 Van Oorschot Desirée¹, Hunjan Manjit², Bracke Benjamin¹, Lorenc Stéphane³, Curran
20 Desmond¹, Starkie Camejo Helen²
21
22

23
24 **AFFILIATIONS:**
25

26 ¹ GSK, Wavre, Belgium; ² GSK, Uxbridge, UK; ³ Freelance, on behalf of GSK, Wavre,
27 Belgium
28
29

30
31 **CORRESPONDING AUTHOR:**
32

33 Name: Van Oorschot Desirée
34

35 Mailing Address: Avenue Fleming 20, 1300, Wavre, Belgium
36

37 Phone No: +3210855111
38

39 E-mail address: desiree.x.van-oorschot@gsk.com
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

OBJECTIVES

In 2013, the Herpes Zoster (HZ) immunisation programme was introduced in the UK, recommending vaccination of adults 70 years of age (YOA) with the zoster vaccine live (ZVL), the only vaccine available at the time. The recently approved Adjuvanted Recombinant Zoster Vaccine (RZV) has a substantially different clinical profile that may offer additional benefits.

This study aimed to 1) assess the public health impact (PHI) of introducing RZV in the UK compared to the current vaccination strategy and 2) explore via scenario analyses the optimal age-group of vaccination in terms of PHI.

DESIGN

A previously developed health economic model was adapted to the UK setting.

SETTING

Calculations were based on efficacy data from pivotal clinical trials, HZ incidence and PHN probability from a UK study, and HZ-associated complication rates from published literature.

POPULATION

The base-case population considered a 2018-projected UK vaccination cohort of individuals 70 YOA.

INTERVENTIONS

Vaccination with ZVL or RZV, assuming a first-dose coverage of 48.3% for both vaccines and 70% compliance for the second-dose of RZV.

OUTCOME MEASURES

Outcomes included reduction of HZ and postherpetic neuralgia (PHN) cases, complications and the use of health-care resources over a life-time horizon. The impact of coverage and second-dose compliance was also explored.

RESULTS

Compared to no vaccination, RZV would lead to a reduction of 30,262 HZ and 5,409 PHN cases while ZVL would lead to a reduction of 7,909 HZ and 3,567 PHN cases. The number needed to vaccinate to prevent 1 HZ case is 12 with RZV and 45 with ZVL. The highest PHI with RZV could be achieved in individuals 60 or 65 YOA.

CONCLUSION

Under the model assumptions, RZV is predicted to avert more HZ and PHN cases compared to ZVL. Results were robust under different scenario and sensitivity analyses.

KEYWORDS

Herpes Zoster vaccination; adjuvanted recombinant zoster vaccine; public health impact

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The most recent UK-specific data from published literature is included in the ZONA model.
- Model structure and inputs have been validated by external experts.
- Results of this analyses estimate the impact of an RZV program in the UK population in 2018.
- Further analyses have to be performed once long term effectiveness data becomes available on the duration of protection of RZV.
- Assumptions regarding second dose compliance had to be made in absence of real-world data.

INTRODUCTION

The varicella zoster virus (VZV) usually affects children and leads to varicella, also known as chickenpox. The virus remains dormant life-long in patients' dorsal root ganglia.¹ Later in life, VZV specific T-cell-immunity decreases due to immunosenescence or immunosuppressing illnesses or medications. Reactivation of VZV results in herpes zoster (HZ), also called shingles.^{2 3} Over 95% of individuals will have acquired VZV during their childhood or early adulthood.^{4 5} Approximately one in three people will develop HZ during their life-time with the risk increasing sharply after the age of 50 years of age (YOA), leading to an estimated 5 HZ episodes per 1,000 people in the UK, each year.⁶⁻⁸ Similar incidence rates were reported in other European countries and elsewhere.^{2 7} Furthermore, results from observational studies suggest that HZ incidence has risen during the past decade in various countries and is predicted to continue to rise as the average age of the population increases.^{2 9 10}

HZ tends to start with prodromal pain, followed by a dermatomal rash which is usually unilateral and develops typically over the trunk or face. Rash is often accompanied by severe pain. Skin lesions and pain usually disappear completely within 4–6 weeks. Postherpetic neuralgia (PHN), often defined as pain persisting or appearing 30 to 90 days after rash onset, is the most common complication which can last from several weeks to months.^{8 11} Even though mortality due to HZ infection is low, HZ greatly affects quality of life (QoL) in terms of physical and social functioning and the well-being of the patients.¹² Furthermore, severity of pain strongly correlates with the reported QoL.^{11 13} Current treatment options, which mainly rely on antivirals, analgesics and antidepressants, provide only partial symptomatic relief and limited protection against the development of PHN and other complications. Thus, the impact of the disease on patients QoL is not adequately managed with existing interventions.¹¹

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommended universal mass vaccination (UMV) for HZ using Zoster Vaccine Live (ZVL; *Zostavax*)¹⁴, the only vaccine available at the time the UMV programme was introduced in 2013. ZVL is a live-attenuated virus vaccine indicated for the prevention of HZ and, in Europe, of PHN in individuals ≥ 50 YOA.¹⁵ Vaccine efficacy (VE) against HZ (VE_{HZ}) of ZVL in the shingles prevention study (SPS) was 63.9% in individuals 60-69 YOA and 37.6% in individuals ≥ 70 YOA.^{15 16} Long-term clinical trial data and observational effectiveness studies showed that VE of ZVL decreased substantially over time conferring little or no protection against HZ beyond 8 years after vaccination.^{17 18}

1
2
3
4 Even though ZVL is indicated in individuals ≥ 50 YOA, the JCVI recommended
5 vaccination with ZVL at 70 YOA (and a catch-up vaccination for people 78 YOA), based
6 on clinical trial data and an economic model showing that vaccination at 70 YOA would
7 be the most cost-effective option given that the burden of disease increases with age,
8 while VE of ZVL decreases in older individuals and over time.^{3 14} A further limitation to
9 the indicated use of ZVL in individuals ≥ 50 YOA is its contraindication in primary or
10 acquired immunodeficiency states due to blood disorders or other types of cancer,
11 infection with human immunodeficiency virus, or due to high dose
12 immunosuppressive therapy.^{15 19} A proportion of individuals would therefore not be
13 able to receive ZVL.²⁰

14
15
16
17
18
19
20 A novel Adjuvanted Recombinant Zoster Vaccine (RZV, *Shingrix*) has been granted
21 marketing authorisation by the European Medicines Agency (EMA) and is indicated for
22 use in individuals ≥ 50 YOA. RZV is a non-live vaccine consisting of the VZV glycoprotein
23 E (gE), a prominent antigen target of VZV-specific CD4+ T-cell immune responses, and
24 AS01_B adjuvant system, which boosts immunogenicity and duration of the immune
25 response.²¹ RZV is administered in two doses 2 to 6 months apart. Because RZV is a
26 non-live vaccine, it is not contra-indicated in immunocompromised (IC) individuals.
27 While at this point in time, there is only limited data available regarding the use of
28 Shingrix in subjects with confirmed or suspected immunosuppressive or
29 immunodeficient conditions, further studies are ongoing. As with other vaccines, the
30 administration of Shingrix to immunocompromised subjects should be based on
31 careful consideration of potential benefits and risks.²² Two large, phase III trials, i.e.
32 the Zoster Efficacy Studies in Adults 50 and 70 YOA or older [ZOE-50 (NCT01165177)
33 and ZOE-70 (NCT01165229), respectively] demonstrated high VE_{HZ} of RZV in all age-
34 groups; VE_{HZ} was 97.2% in individuals ≥ 50 YOA included in the ZOE-50 study and
35 91.3% in individuals ≥ 70 YOA included in the ZOE-50 and ZOE-70 studies.^{23 24} VE
36 persisted over the four-year duration of the clinical trial.²⁴

37
38
39
40
41
42
43
44
45
46 The objective of this study is to explore the public health impact of introducing the
47 RZV vaccine in the UK in the routine population 70 YOA. The effect of RZV and ZVL on
48 HZ and PHN incidence, complications and health resource utilisation is compared to
49 no vaccination. Different scenario analyses are carried out to assess the impact of first-
50 dose RZV coverage and second-dose RZV compliance and to determine the optimal
51 age for vaccination.
52
53
54
55
56
57
58
59
60

METHODS

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were not involved as the analysis is based on mathematical modeling.

MODEL STRUCTURE

The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting. The economic model considers up to five various age cohorts that can transition between different health states, including no HZ, HZ, health states associated with complications of HZ (PHN and non-PHN complications) and death from HZ or natural causes.²⁵ Cycle length is set to one year and follows all subjects from the year of intervention over their remaining life-time. The model has three different arms, having the same yearly model structure: No vaccination, vaccination with RZV and vaccination with ZVL. Within the vaccine strategy, individuals can be fully compliant with the vaccine dosing schedule, only partially or not vaccinated at all (depending on the compliance rate). Further details regarding the model structure are reported in the Supplementary information (SI) Figure 1 and in Curran et al, 2017.²⁵

MODEL INPUT PARAMETERS

Wherever possible, UK-specific data were used. Efficacy data for RZV and ZVL were derived from pivotal clinical trials conducted for ZVL and RZV.^{16 23 24 26} Both model structure and global inputs such as VE and waning were validated with an external expert panel (epidemiologists, clinicians and health economists with a background in HZ) in September 2016.

DEMOGRAPHICS

Populations in the model are projected to 2018 values. The base-case population consisted of the routine vaccination cohort 70 YOA. Based on projections by the Office of National Statistics (ONS)²⁷, the predicted population numbers in the routine cohort of 70 YOA is 722,616, in 2018. Different age cohorts were modelled for use in scenario analyses (Table 1).

All-cause mortality rates were derived from ONS data projected to the year 2018/2019

(SI Table 1).²⁷

EPIDEMIOLOGY

HZ INCIDENCE

HZ incidence was derived from a recent UK Clinical Practice Research Datalink (CPRD) study, which assessed the incidence of HZ in immunocompetent (IC-free) and IC individuals between 2000 and 2012²⁸ (SI Table 2). The CPRD database study presents the most recent real-world data on HZ incidence and was therefore considered the most appropriate source for this parameter. The IC-free and IC population were matched by age, gender and location of general practitioner (GP) and the proportion of IC individuals was adjusted in the whole population to account for an increase in immunodeficiencies in older individuals. In the age-group 70-79 YOA, 35% of individuals had primary or acquired immunodeficiency and a subgroup of this IC population is contraindicated to receive ZVL. Incidence numbers were converted to annual probabilities of developing HZ (Table 1). Lower and upper ranges of probabilities for HZ incidence in the whole population were obtained from published data since it was not possible to derive it from the split IC and IC-free data set analysed in the CPRD study³ (SI Table 3).

Incidence rate of recurrent HZ is assumed to be the same as the incidence of the initial event. This assumption is supported by published data which indicates that the incidence rates of initial and recurrent HZ events are similar.^{2 29 30}

PHN PROBABILITY

PHN is defined as pain appearing or persisting for more than 3 months after initiation of HZ. PHN incidence was derived from published data.^{8 31} Gauthier et al. derived PHN incidence from the CPRD in the population excluding patients with underlying IC conditions using prescription medication records on top of PHN codes to identify these episodes. Forbes et al reported odds ratios of developing PHN for people with human immunodeficiency virus and hematopoietic stem cell transplantation compared to IC-free population and these data were used in combination with data reported by Gauthier et al. to model the proportion of PHN cases following an episode of HZ in the general population (Table 1, SI Table 4). As for HZ, the model assumes that the incidence of recurrent PHN is the same as for first-time PHN.

HZ-RELATED MORTALITY

Values for HZ-associated mortality are based on published literature³² (SI Table 5). The study by Edmunds et al. was the only report including a granular breakdown of HZ case fatality rate by age-group in the UK and was therefore considered to be the most appropriate source for HZ-associated mortality. The published data are based on the population of England and Wales. However, increasing mortality with increasing age is consistent with observations from studies conducted in other countries³³ and it is assumed that these rates apply to the entire UK population.

NON-PHN COMPLICATIONS

A wide range of complications other than PHN can occur in people experiencing an episode of HZ and could have a substantial impact on the burden of the disease. In the model, four main categories of complications were included, i.e., ocular, neurological, cutaneous and other non-pain complications. Probabilities of developing these complications after the initial HZ episodes were taken from published literature²⁹ (Table 1).

HOSPITALISATION AND GP VISITS DUE TO COMPLICATIONS

The CPRD study was used to derive the proportion of patients being hospitalised or visiting their GP due to HZ-related complications.²⁸ Hospitalisation rates were higher in the IC cohort for all age-groups. In addition, health-care resource use was higher in older adults (SI Tables 6 & 7).

VACCINE EFFICACY AND SAFETY

EFFICACY

Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the ZOE-50 and ZOE-70 trials for RZV^{16 23 24 26} (Table 1, SI Table 8). VE for RZV is based on a 2-dose schedule given 2 months apart. However, compliance with 2nd dose RZV is likely to be lower than 100%, as such there is a cohort of individuals who are only vaccinated with one dose. Therefore, efficacy data for 1-dose RZV were analysed post-hoc based on limited clinical data from individuals in the ZOE trials receiving only 1-dose RZV.²⁵

Waning for both vaccines was modelled by linear fitting, using data from the above-

mentioned trials as well as from the long-term persistence study (LTPS) for ZVL.²⁵ For RZV, waning rates were assumed to be 1% (range: 0%, 2.6%) during the first 4 years after vaccination and 2.3% (range: 0.7%, 4.6%) thereafter in individuals < 70 YOA. In the population ≥ 70 YOA, waning rate was assumed to be constant over time at 3.6% (range: 1.4%, 6.6%).²⁵ For ZVL, the model indicated a waning rate of 5.4% (range: 4.5%, 6.4%) during the first 4 years after vaccination and 5.1% (range: 4.1%, 6.0%) thereafter in all age-groups^{17 25} (SI Table 9).

COVERAGE AND COMPLIANCE

In the base-case analysis, coverage is set at 48.3% in line with latest coverage numbers for the UK.²⁰ The impact of different coverage rates was assessed in sensitivity analyses. Compliance with the second-dose of RZV was set to 70%.

OUTCOMES

The model was used to estimate the avoidance of HZ and PHN cases, complications, deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related deaths and number of GP visits and hospitalisations for three different vaccination strategies, i.e., vaccination with RZV, vaccination with ZVL and no vaccination.

The number needed to vaccinate (NNV) to avert one case of HZ and PHN was also evaluated by applying the following calculation:

$$NNV = \frac{1}{\left(\frac{\text{control cases}}{\text{vaccinated persons}}\right) - \left(\frac{\text{vaccinated cases}}{\text{vaccinated persons}}\right)}$$

SCENARIO ANALYSES

Different scenario analyses were carried out where assumptions regarding vaccination coverage and compliance and age at vaccination were changed.

In a first scenario analysis, the impact of increasing coverage of RZV to 70% was explored. A higher coverage of 70% in the UK was deemed plausible considering that a) the influenza vaccine uptake in people ≥ 65 YOA was 70.5% in 2016/2017³⁴ and b) in the absence of a contraindication, vaccinators might not hesitate to administer the vaccine in IC individuals.

In a second scenario analysis, the second-dose compliance was varied, assuming a

1
2
3 lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of
4 the clinical trial second-dose compliance.²⁵
5
6

7 Finally, the impact of changing the vaccination age on health outcomes was explored.
8 VE is in general higher in younger individuals favouring early vaccination. On the other
9 hand, duration of protection decreases over time and burden of disease (severity and
10 duration of HZ and PHN) is higher in older individuals, favouring vaccination at an older
11 age.³⁵ The relative balance of these factors may be different in case of ZVL and RZV,
12 leading to different conclusions regarding optimal vaccination age.
13
14
15
16

17 *SENSITIVITY ANALYSES*

18
19
20 Deterministic sensitivity analyses (DSA) were conducted to test the robustness of the
21 results subject to changes in input parameters. To this aim, HZ and PHN incidence
22 rates, VE and waning rates for both vaccines, incidence rate of HZ-related
23 complications and vaccine-related adverse events, coverage and second-dose
24 compliance were varied in one-way sensitivity analyses according to pre-defined
25 ranges. Tornado diagrams were used to illustrate parameters that had the largest
26 impact on HZ cases avoided.
27
28
29
30

31
32 Probabilistic sensitivity analysis (PSA) was carried out to assess the variability of results
33 when changing parameters concomitantly using Monte Carlo simulation (5,000
34 simulations). Each parameter could be attributed a value within its predefined range
35 and according to the assigned probability distribution. A beta-distribution was used
36 for all parameters except for vaccine coverage which followed a uniform distribution.
37 Age-specific incidence parameters which varied across age-groups were assumed to
38 be correlated using a correlation of 0.5. The results of the PSA are presented using a
39 histogram displaying the HZ cases avoided with RZV compared with ZVL.
40
41
42
43
44

45 *RESULTS*

46 *BASE-CASE ANALYSIS*

47
48
49 In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN
50 cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a
51 reduction of 7,909 HZ and 3,567 PHN cases (Table 2). Vaccination with RZV reduced
52 the number of HZ-related complications and the health-resource use (Table 2). There
53 were few HZ-related deaths; compared to no vaccination, RZV prevented 8 HZ-related
54
55
56
57
58
59
60

1
2
3
4 deaths while ZVL prevented none. The NNV to prevent one case of HZ was 12 with RZV
5 and 45 with ZVL. The NNV to avoid one case of PHN was 65 with RZV and 98 with ZVL,
6 respectively.
7

8 9 *SCENARIO ANALYSES*

10
11 In a first scenario analysis, we increased coverage from 48.3% to 70% for RZV. In this
12 scenario, an additional 13,596 HZ and 2,430 PHN cases would be prevented in the
13 routine vaccination cohort (70 YOA) (Figure 1, light blue bar showing the additional
14 proportion of HZ and PHN cases avoided with RZV compared to no vaccination).
15
16

17
18 In a second scenario analysis, compliance with second-dose of RZV was set to lower
19 and upper limits of 60% and 89%. Compared to no vaccination, the numbers of HZ
20 cases avoided with RZV were 28,145 and 34,284 at the lower and upper limits for
21 compliance, respectively (Figure 2).
22
23

24
25 To determine the optimal age for vaccination, scenario analyses were carried out to
26 evaluate the public health impact in different age cohorts (50, 60, 65, 70 and 80 YOA)
27 in terms of NNV, HZ and PHN cases avoided and resource utilisation per 100,000
28 people.
29
30

31
32 In case of RZV, the scenario that led to avoidance of the most HZ cases per 100,000
33 people would be vaccinating at 60 YOA, while slightly more PHN cases per 100,000
34 people could be avoided by vaccinating at 65 YOA. In case of ZVL, the number of HZ
35 cases avoided per 100,000 people would be highest in the 65 YOA cohort, but more
36 PHN cases per 100,000 people would be avoided in the 70 YOA cohort (Figure 3). In all
37 age-groups, number of HZ and PHN cases avoided per 100,000 people was higher for
38 RZV compared to ZVL. Complications avoided ranged from 689 with RZV and 250 with
39 ZVL in the 65 YOA cohort, to 434 with RZV and 46 with ZVL in the 80 YOA cohort.
40
41

42
43 Consistent with these results, for RZV, the NNV to avoid one case of HZ was lowest in
44 the 60 YOA (NNV = 9) and the NNV to avoid one case of PHN was lowest in the 65 YOA
45 cohort (NNV = 54) (Table 3).
46
47

48
49 The higher number of HZ and PHN cases avoided with RZV compared to ZVL across all
50 age cohorts leads to an important reduction in the use of health care resources, which
51 might be an indicator of a reduction in direct costs due to HZ (Table 4). The number of
52 GP visits per 100,000 people avoided is highest for the 60 YOA and 65 YOA cohorts for
53 both vaccines, and consistently higher for RZV compared to ZVL. The number of
54
55
56
57
58
59
60

1
2
3
4 hospitalisations avoided increases with increasing age for RZV, reflecting the increased
5 risk of hospitalisation due to HZ in older individuals.
6

7 8 *SENSITIVITY ANALYSES* 9

10 In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the
11 robustness of results was tested by changing input parameters to their lower and
12 upper estimated confidence ranges (SI Tables 3 – 5; SI Tables 8 – 9). In the base case
13 analyses, RZV prevented an additional 22,353 HZ cases as compared to ZVL. The
14 parameter with the highest impact on the relative advantage of RZV over ZVL was
15 annual waning of RZV (2 doses) VE_{HZ} in people ≥ 70 YOA, although the highest waning
16 for RZV would still lead to a reduction of over 13,000 HZ cases compared to ZVL. Other
17 parameters influencing the number of HZ cases avoided include initial VE_{HZ} in people
18 ≥ 70 YOA for ZVL and RZV single dose, HZ incidence, and RZV compliance to second-
19 dose (Figure 4).
20
21
22
23
24

25
26 During PSA, all parameters were varied simultaneously along their predefined ranges.
27 In all simulations ($n = 5,000$), RZV led to a reduction of HZ cases as compared to ZVL.
28 The distribution of the number of HZ cases avoided by RZV relative to ZVL is shown in
29 Figure 5. Overall, 83.1% of simulations predicted that RZV would prevent at least
30 15,000 additional HZ cases compared with ZVL in the age-group 70 YOA.
31
32
33
34

35 **DISCUSSION** 36

37
38 UMV against HZ using ZVL was introduced in the UK in 2013 and observational studies
39 suggest that the programme has brought down HZ incidence by approximately one
40 third in the vaccinated cohorts.^{36 37} RZV has been approved by the EMA in individuals
41 ≥ 50 YOA, thereby offering an alternative option to vaccinate people against HZ in
42 addition to the existing ZVL. The aim of this study was to evaluate the public health
43 impact of RZV in terms of HZ prevention compared to ZVL or no vaccination in the UK
44 setting.
45
46
47
48

49 In the base-case considering the current vaccination cohort of people 70 YOA, RZV
50 reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no
51 vaccination. In comparison, ZVL prevented 7,909 HZ and 3,567 PHN cases as compared
52 to no vaccination. NNV to prevent one episode of HZ was almost four times lower with
53 RZV compared to ZVL, i.e., 12 with RZV vs 45 with ZVL. In addition, the estimated
54 number of hospitalisations and GP visits due to HZ and PHN were substantially lower
55
56
57
58
59
60

1
2
3
4 with RZV compared with HZ. HZ-related mortality is in general low; nevertheless, our
5 simulations predicted that 8 deaths could be prevented with an RZV vaccination
6 strategy while no HZ-related deaths were prevented adopting a ZVL vaccination
7 strategy.
8
9

10 Results were robust under deterministic and probabilistic sensitivity analyses. Annual
11 waning of RZV VE in people ≥ 70 YOA had the greatest impact on the number of HZ
12 avoided relative to ZVL, but even assuming an extreme assumption on waning, with
13 an annual waning rate of 6.6%, RZV would prevent an additional 13,816 HZ cases as
14 compared to ZVL. Other parameters to which the relative vaccination strategies
15 proved sensitive included annual HZ incidence and VE_{HZ} of RZV and ZVL. Probabilistic
16 sensitivity analyses were always in favour of the RZV vaccination strategy with 83.1%
17 of simulations showing a reduction of at least $\geq 15,000$ HZ cases with respect to ZVL.
18 We also tested different scenarios in which coverage and compliance were varied,
19 assuming that the public health impact would increase as a greater proportion of
20 individuals would be vaccinated. Increasing the coverage estimate of the first-dose of
21 RZV from 48.3% to 70% would further reduce HZ and PHN incidence thereby leading
22 to a greater reduction in healthcare resources used. We hypothesise that the coverage
23 with RZV might be higher because a proportion of the eligible individuals are currently
24 not receiving the vaccine with ZVL. Even though the proportion of individuals with a
25 true contraindication to ZVL is estimated to be small (2.8%²⁰) HZ vaccination with ZVL
26 might be withheld even in those IC individuals who have no contraindications as
27 vaccinators may have been risk averse. Reducing RZV compliance to 60%, RZV would
28 still prevent approximately three times more HZ cases compared to ZVL. This is in line
29 with a recent public health impact study carried out for the German setting where a
30 compliance rate of 50% would still lead to an improvement of 200% over ZVL in terms
31 of HZ prevention.²⁵ Although results are in line with the German study, this UK model
32 adaptation has some different methodological considerations that are of importance
33 to potential decision-making bodies. Firstly, this manuscript also assesses single year
34 cohorts versus multiple year cohorts. This was chosen to reflect the current HZ
35 vaccination programme in the UK where people get vaccinated with ZVL at 70 YOA
36 and 79 YOA within the catch-up programme. Secondly, the HZ incidence is calculated
37 based upon a weighting method of IC-free and IC populations using the prevalence of
38 IC in the different age groups. This is important to estimate the actual HZ incidence in
39 the general population.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

56 The recommended vaccination strategy was based on the clinical profile of ZVL, the
57
58
59
60

1
2
3
4 only vaccine available at the time. In its recommendation, the JCVI noted that ZVL VE
5 decreases with increasing age and over time; hence, the current age cohort eligible
6 for vaccination, i.e., individuals 70 YOA, is a compromise to optimise limited efficacy
7 and duration of protection against HZ. The JCVI also stated that optimal age at
8 vaccination would depend on the characteristics of any given vaccine.³⁸ Therefore, the
9 impact of vaccination age on HZ and PHN incidence was explored through scenario
10 analyses including different age-cohorts (50, 60, 65, 70 and 80 YOA). The number of
11 HZ and PHN cases avoided per 100,000 people was higher with RZV than with ZVL
12 across all age cohorts. In case of RZV, most HZ cases were avoided in the 60 YOA
13 cohort, while PHN case avoidance was highest in the 65 YOA cohort. This observation
14 is consistent with a higher probability of developing PHN at an increased age. On the
15 other hand, the projected number of PHN cases avoided with ZVL was highest in the
16 70 YOA. This finding is due to a top-up efficacy seen with ZVL against PHN in the
17 population ≥ 70 YOA: vaccinated individuals with breakthrough HZ are at a lower risk
18 of developing PHN as compared to unvaccinated individuals with HZ. In the individuals
19 < 70 YOA, no additional protection against PHN was observed in clinical studies with
20 ZVL. For RZV no additional top-up efficacy could be calculated based on the limited
21 number of breakthrough cases, and thus VE_{HZ} and VE_{PHN} were assumed to be the
22 same. As a result, for RZV, the NNV to avoid one case of HZ and PHN was lowest for
23 the 60 YOA and 65 YOA cohorts. NNV increased in the 70 YOA and more so in the 80
24 YOA, where a proportion of the simulated cohort died due to natural causes before
25 any health benefit of vaccination occurred.

26
27
28
29
30
31
32
33
34
35
36
37 From a health care utilisation perspective, RZV reduced the number of GP visits by
38 more than 13,000 compared to ZVL in all age-groups. The highest reduction in GP visits
39 was predicted in the 65 YOA cohort, while the largest impact on hospitalisations was
40 predicted in the 80 YOA cohort. The latter might be explained by the higher risk of
41 hospitalisation inherent to older individuals due to a higher degree of frailty.
42 Nevertheless, it should be noted that the reduction in hospitalisations was predicted
43 to be several-fold higher with RZV compared to ZVL in all age-cohorts. Reduction
44 in the use of health care resources is a good indicator of potential decrease in direct
45 costs of new health care interventions; however, this requires further investigation in
46 a cost-effectiveness analysis with RZV in the UK context.

47
48
49
50
51
52
53 The potential public health impact of RZV in the UK setting has previously been studied
54 by our group.³⁹ The study showed a substantial reduction in HZ and PHN cases
55 compared to no vaccination; however, no comparison was made to ZVL. A number of
56
57
58
59
60

1
2
3
4 studies have evaluated the impact of ZVL on disease burden and associated cost-
5 effectiveness in the UK setting. Van Hoek et al. analysed cost-effectiveness of ZVL in
6 different age-groups with the base-case considering a cohort of immunocompetent
7 65-year-old individuals in the UK. This cohort was modelled over a life-time and a
8 vaccine coverage of 73.5%.³ Waning rates might have been underestimated in this
9 model since long-term data from the LTPS study for persistence of efficacy of the ZVL
10 vaccination were not yet taken into account.²⁵ The LTPS study showed that VE_{HZ} of ZVL
11 decreases significantly over time with no statistically significant protection observed
12 after 8 years of vaccination.^{17 18} In the economic model published by Moore et al., the
13 NNV of ZVL to prevent one case of HZ was 15, and hence lower than that found in our
14 simulations. However, the authors assumed a waning rate of 0%.¹⁰

20
21 The public health impact of RZV was also evaluated for other settings, including
22 Germany, US, Canada and Australia. These studies used a wide range of assumptions
23 regarding coverage, compliance and duration of vaccine protection for both RZV and
24 ZVL.^{28 40-42} Despite differences in these assumptions, all studies showed a consistent
25 improvement in the reduction of HZ cases and its complications compared to no
26 vaccination or vaccination with ZVL. In a recent independent cost-effectiveness study
27 for the US setting, employing conservative assumptions regarding RZV waning rate,
28 coverage and compliance, the authors concluded that RZV was more effective
29 compared to ZVL under the vast majority of assumptions evaluated.⁴⁰

30
31
32
33
34
35
36 As with every model, there are strengths and limitations associated with the modelling
37 strategy employed. For RZV, most recent UK-specific data available at the time we
38 conducted this study were used; for HZ incidence the CPRD database, a large UK-
39 specific database, was analysed and values for both IC and non-IC cohorts were
40 combined.^{28 43} For PHN incidence, published data from two reports were used to
41 estimate the PHN probability in the total population including individuals with
42 immunodeficient states. The estimates of PHN cases prevented are close to real
43 values, validating our approach. Demographic data projected to the year 2018 were
44 used based on numbers reported by the ONS.²⁷ The limitations in this study are related
45 to assumptions that had to be made in the absence of real-world data, including
46 coverage with RZV, compliance and long-term waning for RZV. Coverage and
47 compliance were set to values observed in comparable vaccination programs and
48 these parameters were varied in scenario and one-way sensitivity analyses. Results
49 from long-term studies with RZV are still outstanding and follow-up data is currently
50 limited to 4 years. However, the model has been developed such that it can be
51
52
53
54
55
56
57
58
59
60

1
2
3 updated once additional data becomes available. For ZVL waning rates, we included
4 both data from the SPS and the LTPS study²⁵ to ensure that we could compare ZVL
5 and RZV in the ZONA model. Recent observational studies looking into the vaccine
6 effectiveness of ZVL show that the vaccine wanes rapidly and has little to no protection
7 left beyond year 8 after vaccination.^{18 37} Finally, the rate of HZ-associated
8 complications was assumed to be the same in all individuals with HZ regardless of their
9 vaccination status. This assumption ignores the potential benefit vaccination might
10 have by lowering the severity and duration of break-through HZ cases. Clinical trial
11 data suggest that VE_{HZ} and VE_{PHN} are similar and there is some evidence that duration
12 and severity of HZ/PHN pain is lower in individuals having received RZV as compared
13 to unvaccinated individuals.⁴⁴

20
21 Future research might be directed towards assessing severity and duration of HZ and
22 PHN cases depending on vaccination status, identifying subgroups of the population
23 that may have enhanced benefit from the vaccine and evaluating cost-effectiveness
24 in the current UMV cohort and across different age-cohorts.

25
26 A lay language summary contextualizing the outcomes and potential impact of this
27 study for healthcare providers is displayed in Figure 6.

34 **CONCLUSION**

35
36
37 Within the model assumptions, RZV has the greater public health impact in terms of
38 HZ and PHN case avoidance and reduction in health care utilisation. When the UMV
39 was introduced in 2013, vaccinating people at 70 YOA was the best option based on
40 the vaccine characteristics of ZVL. With the approval of RZV in the US, Canada, Japan
41 and Europe in adults ≥ 50 YOA the optimal HZ prevention strategy needs to be re-
42 evaluated. The model projects for RZV a longer duration of protection and the VE
43 remains high in older age groups compared to ZVL. Therefore, the results of this model
44 show that the difference in clinical profile of RZV leads to a different optimal age of
45 vaccination. Vaccinating the UK population with RZV at 60 YOA or 65 YOA is the
46 optimal vaccination strategy in terms of public health impact, while being superior to
47 ZVL in all age cohorts studied.

ACKNOWLEDGEMENTS

Authors would like to Lijoy Varghese for this contribution to the study. They also want to thank Business & Decision Life Sciences platform for editorial assistance and publications coordination, on behalf of GSK. Stephanie Garcia coordinated manuscript development and editorial support. Katrin Spiegel provided writing support.

REFERENCES

1. Mueller NH, Gilden DH, Cohrs RJ, et al. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. *Neurol Clin* 2008;**26**(3):675-97. doi:10.1016/j.ncl.2008.03.011.
2. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* 2014;**4**:e004833. doi:10.1136/bmjopen-2014-004833
3. van Hoek AJ, Gay N, Melegaro A, et al. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. *Vaccine* 2009;**27**(9):1454-67. doi:10.1016/j.vaccine.2008.12.024
4. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Therapeutic Advances in Vaccines* 2015;**3**(4):109-20. doi:10.1177/2051013615599151
5. Bollaerts K, Riera-Montes M, Heininger U, et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: deriving incidence from seroprevalence data. *Epidemiol Infect* 2017;**145**(13):2666-77. doi:10.1017/S0950268817001546
6. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect* 2001;**127**:305-14. doi:10.1017/S0950268801005921
7. Pinchinat S, Cebrián-Cuenca AM, Bricout H, et al. Similar herpes zoster incidence across Europe: Results from a systematic literature review. *BMC Infect Dis* 2013;**13**:170. doi:10.1186/1471-2334-13-170
8. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiol Infect* 2009;**137**(1):38-47. doi:10.1017/S0950268808000678
9. Varghese L, Standaert B, Olivieri A, et al. The temporal impact of aging on the burden of herpes zoster. *BMC Geriatr* 2017;**17**:30. doi:10.1186/s12877-017-0420-9
10. Moore L, Remy V, Martin M, et al. A health economic model for evaluating a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in the UK. *Cost effectiveness and resource allocation : C/E* 2010;**8**:7-7. doi:10.1186/1478-7547-8-7
11. Gater A, Abetz-Webb L, Carroll S, et al. Burden of herpes zoster in the UK: Findings from the zoster quality of life (ZQOL) study. *BMC Infect Dis* 2014;**14**:402. doi:10.1186/1471-2334-14-402
12. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: A prospective study. *CMAJ* 2010;**182**(16):1731-36. doi:10.1503/cmaj.091711
13. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *The Clinical journal of pain* 2007;**23**(6):490-6. doi:10.1097/AJP.0b013e318065b6c9
14. Joint Committee on Vaccination and Immunisation. Joint Committee on Vaccination and Immunisation Statement on varicella and herpes zoster vaccines. available from: <http://webarchive.nationalarchives.gov.uk/20120907151317/http://www.dh.gov>

- v.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf [accessed June 26, 2018].
15. Merck Sharp Dohme Ltd. Zostavax Summary of Product Characteristics (SmPC). available from: <https://www.medicines.org.uk/emc/product/6101/smcp> [accessed June 26, 2018].
 16. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *NEnglJMed* 2012;**366**(20):1859-69. doi:10.1056/NEJMoA1208410
 17. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 2015;**60**(6):900-09. doi:10.1093/cid/ciu918
 18. Tseng HF, Harpaz R, Luo Y, et al. Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged ≥ 60 Years. *J Infect Dis* 2016;**213**(12):1872-75. doi:10.1093/infdis/jiw047
 19. Public Health England. Shingles (herpes zoster), 2016:Chapter 28a.
 20. Public Health England. Herpes zoster (shingles) immunisation programme : September 2016 to August 2017 Report for England. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667636/Annual_shingles_report_2016-2017_.pdf [accessed June 26, 2018].
 21. Chlibek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. *Vaccine* 2016;**34**(6):863-68. doi:10.1016/j.vaccine.2015.09.073
 22. GlaxoSmithKline Biologicals SA. Shingrix Summary of Product Characteristics (SmPC). available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004336/WC500246550.pdf [accessed June 26, 2018].
 23. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med* 2015;**372**(22):2087-96. doi:10.1056/NEJMoA1501184
 24. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med* 2016;**375**(11):1019-32. doi:10.1056/NEJMoA1603800
 25. Curran D, Van Oorschot D, Varghese L, et al. Assessment of the potential public health impact of Herpes Zoster vaccination in Germany. *Hum Vaccin Immunother* 2017;**13**(10):2213-21. doi:10.1080/21645515.2017.1345399
 26. Schmader KE, Levin MJ, Gnann JW, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis* 2012;**54**(7):922-28. doi:10.1093/cid/cir970
 27. Office of National Statistics. 2014 based National population projections. available from: <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
 28. Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012. *BMJ Open* 2018;**8**(6). doi:10.1136/bmjopen-2017-020528

- 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
29. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;**82**(11):1341-9.
30. Yawn BP, Wollan PC, Kurland MJ, et al. Herpes Zoster Recurrences More Frequent Than Previously Reported. *Mayo Clin Proc* 2011;**86**(2):88-93. doi:10.4065/mcp.2010.0618
31. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;**157**(1):30-54. doi:10.1097/j.pain.0000000000000307
32. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine* 2001;**19**(23-24):3076-90. doi:10.1016/S0264-410X(01)00044-5
33. Bricout H, Haugh M, Olatunde O, et al. Herpes zoster-associated mortality in Europe: A systematic review. *BMC Public Health* 2015;**15**(1):466. doi:10.1186/s12889-015-1753-y
34. Public Health England. Influenza: the green book, chapter 19. available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/663694/Greenbook_chapter_19_Influenza_.pdf [accessed June 29, 2018].
35. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (Shingles) and postherpetic neuralgia. *Mayo Clin Proc* 2009;**84**(3):274-80. doi:10.4065/84.3.274
36. Amirhalingam GA, Nick. Keel, Philip. Mullett, David. Correa, Ana. de Lusignan, Simon. Ramsay, Mary. Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study. *Lancet Public Health* 2018;**3**:e82-90. doi:10.1016/S2468-2667(17)30234-7
37. Walker JL, Andrews NJ, Amirhalingam G, et al. Effectiveness of herpes zoster vaccination in an older United Kingdom population. *Vaccine* 2018;**36**(17):2371-77. doi:10.1016/j.vaccine.2018.02.021
38. Joint Committee on Vaccination Immunisation. Minute of the meeting on 4 October 2017. available from: https://www.jostrust.org.uk/sites/default/files/minute_2017_10_draft.pdf <https://www.bmj.com/content/bmj/345/bmj.e6879.full.pdf> [accessed June 26, 2018].
39. Van Oorschoot D, Hunjan M, Varghese L, et al. The public health perspective of an investigational herpes zoster vaccine in the united kingdom (UK). *Value Health* 2016;**19**(7):A400-A00. doi:10.1016/j.jval.2016.09.309
40. Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. *JAMA Internal Medicine* 2018;**178**(2):248-58. doi:10.1001/jamainternmed.2017.7431
41. Varghese L, Curran D, Yan S, et al. Estimating the Potential Public Health Impact of Introducing the HZ/su Vaccine in the US Population Aged ≥ 50 Years. *Open Forum Infectious Diseases* 2015;**2**(suppl_1). doi:10.1093/ofid/ofv133.1477
42. Varghese L, Nissen M, Olivieri A, et al. Public health perspective of phase III results of an investigational Herpes Zoster vaccine. Public Health Association of Australia. *Public Health Association of Australia - Communicable Disease Control Conference*, Brisbane 2015:42. <https://www.phaa.net.au/documents/item/581> (accessed June 26, 2018).
43. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The

- 1
2
3 United Kingdom. *Value Health* 2017;**20**(9):A786.
4 doi:10.1016/j.jval.2017.08.2296
5
6 44. Curran D, Athan E, Diez-Domingo J, et al. Quality-of-Life Impact of an
7 Investigational Subunit-Adjuvanted Herpes Zoster Vaccine in Adults ≥ 50 Years
8 of Age. *Open Forum Infectious Diseases* 2016;**3**(suppl_1).
9 doi:10.1093/ofid/ofw194.77
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

FOOTNOTES

TRADEMARK

Shingrix is a trademark of the GSK group of companies.

Zostavax is a trademark from Merck Sharp & Dohme Corp.

AUTHORS' CONTRIBUTION

DVO, DC, SL, BB participated to the conception and design of the analysis; DVO, DC, MH developed and adapted the model; DVO, DC, MH, HSC, BB were involved in the collection, analysis and/or interpretation of the data. All authors had full access to the data and approved the final version of the paper for submission.

CONFLICTS OF INTEREST

DVO, MH, BB, DC and HSC are employees of the GSK group of companies. MH, DC, and HSC hold shares in the GSK group of companies. SL is a freelance consultant working on behalf of the GSK group of companies.

DATA SHARING STATEMENT

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

ETHICAL APPROVAL

Ethical approval is not applicable for this public health impact modelling analysis.

FUNDING SECTION

GlaxoSmithKline Biologicals SA funded this study (GSK study identifier: HO-17-18511) and was involved in all stages of study conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also covered all costs associated with the development and publication of this manuscript.

TABLES AND FIGURES

Table 1: Demographic, epidemiological and efficacy data according to age group

Age		50 YOA	60 YOA	65 YOA	70 YOA	80 YOA
Number of people in-age group in 2018		908,255	783,067	686,215	722,616	389,107
HZ incidence per 1,000 individuals	IC	6.85	8.80	9.93	11.32	12.61
	IC-Free	4.9	6.92	8.62	11.04	11.02
Proportion developing PHN (%)		11.42	13.89	15.71	17.12	20.42
Non-PHN complications incidence (%)	Ocular	2.87	3.82	3.82	4.14	5.41
	Neurological	2.46	3.17	3.17	5.99	4.23
	Cutaneous	1.74	1.05	1.05	2.09	2.44
	Other	2.03	1.63	1.63	2.44	2.85
HZ - Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95-100)	98.4 (95-100)	98.4 (95-100)	97.8 (94.1-100)	97.8 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (54.1-80.6)	63.9 (56.0-71.0)	63.9 (56.0-71.0)	40.85 (28.0-52.0)	18.25 (0-48.0)
PHN Vaccine Efficacy – % (Range)	RZV 2 doses	98.4 (95.0-100)	98.4 (95.0-100)	98.4 (95.0-100)	97.84 (94.1-100)	97.84 (94.1-100)
	RZV 1 dose	90.0 (58.9-98.9)	90.0 (58.9-98.9)	90.0 (58.9-98.9)	69.5 (24.9-89.1)	69.5 (24.9-89.1)
	ZVL	69.8 (30.8-89.6)	65.69 (25.4-84.2)	65.69 (25.4-84.2)	73.38 (51.6-85.8)	39.51 (0-73.8)

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live.

Table 2: Health outcomes and health resource utilisation in the vaccination cohort 70 YOA - base-case analysis, N=722,616

	RZV	ZVL	No vaccination	RZV vs no vaccination	ZVL vs no vaccination
HZ cases, n	88,643	110,996	118,905	30,262	7,909
PHN cases, n	16,570	18,411	21,979	5,409	3,567
HZ-related complications					
Total, n	13,109	16,405	17,565	4,455	1,160
Ocular, n	4,207	5,221	5,548	1,341	327
Neurological, n	4,565	5,782	6,255	1,691	474
Cutaneous, n	2,001	2,492	2,658	657	165
Other non-pain, n	2,336	2,910	3,103	767	193
Deaths					
HZ-related deaths, n	56	64	64	8	0
Resource utilisation					
Hospitalisation, n	7,827	9,463	9,820	1,993	357
GP visits, n	438,328	546,691	583,612	145,284	36,921

GP: general practitioner; HZ: herpes zoster; PHN: postherpetic neuralgia; n: number of cases; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live.

Coverage for both RZV and ZVL was set to 48.3 %. Second-dose compliance for RZV was set to 70%.

Table 3 NNV to avoid one case of HZ or PHN according to age at vaccination

Age cohort	NNV HZ		NNV PHN	
	RZV	ZVL	RZV	ZVL
50 YOA	10	39	69	328
60 YOA	9	27	55	171
65 YOA	10	23	54	134
70 YOA	12	45	65	98
80 YOA	17	156	82	258

RZV: adjuvanted recombinant zoster vaccine; HZ: herpes zoster ; YOA: years of age; ZVL: zoster vaccine live; NNV: number needed to vaccinate.

Coverage for both RZV and ZVL was set to 48.3 %. Second-dose compliance for RZV was set to 70%.

Table 4 Reduction on resource utilisation per 100,000 people

	GP visits avoided		Hospitalisations avoided	
	RZV	ZVL	RZV	ZVL
50 YOA	17,481	3,652	126	17
60 YOA	22,078	6,375	216	42
65 YOA	23,447	8,702	266	69
70 YOA	20,105	5,109	276	49
80 YOA	15,243	1,629	394	42

GP: general practitioner; HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live.

Coverage for both RZV and ZVL was set to 48.3 %. Second-dose compliance for RZV was set to 70%.

1
2
3 **Figure 1 Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light blue**
4 **bars) comparing RZV vs no vaccination in people 70 YOA**
5

6 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; PHN: postherpetic neuralgia; YOA: years of age.

7
8 Second-dose compliance for RZV was set to 70%.

9 **Figure 2 Impact of second-dose RZV compliance on HZ incidence**

10 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live

11
12 **Figure 3 Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for**
13 **different vaccination cohorts.**
14

15 HZ: herpes zoster; no vac: no vaccination; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster
16 vaccine; YOA: years of age; ZVL: zoster vaccine live.

17
18 Coverage for both RZV and ZVL was set to 48.3 %. Second dose compliance for RZV was set to 70%

19 **Figure 4 Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70**
20 **YOA; coverage 48.3%; compliance 70%)**
21

22 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live.

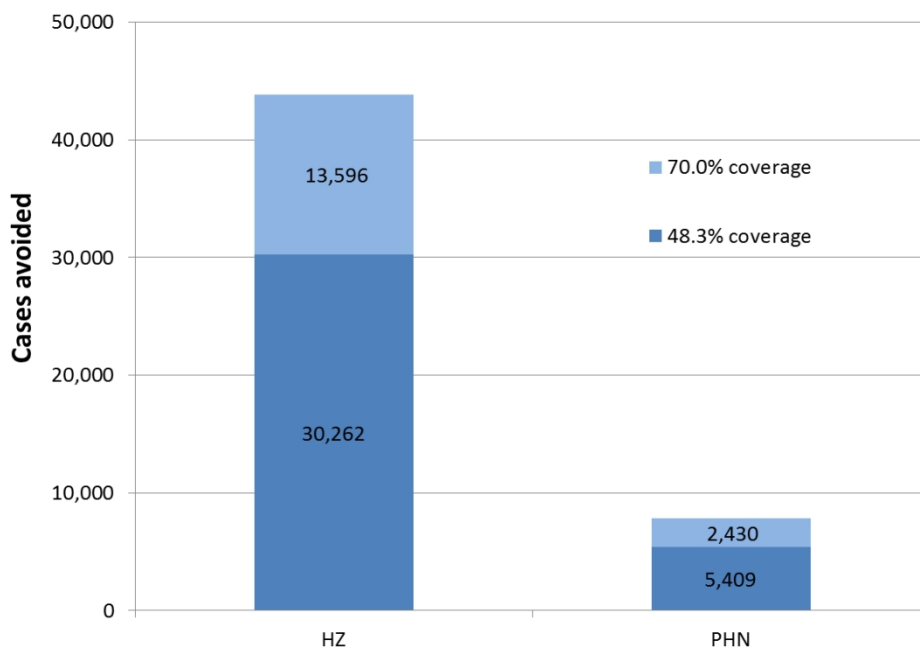
23
24 Lower values are in orange and upper values are in grey.

25 **Figure 5 Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL**

26 HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; ZVL: zoster vaccine live.

27
28
29 The orange line shows the percentage of simulations averting at least the number of HZ cases shown on the x-axis.

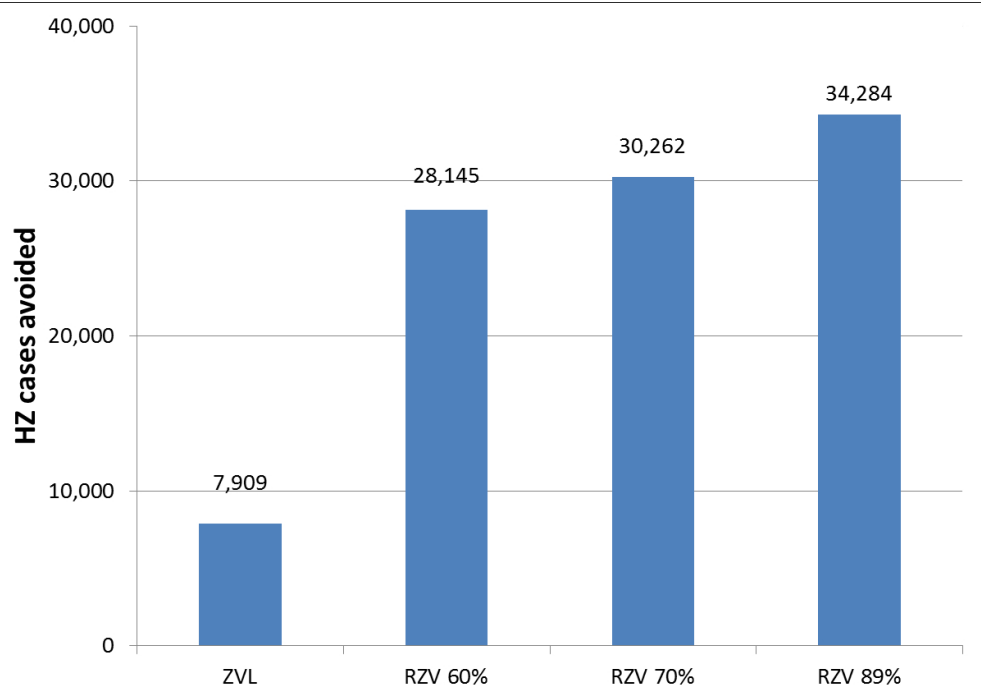
30
31 **Figure 6 Lay language summary of the study**
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Impact of increasing RZV coverage to 70% - Additional HZ and PHN cases avoided (light blue bars) comparing RZV vs no vaccination in people 70 YOA

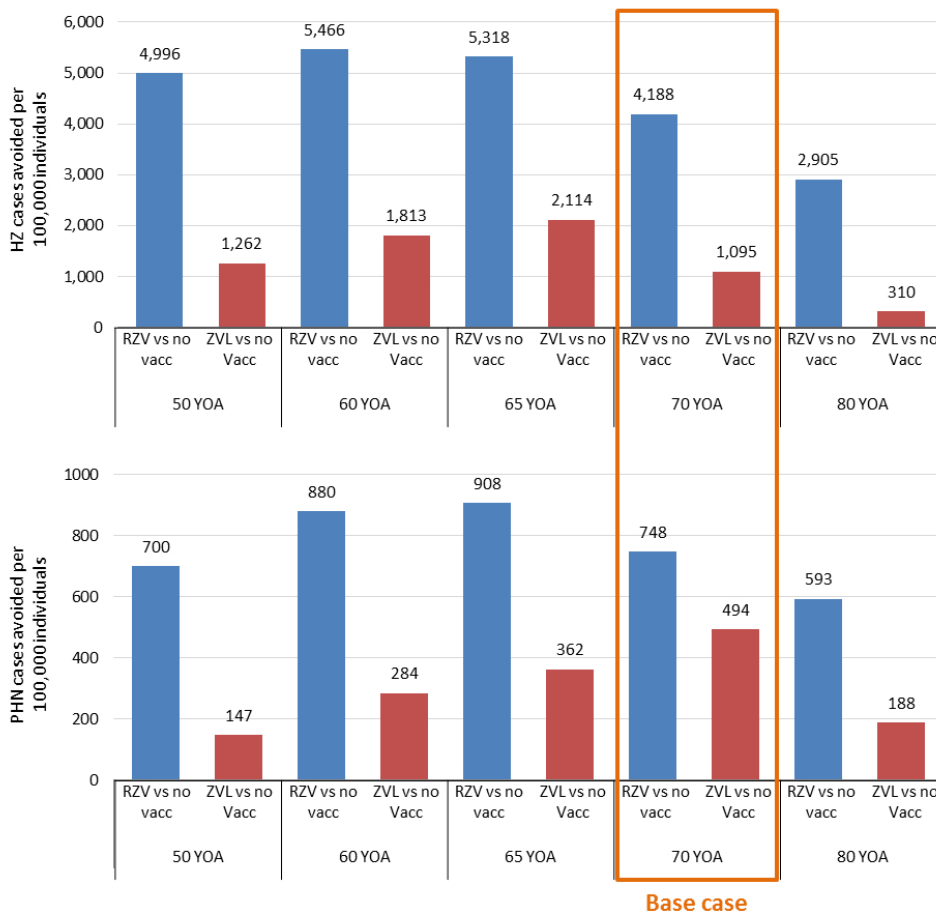
109x75mm (300 x 300 DPI)

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



Impact of second-dose RZV compliance on HZ incidence

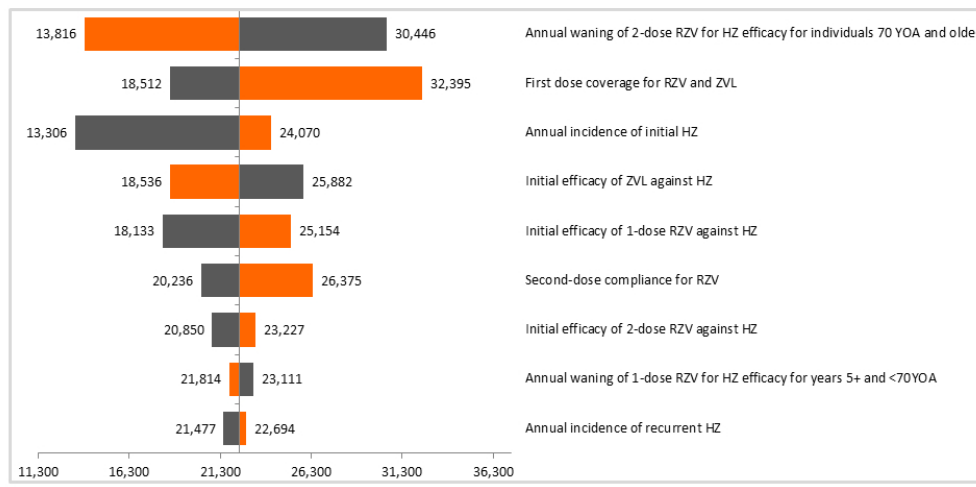
103x72mm (300 x 300 DPI)



Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

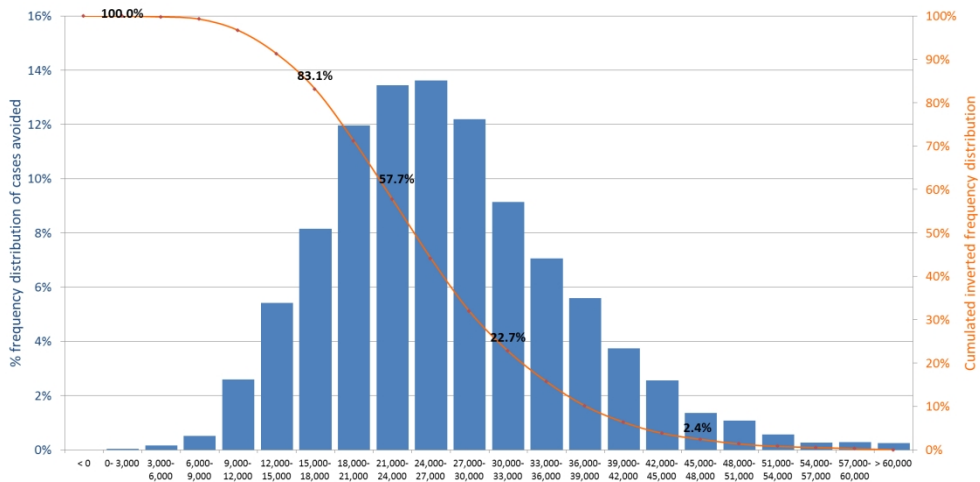
81x80mm (300 x 300 DPI)

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



Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

81x60mm (300 x 300 DPI)



Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

177x86mm (300 x 300 DPI)



Focus on the Patient

What is the context?

Herpes zoster (shingles) is a painful rash that lasts for several weeks and which can lead to prolonged pain even after the initial rash has cleared. Herpes zoster arises when varicella zoster virus, acquired during varicella, reactivates. This happens especially in older people with a weakened immune system. Herpes zoster has a detrimental impact on the quality of life and current treatment options provide only partial symptom relief.

What is new?

In the UK, a universal mass vaccination programme against herpes zoster has been introduced in 2013. The programme recommends vaccination of people aged 70 or 78 years with *Zostavax*, the only vaccine available at that time. In 2018, a new vaccine against herpes zoster, *Shingrix*, has become available. The goal of this study was to explore the impact of different vaccination strategies using a mathematical model.

What is the impact?

The model predicts that *Shingrix* would lead to a greater reduction in the number of herpes zoster episodes compared to *Zostavax*. If adopting a vaccination strategy with *Shingrix*, the optimal age at vaccination would be 60 or 65 years old.

Lay language summary of the study

108x60mm (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

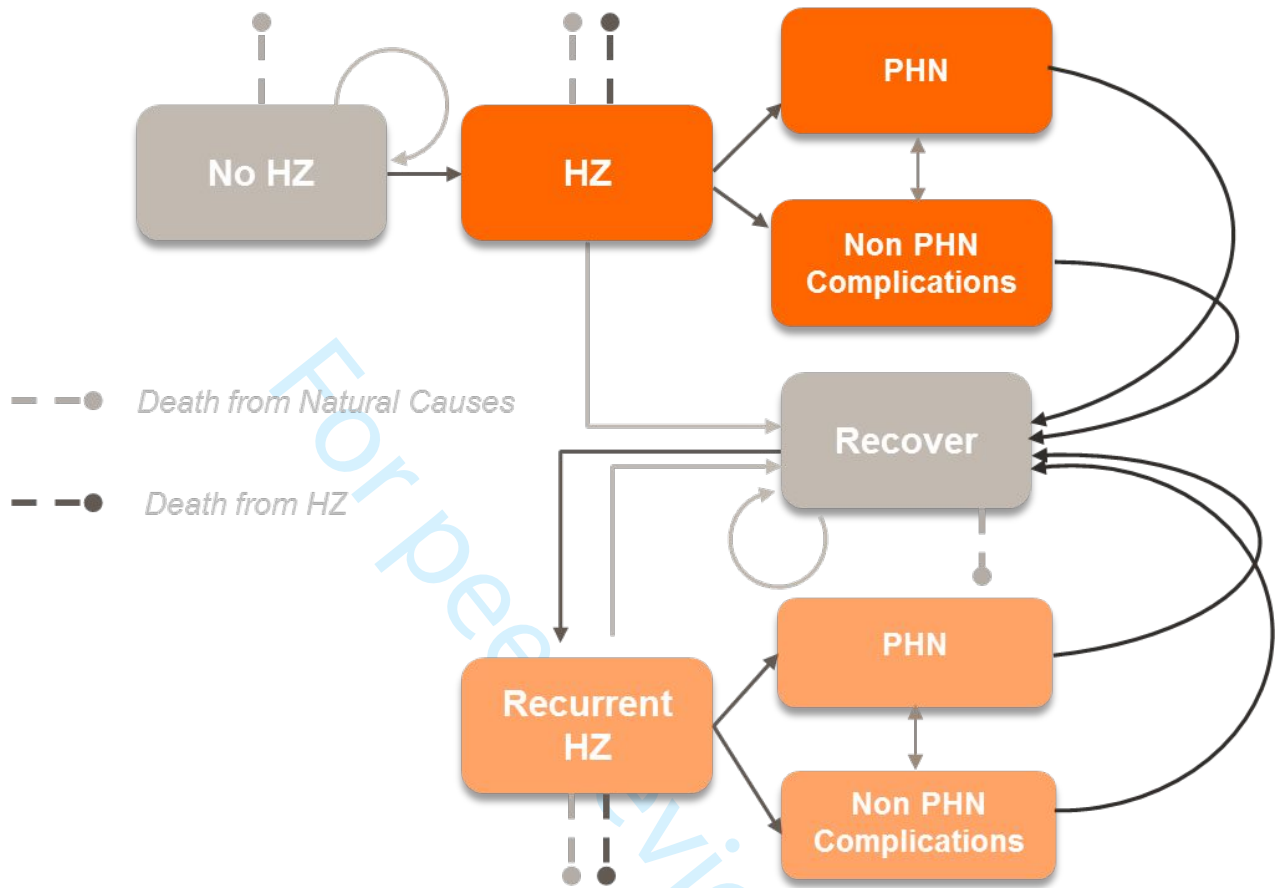
Supplementary Material

Evaluation of the public health impact of introducing a novel Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme

Van Oorschot Desirée, Hunjan Manjit, Bracke Benjamin, Lorenc Stéphane, Curran Desmond, Starkie Camejo Helen

BMJ Open

SI Figure 1: Schematic overview of the ZONA model



HZ: herpes zoster; PHN: postherpetic neuralgia.

Figure originally published in Curran et al. 2017.¹

SI Table 1: Mortality in the general UK population in 2018/2019

Age (YOA)	Number of deaths	Annual probability of death
50-54	15,903	0.00342
55-59	22,590	0.00544
60-64	29,886	0.008366
65-69	45,562	0.013091
70-74	65,747	0.021570
75-79	78,692	0.036493
80-84	104,536	0.065713
85-89	114,461	0.117689
90-94	82,948	0.198093
95-99	33,361	0.304037
≥ 100	5,496	0.436439

YOA: years of age.

Projected numbers using data reported by the Office of National Statistics based on observed numbers of the UK population in 2014.²

The immunocompromised (IC) population was identified as individuals presenting one of the following conditions: Hematopoietic stem cell transplantation, solid organ transplantation, solid organ malignancies, haematological malignancies, human immunodeficiency virus, end-stage renal disease, corticosteroid exposure, other immunosuppressive therapy, other immunodeficiency conditions and autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, multiple sclerosis, polymyalgia rheumatica and autoimmune thyroiditis).³

Herpes Zoster (HZ) incidence for the whole (IC and IC-free) population was calculated by applying a weighting for IC proportion by age group.⁴ A unitary weight across the populations was not deemed to be appropriate or robust as prevalence of herpes zoster varies between the age groups; rising with increasing age. This is because applying IC incidence, accounting for the overall proportion of IC (16.2%) irrespective of age group would underestimate the incidence in older people and overestimate it in younger people.

SI Table 2: Weighting CPRD population for IC proportion by age

Age Group (YOA)	Prevalence of IC (%)	IC weighting	IC-free weighting
50-59	16.13	0.161	0.839
60-64	22.26	0.223	0.777
65-69	27.56	0.276	0.724
70-79	34.88	0.349	0.651
≥ 80	42.16	0.422	0.578

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 3: Incidence and probability of HZ in the whole population

Age (YOA)	Incidence rate/1,000 patient years		Probability	Range	
	IC	IC-Free		Lower limit	Upper limit
50-59	6.85	4.9	0.0052	0.00375	0.00791
60-64	8.8	6.92	0.0073	0.004392	0.009001
65-69	9.93	8.62	0.0089	0.005108	0.010147
70-79	11.32	11.04	0.0111	0.005975	0.011605
≥ 80	12.61	11.02	0.0116	0.007363	0.013955

HZ: herpes zoster; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 4: Proportion of PHN (after 3 months)

Age (YOA)	Proportion (%)	Lower limit (%)	Upper limit (%)
50-59	11.418	8.91	14.13
60-64	13.894	12.03	15.88
65-69	15.705	13.95	17.57
70-79	17.116	13.53	20.94
≥ 80	20.418	17.08	23.82

PHN: postherpetic neuralgia; YOA: years of age

SI Table 5 HZ-associated mortality

Age (YOA)	Probability	Lower limit	Upper limit
50-54	0.00001	0.0000063	0.000012
55-59	0.00001	0.0000063	0.000012
60-64	0.00003	0.0000189	0.000035
65-69	0.00003	0.0000189	0.000035
70-74	0.00004	0.0000245	0.000046
75-79	0.00009	0.0000644	0.000120
80-84	0.00049	0.0003409	0.000633
85-89	0.00202	0.0014126	0.002623
90-94	0.00202	0.0014126	0.002623
95-99	0.00202	0.0014126	0.002623
≥ 100	0.00202	0.0014126	0.002623

HZ: herpes zoster; YOA: years of age

SI Table 6: Hospitalisation rates in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	0.044	0.007	0.012622
60-64	0.054	0.009	0.019245
65-69	0.050	0.014	0.023713
70-79	0.074	0.030	0.045143
≥ 80	0.168	0.115	0.135529

CPRD: Clinical Practice Research Datalink; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age; IC-free: immunocompetent

*Weighted averages calculated using IC proportions in the CPRD study.

SI Table 7 GP visits in IC and IC-free cohort, derived from CPRD database

Age (YOA)	IC	IC-free	ALL
	Mean Events 90-365 days	Mean Events 90-365 days	Weighted Average*
50-59	3.75	2.69	2.86
60-64	4.41	2.86	3.20
65-69	5.05	3.19	3.70
70-79	5.75	4.09	4.67
≥ 80	6.15	4.59	5.25

*Weighted averages calculated using IC proportions in the CPRD study.

CPRD: Clinical Practice Research Datalink; GP: general practitioner; IC: immunocompromised; IC-free: immunocompetent; YOA: years of age

SI Table 8: Vaccine Efficacy against HZ and PHN

Age (YOA)	ZVL			RZV – 2-dose			RZV – 1-dose		
	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit	Efficacy	Lower limit	Upper limit
HZ									
50-59	0.698	0.5410	0.8060	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6389	0.5600	0.7100	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.4085	0.2800	0.5200	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.1825	0.0000	0.4800	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
PHN									
50-59	0.698	0.3080	0.8960	0.984	0.9500	1.0000	0.9	0.5890	0.9890
60-64	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
65-69	0.6569	0.2540	0.8420	0.984	0.9500	1.0000	0.9	0.5890	0.9890
70-79	0.7338	0.5160	0.8580	0.9784	0.9410	1.0000	0.695	0.2490	0.8910
≥ 80	0.3951	0.0000	0.7380	0.9784	0.9410	1.0000	0.695	0.2490	0.8910

HZ: herpes zoster; PHN: postherpetic neuralgia; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

SI Table 9: Vaccine Waning

Vaccine	Age group (YOA)/years after vaccination	Value	5% CI	95% CI
ZVL – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600
RZV – 2-dose	< 70 YOA/Years 1-4	0.010	0.0000	0.0260
	< 70 YOA/Years 4+	0.0230	0.0070	0.0460
	≥70 YOA/ all years after vaccination	0.0360	0.0140	0.0660
RZV – 1-dose	All ages/Years 1-4	0.0543	0.0450	0.0640
	All ages/Years 4+	0.0510	0.0410	0.0600

CI: confidence interval; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

REFERENCES

1. Curran D, Van Oorschot D, Varghese L, et al. Assessment of the potential public health impact of Herpes Zoster vaccination in Germany. *Hum Vaccin Immunother* 2017;**13**(10):2213-21. doi: 10.1080/21645515.2017.1345399
2. Office of National Statistics. 2014 based National population projections. available from: <https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/localauthoritiesinenglandtable2/2014based/table2.xls> [accessed June 13, 2018].
3. Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012. *BMJ Open* 2018;**8**(6). doi:10.1136/bmjopen-2017-020528
4. Curran D, Hunjan M, El Ghachi A, et al. Herpes Zoster Related Healthcare Burden And Costs In Both Immunocompromised (IC) And IC-Free Populations In The United Kingdom. *Value Health* 2017;**20**(9):A786. doi:10.1016/j.jval.2017.08.2296

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

Section/Item	Item no	Recommendation	Reported on page no/line no	Comment
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared	p 1	Strictly speaking, this is not an economic evaluation but public health impact study, as stated in the title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P 4/5	
Introduction				
Background and Objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	p. 7 p. 8	Context provided in first paragraph (epidemiology and rise of HZ episodes during past decades) “The objective of this study is to explore the public health impact of introducing the RZV vaccine in the UK in the routine population 70 YOA.”
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen	p. 8 p. 8/p. 12	See sentence above for base-case scenario (routine population 70 YOA). “Different scenario analyses are carried out to assess the impact of first dose RZV coverage and second dose RZV compliance and to determine the optimal age for vaccination.” Base-case was chosen because representing the current routine vaccination cohort in the UK. Scenario analyses chosen to test uncertainties in coverage and potential

				differences in optimal vaccination age between RZV and ZVL as explained on page 12.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	p. 8 p. 9	UK setting where there is UMV currently in place. “The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting”
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	NA	Public health impact study, not cost-effectiveness study.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	p. 9 p. 8	Vaccination with RZV, with ZVL and no vaccination UK setting with current UMV with ZVL And a small portion of patients contraindicated to ZVL (no vaccination)
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	p. 10	“Cycle length is set to one year and a life-long time horizon is assumed.”
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	NA	Public health impact study, not cost-effectiveness study.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	p. 12	“The model was used to estimate the avoidance of HZ and PHN cases, complications, deaths, GP visits and hospitalisations cases, complications due to HZ, HZ-related deaths and number of GP visits and hospitalisations for three different vaccination strategies...”
Measurements of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study	NA	

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

		was a sufficient source of clinical effectiveness data		
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	p. 11	“Vaccine efficacy against HZ and PHN (VE_{HZ} and VE_{PHN} , respectively) were derived from the SPS trial and the Zoster Efficacy and Safety Study (ZEST) for ZVL and from the ZOE-50 and ZOE-70 trials for RZV (Table 1, SI Table 8).” And following paragraphs for efficacy/waning
Measurement of valuation based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	NA	Public health impact study, not cost-effectiveness study.
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	NA	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	P. 11	“The CPRD study was used to derive the proportion of patients being hospitalised or visiting their GP due to HZ-related complications. Hospitalisation rates were higher in the IC cohort for all age-groups. In addition, health-care resource use was higher in older adults (SI Tables 6 & 7).” No unit costs, since PHI study
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe	NA	

		methods for converting costs into a common currency base and the exchange rate		
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	p. 9	“The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting.” Reference is made to Curran et al, 2017 which shows Figure and additional details regarding model structure
Assumptions	16	Describe all structural or other assumptions underpinning the decision analytical model	p. 9 p. 12	First paragraph (Model structure) and Curran et al, 2017 Coverage and compliance assumptions: “In the base-case analysis, coverage is set at 48.3% in line with latest coverage numbers for the UK. The impact of different coverage rates was assessed in sensitivity analyses. Compliance with the second-dose of RZV was set to 70%.”
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	p. 12 p. 13	“Different scenario analyses were carried out where assumptions regarding vaccination coverage and compliance and age at vaccination were changed” And rest of paragraph Sensitivity analyses (DSA and PSA) described
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to	p. 15 SI Tables 3 – 5 and Tables 8 - 11	“In DSA analyses carried out for the base-case scenario in the age-cohort 70 YOA, the robustness of results was tested by changing input parameters to their lower and upper estimated confidence ranges (SI Tables 3 – 5;

		show the input values is strongly recommended		SI Tables 8 - 11)"
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	p. 14 Table 2	"In the base-case scenario (cohort 70 YOA) RZV reduced the number of HZ and PHN cases by 30,262 and 5,409, respectively, compared to no vaccination. ZVL led to a reduction of 7,909 HZ and 3,567 PHN cases (Error! Reference source not found.)"
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	NA	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	p. 13/14 Figure 1-3 Table 3 p. 15 Figure 4	Scenario analyses Sensitivity analyses
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	p. 14 Figure 3	Subgroup analyses according to age cohorts
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	p. 15	"In the base-case considering the current vaccination cohort of people 70 YOA, RZV reduced the number of HZ and PHN cases by 30,262 and 5,409 compared to no vaccination..." and subsequent paragraphs

			p. 18	“As with every model, there are strengths and limitations associated with the modelling strategy employed....”
			p. 17/18	Comparison to existing PHI and CE studies.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	p. 20	Funding
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	p. 20	Conflict of interest