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

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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

substantially over time conferring no protection against HZ beyond 8 years after vaccination.[17 18]

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

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

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 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 2012[28] (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 study[3] (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 literature[31] (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 countries [32] 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 literature[29] (**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-

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.

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 2016/2017[33] 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 lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of the clinical trial second-dose compliance.[25]

Finally, the impact of changing the vaccination age on health outcomes was

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

SENSITIVITY ANALYSES

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

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

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 (

Table 2). Vaccination with RZV reduced the number of HZ-related complications and the health-resource use (

Table 2). There were few HZ-related deaths; compared to no vaccination, RZV prevented 8 HZ-related deaths while ZVL prevented none. The NNV to prevent one case of HZ was 12 with RZV and 45 with ZVL. The NNV to avoid one case of PHN was 65 with RZV and 98 with ZVL, respectively.

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 HZ and PHN cases avoided, resource utilisation and NNV 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**Error! Reference source not found.**). 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.[35 36] 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 RZV, 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 HZ. 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 strategy.

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

The recommended vaccination strategy was based on the clinical profile of ZVL, the only vaccine available at the time. In its recommendation, the JCVI noted that ZVL VE decreases with increasing age and over time; hence, the current age cohort eligible for vaccination, i.e., individuals 70 YOA, is a compromise to optimise limited efficacy and duration of protection against HZ. The JCVI also stated that optimal age at vaccination would depend on the characteristics of any given vaccine.[37] Therefore,

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

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

The potential public health impact of RZV in the UK setting has previously been studied by our group.[38] The study showed a substantial reduction in HZ and PHN cases compared to no vaccination; however, no comparison was made to ZVL. A number of studies have evaluated the impact of ZVL on disease burden and associated cost-effectiveness in the UK setting. Van Hoek et al. analysed cost-effectiveness of ZVL in different age-groups with the base-case considering a cohort of immunocompetent 65-year-old individuals in the UK. This cohort was modelled

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

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

As with every model, there are strengths and limitations associated with the modelling strategy employed. For RZV, most recent UK-specific data available at the time we conducted this study were used; for HZ incidence the CPRD database, a large UK-specific database, was analysed and values for both IC and non-IC cohorts were combined.[28] For PHN incidence, published data from two reports were used to estimate the PHN probability in the total population including individuals with immunodeficient states. The estimates of PHN cases prevented are close to real values, validating our approach. Demographic data projected to the year 2018 were used based on numbers reported by the ONS.[27] The limitations in this study are related to assumptions that had to be made in the absence of real-world data, including coverage with RZV, compliance and long-term waning for RZV. Coverage and compliance were set to values observed in comparable vaccination programs and these parameters were varied in scenario and one-way sensitivity analyses. Results from long-term studies with RZV are still outstanding and follow-up data is currently limited to 4 years. However, the model has been developed such that it can be updated once additional data becomes available. For ZVL waning rates, we included both data from the SPS and the LTPS study [25]; however, data from a recent observational study evaluating effectiveness of ZVL in the UK were not included as

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

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

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

CONCLUSION

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

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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.

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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

	NNV HZ		NNV PHN	
Age cohort	**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

Figure 1 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

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

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

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

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

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

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

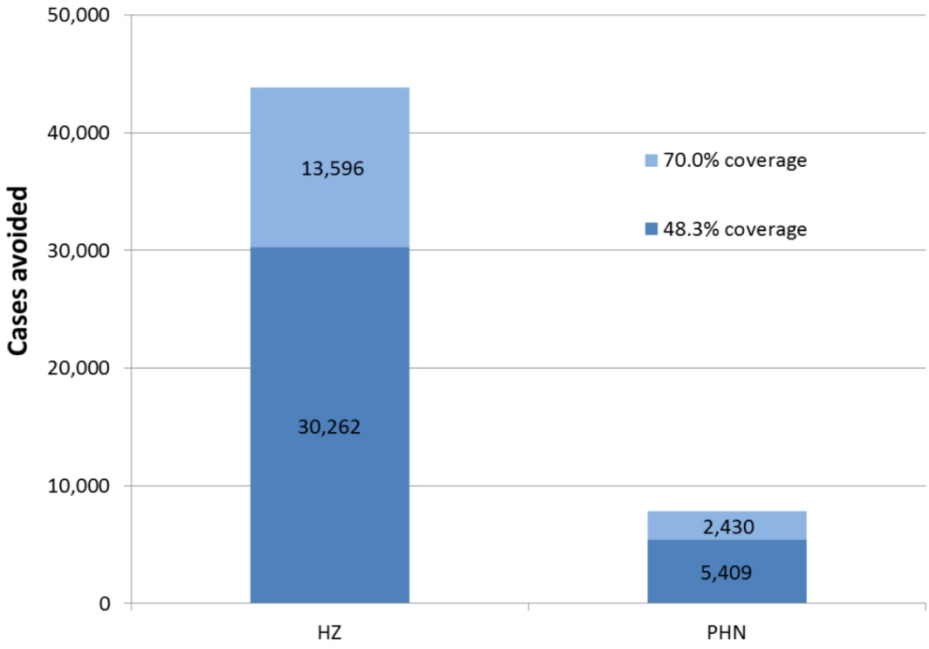
HZ: herpes zoster; RZV: adjuvanted recombinant zoster vaccine; YOA: years of age; ZVL: zoster vaccine live

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

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

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

Figure 6 Lay language summary of the study



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

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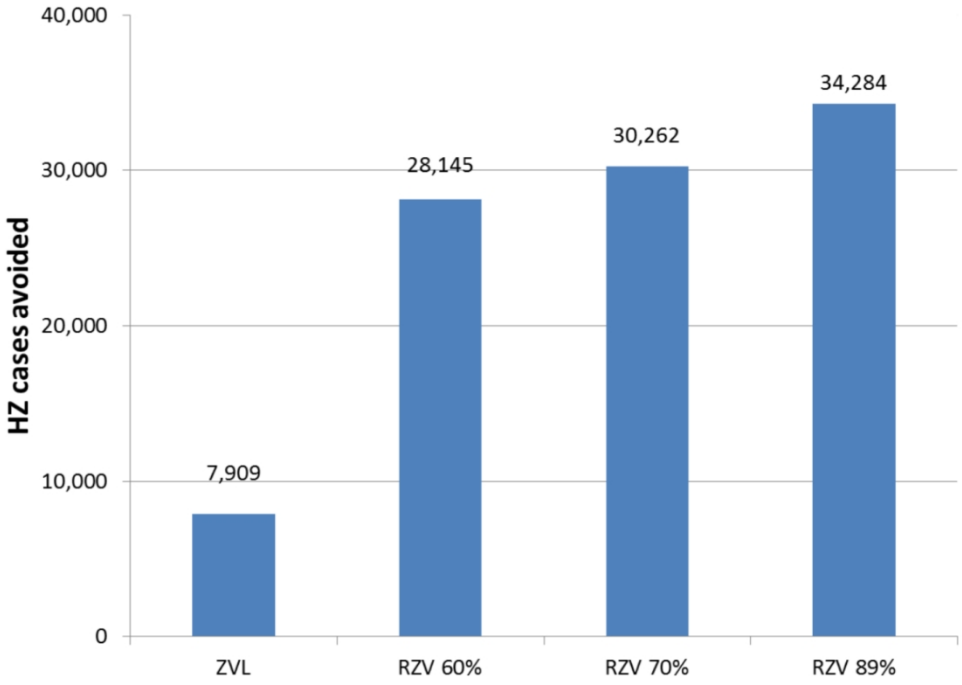

Impact of second-dose RZV compliance on HZ incidence

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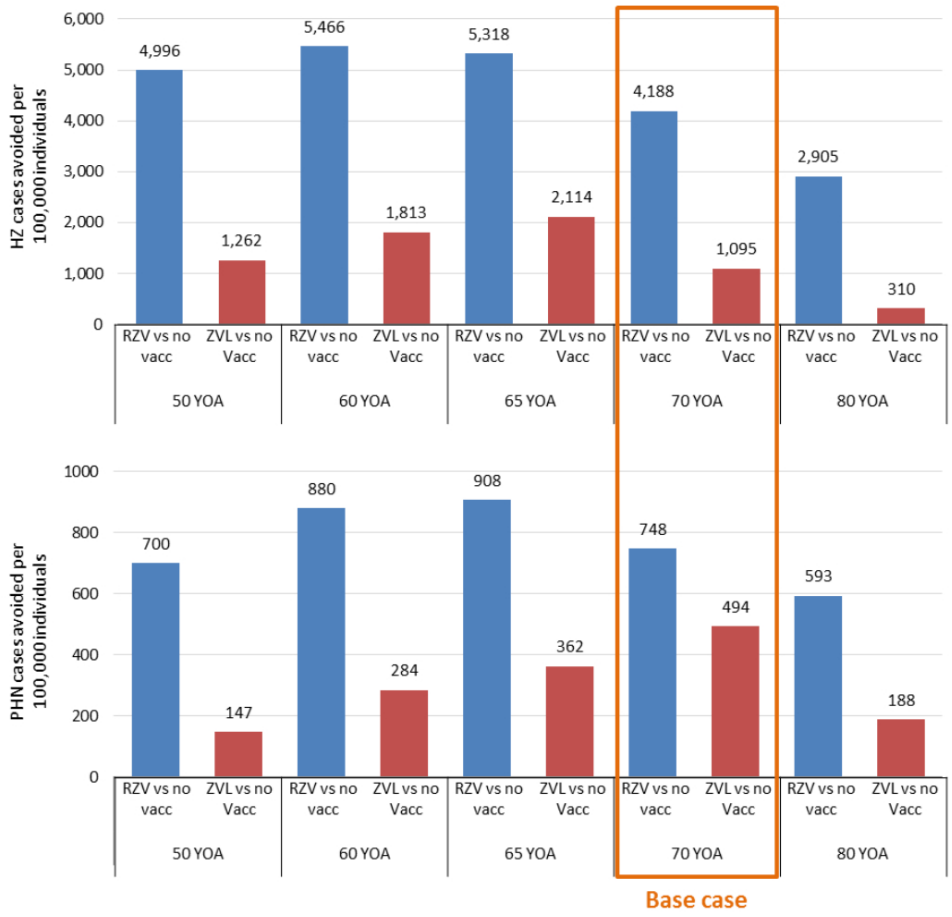

Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

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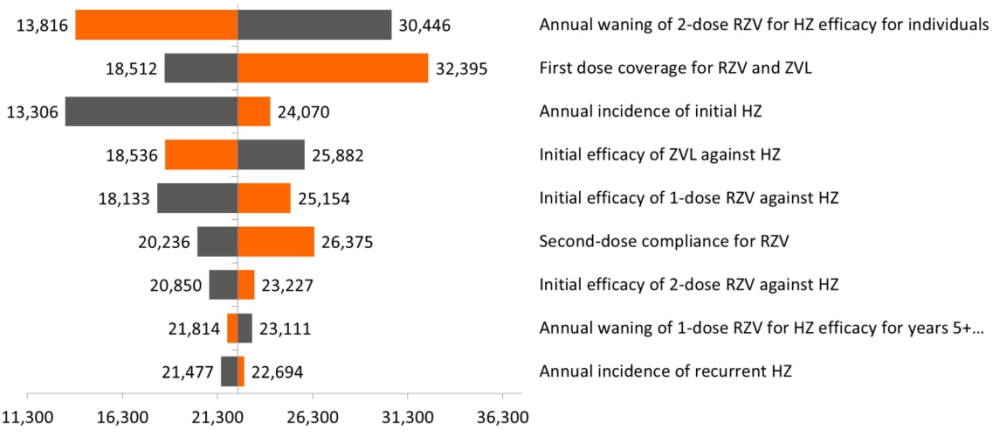

Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

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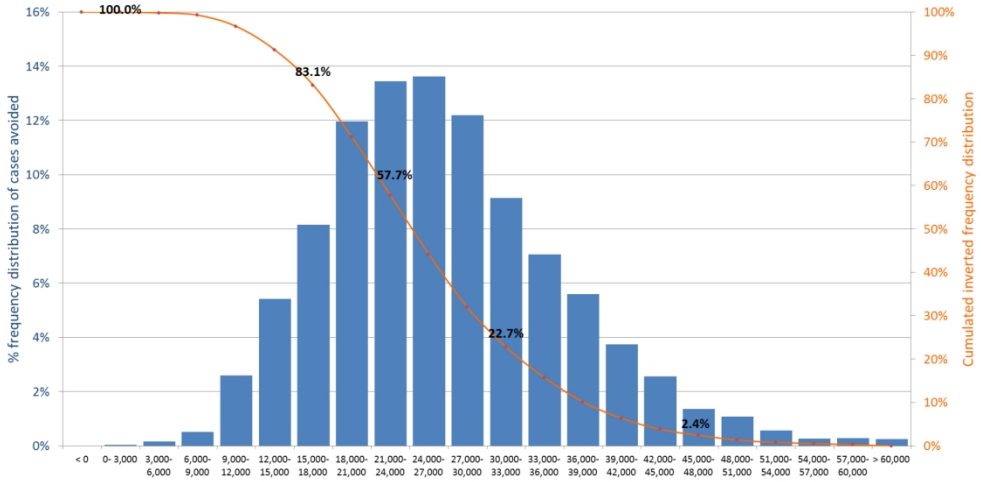

Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

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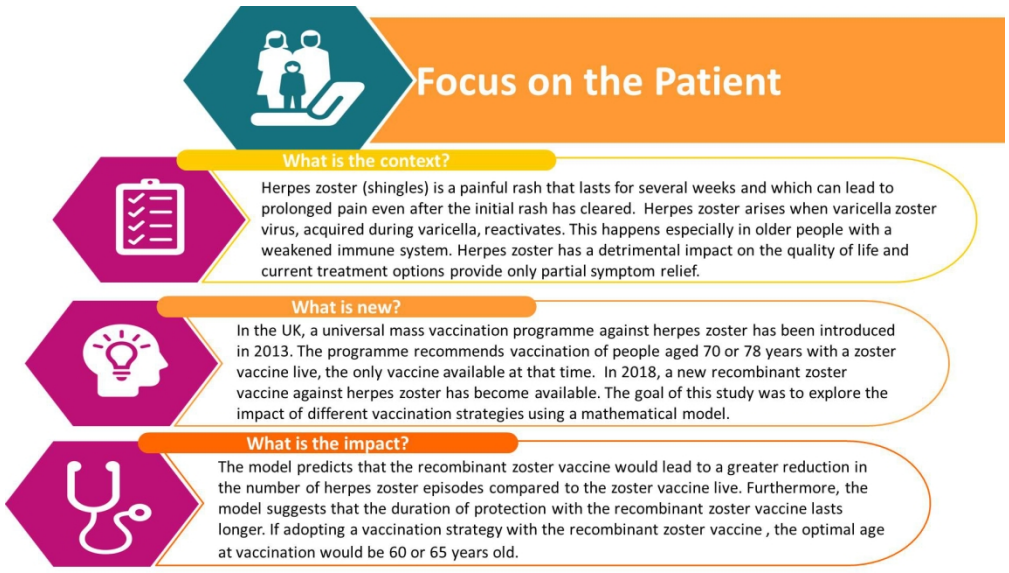

Lay language summary of the study

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	ALL	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

	ZVL			RZV – 2-dose			RZV – 1-dose		
Age (YOA)	**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

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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

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 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

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

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

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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]

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

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

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 2012[28] (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 study[3] (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 literature[32] (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 countries [33] 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 literature[29] (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:

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

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 2016/2017[34] 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 lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of the clinical trial second-dose compliance.[25]

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

SENSITIVITY ANALYSES

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

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

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

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 RZV, 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 HZ. 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

strategy.

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

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

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

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

The potential public health impact of RZV in the UK setting has previously been studied by our group.[39] The study showed a substantial reduction in HZ and PHN cases compared to no vaccination; however, no comparison was made to ZVL. A number of studies have evaluated the impact of ZVL on disease burden and associated cost-effectiveness in the UK setting. Van Hoek et al. analysed cost-effectiveness of ZVL in different age-groups with the base-case considering a cohort of immunocompetent

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

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

As with every model, there are strengths and limitations associated with the modelling strategy employed. For RZV, most recent UK-specific data available at the time we conducted this study were used; for HZ incidence the CPRD database, a large UK-specific database, was analysed and values for both IC and non-IC cohorts were combined.[28 43] For PHN incidence, published data from two reports were used to estimate the PHN probability in the total population including individuals with immunodeficient states. The estimates of PHN cases prevented are close to real values, validating our approach. Demographic data projected to the year 2018 were used based on numbers reported by the ONS.[27] The limitations in this study are related to assumptions that had to be made in the absence of real-world data, including coverage with RZV, compliance and long-term waning for RZV. Coverage and compliance were set to values observed in comparable vaccination programs and these parameters were varied in scenario and one-way sensitivity analyses. Results from long-term studies with RZV are still outstanding and follow-up data is currently limited to 4 years. However, the model has been developed such that it can be updated once additional data becomes available. For ZVL waning rates, we included both data from the SPS and the LTPS study [25] to ensure that we could compare ZVL and RZV in the ZONA model. Recent observational studies looking into the vaccine

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

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

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

CONCLUSION

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

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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

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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

	NNV HZ		NNV PHN	
Age cohort	**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

Figure 1 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

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

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

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

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

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

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

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

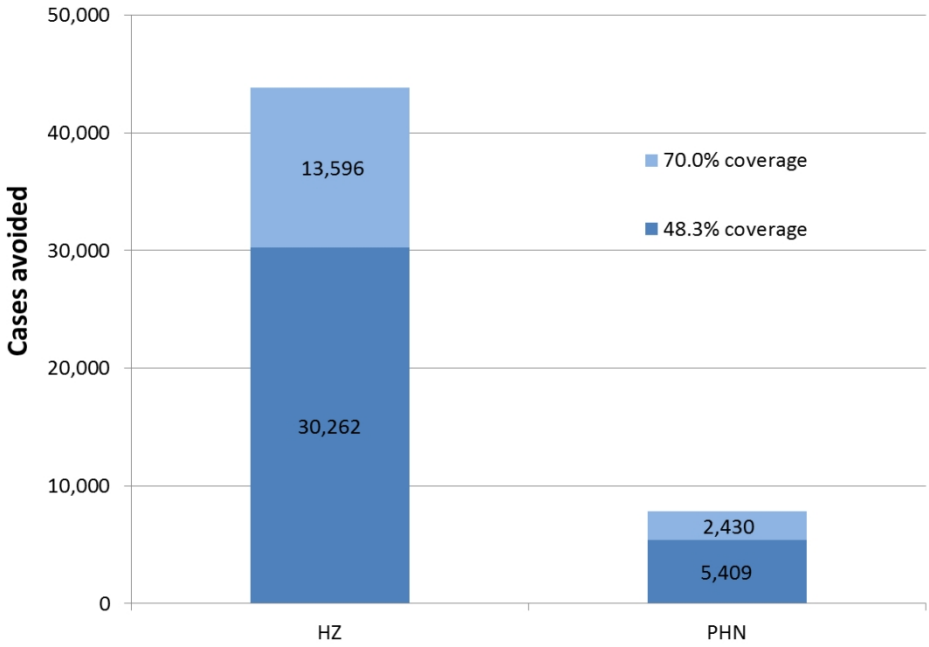
Lower values are in orange and upper values are in grey

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

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

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

Figure 6 Lay language summary of the study



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

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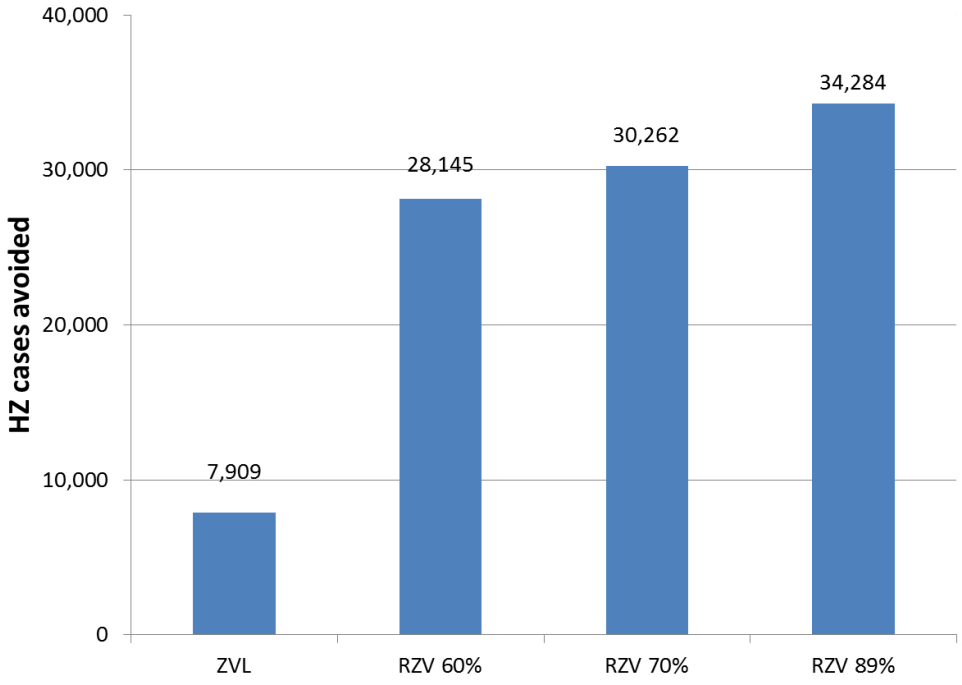

Impact of second-dose RZV compliance on HZ incidence

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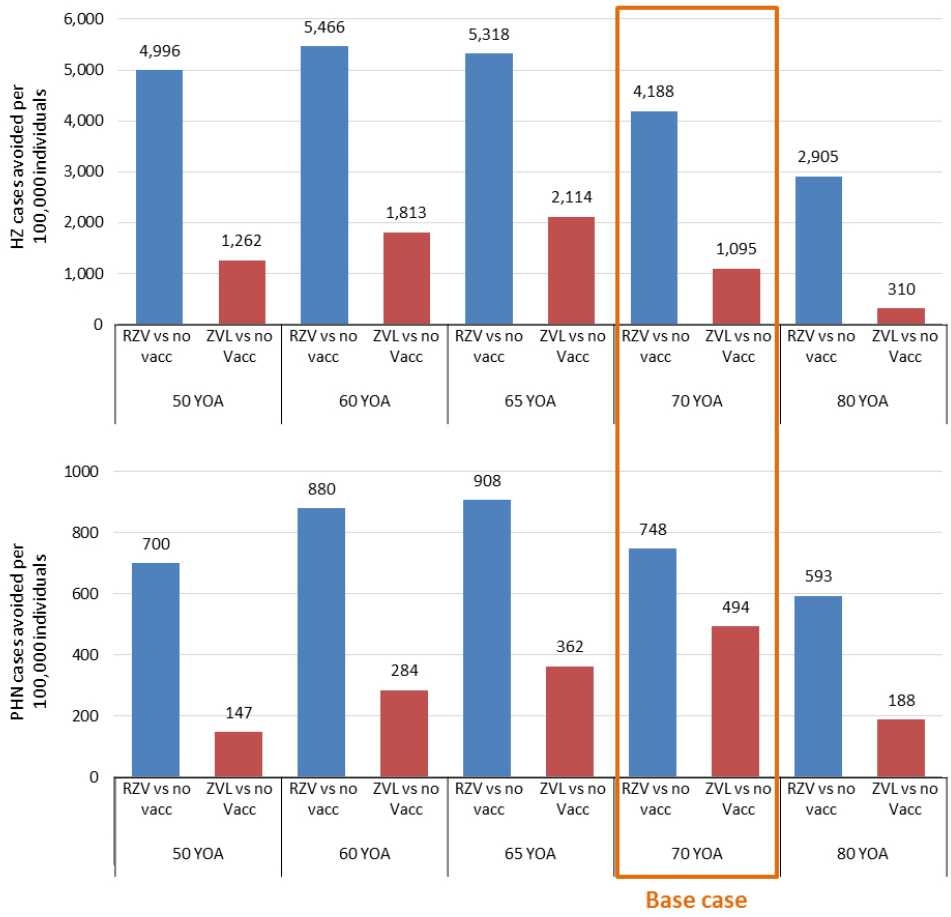

Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

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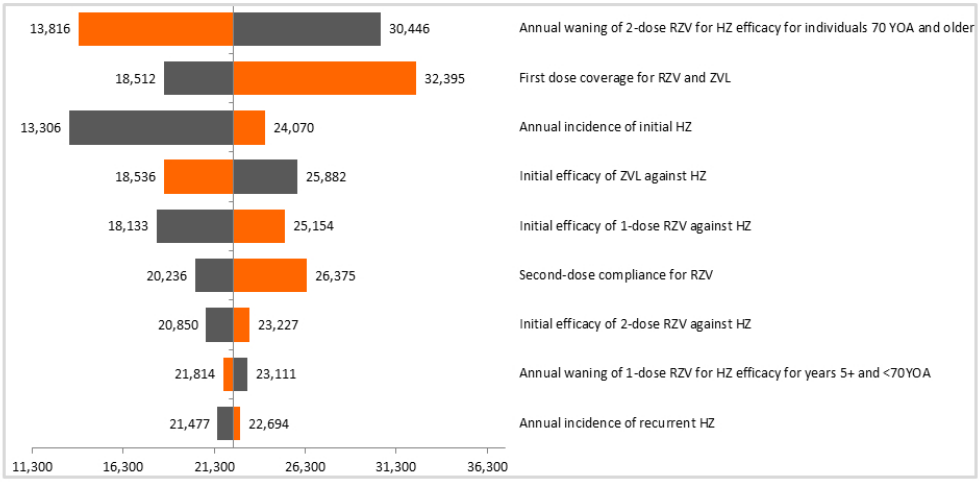

Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

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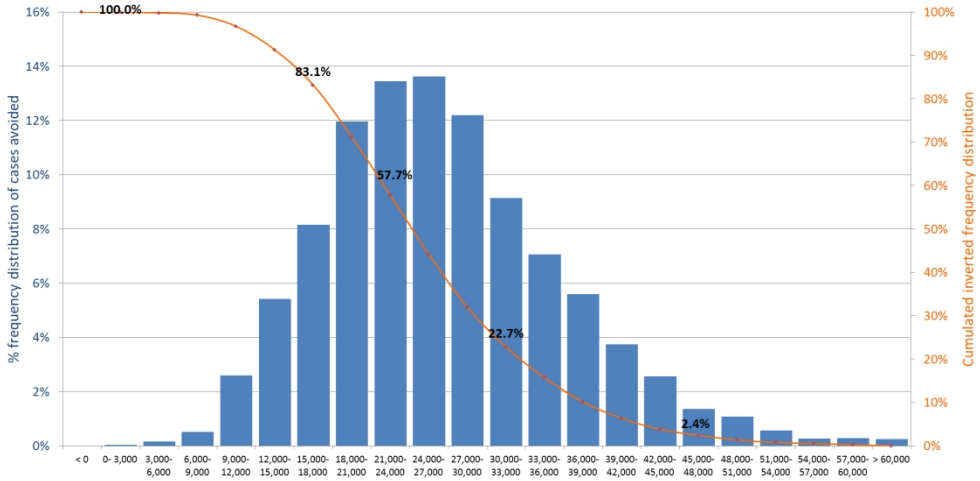

Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

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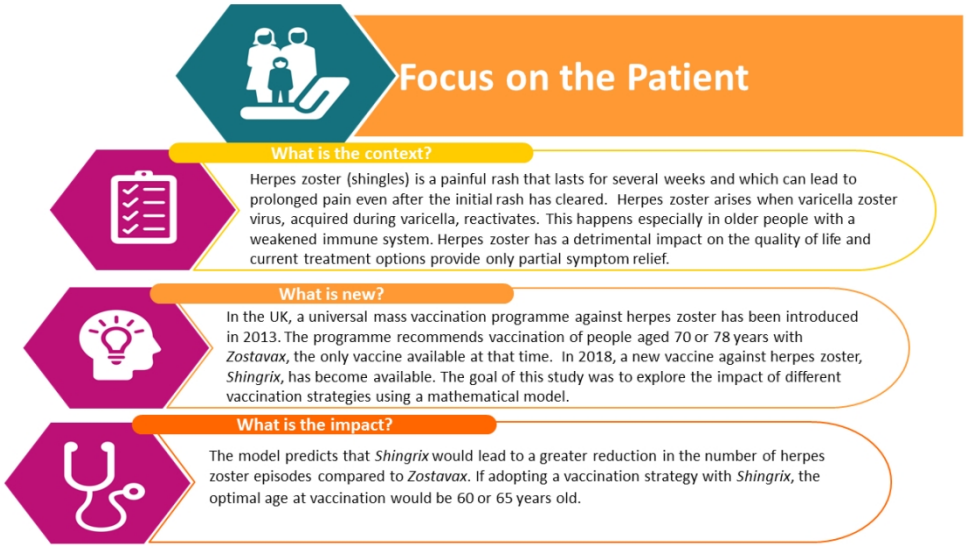

Lay language summary of the study

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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	ALL	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

	ZVL			RZV – 2-dose			RZV – 1-dose		
Age (YOA)	**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

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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

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 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

BMJ Open

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

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

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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]

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

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

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 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 2012[28] (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 study[3] (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 literature[32] (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 countries [33] 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 literature[29] (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:

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

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 2016/2017[34] 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

lower limit of 60% and an upper limit of 89% reflecting the lowest 10th percentile of the clinical trial second-dose compliance.[25]

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

SENSITIVITY ANALYSES

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

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

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 (Table 2). Vaccination with RZV reduced the number of HZ-related complications and the health-resource use (Table 2). There were few HZ-related deaths; compared to no vaccination, RZV prevented 8 HZ-related

deaths while ZVL prevented none. The NNV to prevent one case of HZ was 12 with RZV and 45 with ZVL. The NNV to avoid one case of PHN was 65 with RZV and 98 with ZVL, respectively.

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 RZV, 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 HZ. 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 strategy.

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

The recommended vaccination strategy was based on the clinical profile of ZVL, the

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

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

The potential public health impact of RZV in the UK setting has previously been studied by our group.[39] The study showed a substantial reduction in HZ and PHN cases compared to no vaccination; however, no comparison was made to ZVL. A number of

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

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

As with every model, there are strengths and limitations associated with the modelling strategy employed. For RZV, most recent UK-specific data available at the time we conducted this study were used; for HZ incidence the CPRD database, a large UK-specific database, was analysed and values for both IC and non-IC cohorts were combined.[28 43] For PHN incidence, published data from two reports were used to estimate the PHN probability in the total population including individuals with immunodeficient states. The estimates of PHN cases prevented are close to real values, validating our approach. Demographic data projected to the year 2018 were used based on numbers reported by the ONS.[27] The limitations in this study are related to assumptions that had to be made in the absence of real-world data, including coverage with RZV, compliance and long-term waning for RZV. Coverage and compliance were set to values observed in comparable vaccination programs and these parameters were varied in scenario and one-way sensitivity analyses. Results from long-term studies with RZV are still outstanding and follow-up data is currently limited to 4 years. However, the model has been developed such that it can be

updated once additional data becomes available. For ZVL waning rates, we included both data from the SPS and the LTPS study [25] to ensure that we could compare ZVL and RZV in the ZONA model. Recent observational studies looking into the vaccine effectiveness of ZVL show that the vaccine wanes rapidly and has little to no protection left beyond year 8 after vaccination.[18] [37] Finally, the rate of HZ-associated complications was assumed to be the same in all individuals with HZ regardless of their vaccination status. This assumption ignores the potential benefit vaccination might have by lowering the severity and duration of break-through HZ cases. Clinical trial data suggest that VE_{HZ} and VE_{PHN} are similar and there is some evidence that duration and severity of HZ/PHN pain is lower in individuals having received RZV as compared to unvaccinated individuals.[44]

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

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

CONCLUSION

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

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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

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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

	NNV HZ		NNV PHN	
Age cohort	**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%.

Figure 1 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

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

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

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

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

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

HZ: herpes zoster; no vac: no vaccination; PHN: postherpetic neuralgia; 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%

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

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

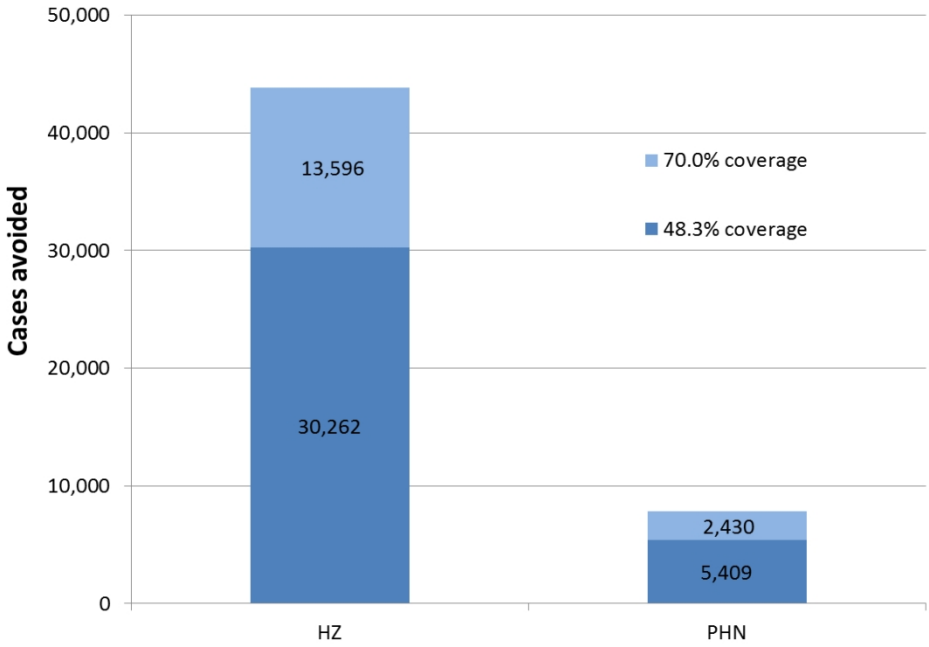
Lower values are in orange and upper values are in grey.

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

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

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

Figure 6 Lay language summary of the study



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

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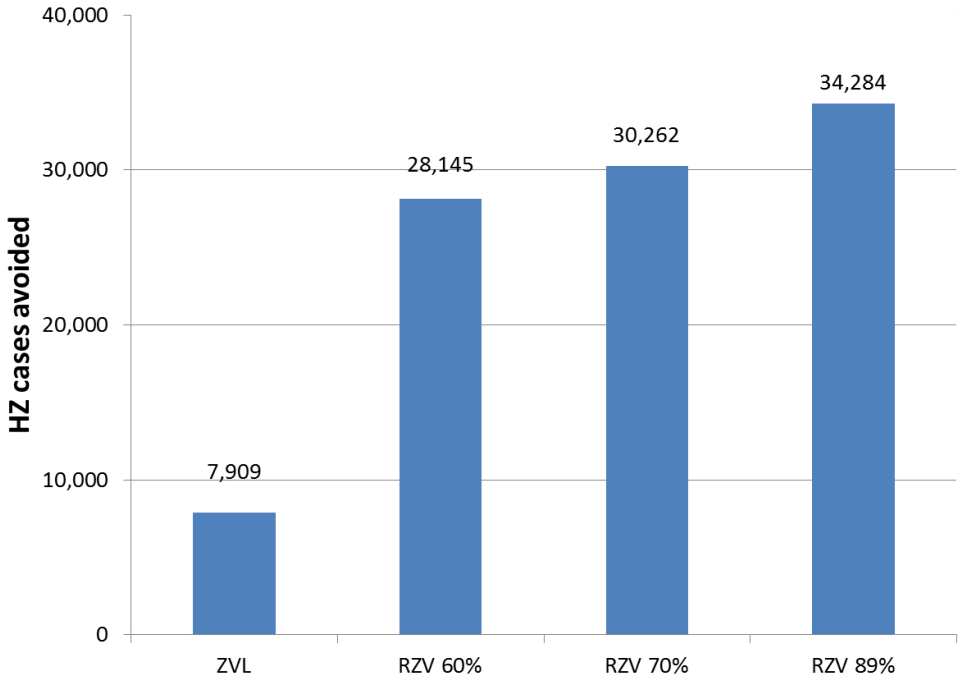

Impact of second-dose RZV compliance on HZ incidence

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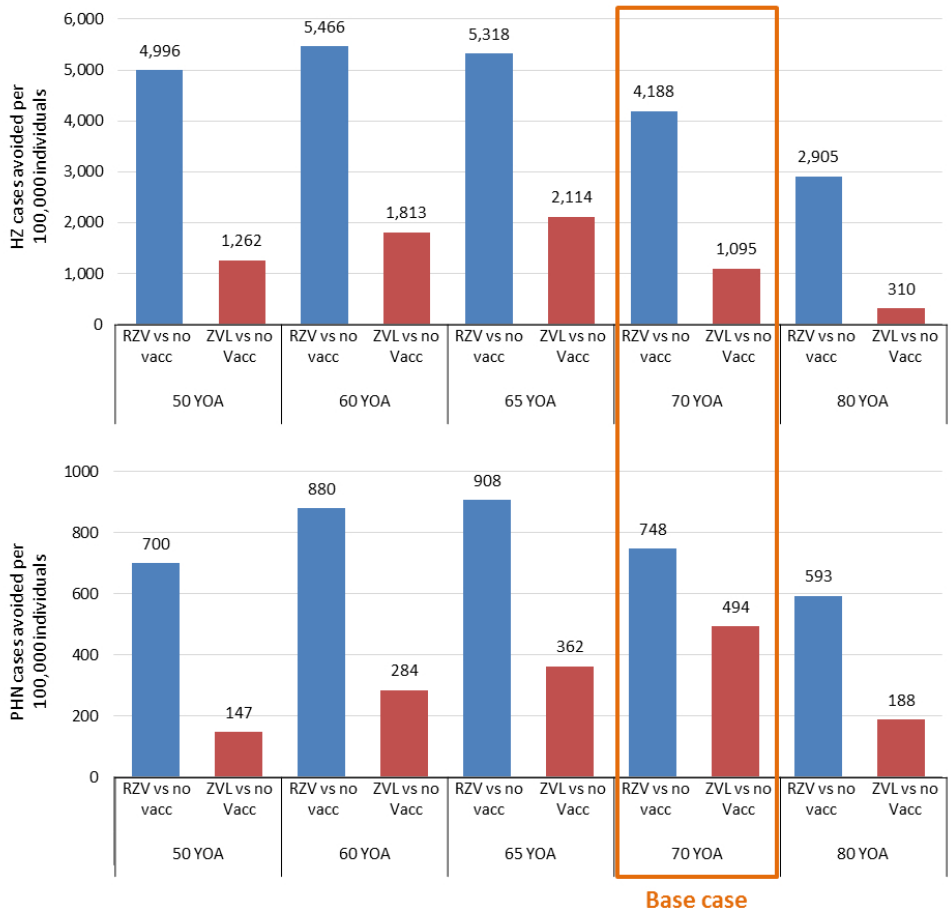

Scenario analyses: HZ (top) and PHN (down) cases avoided per 100,000 individuals for different vaccination cohorts.

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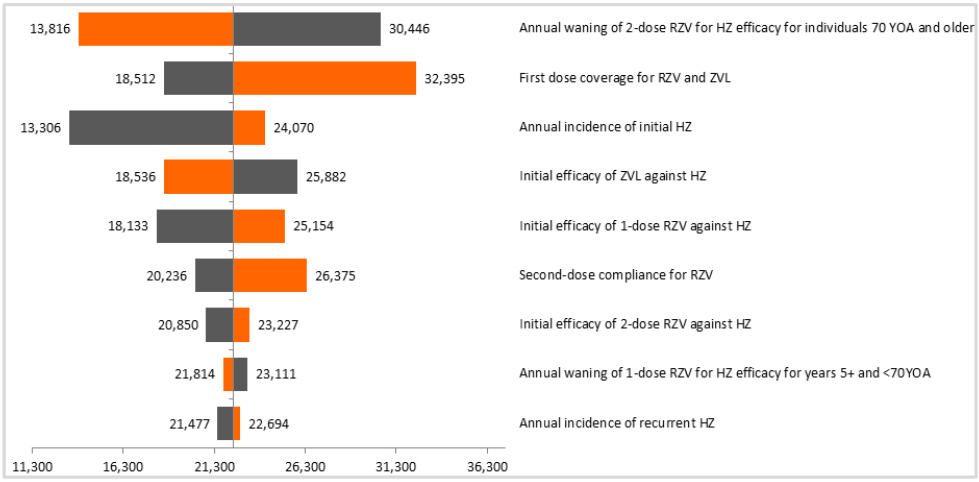

Tornado Diagram: HZ cases avoided with RZV compared with ZVL – Base-case analysis (70 YOA; coverage 48.3%; compliance 70%)

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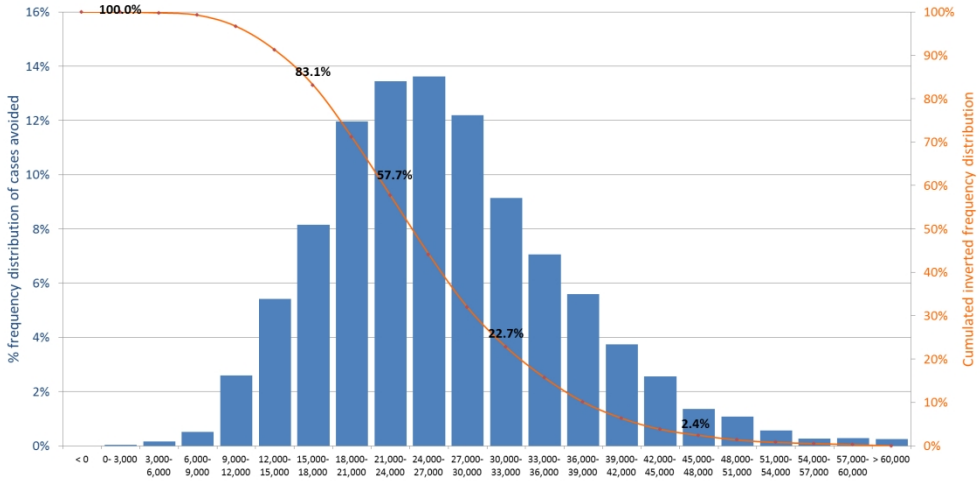

Probabilistic Sensitivity Analysis: HZ cases avoided with RZV compared to ZVL

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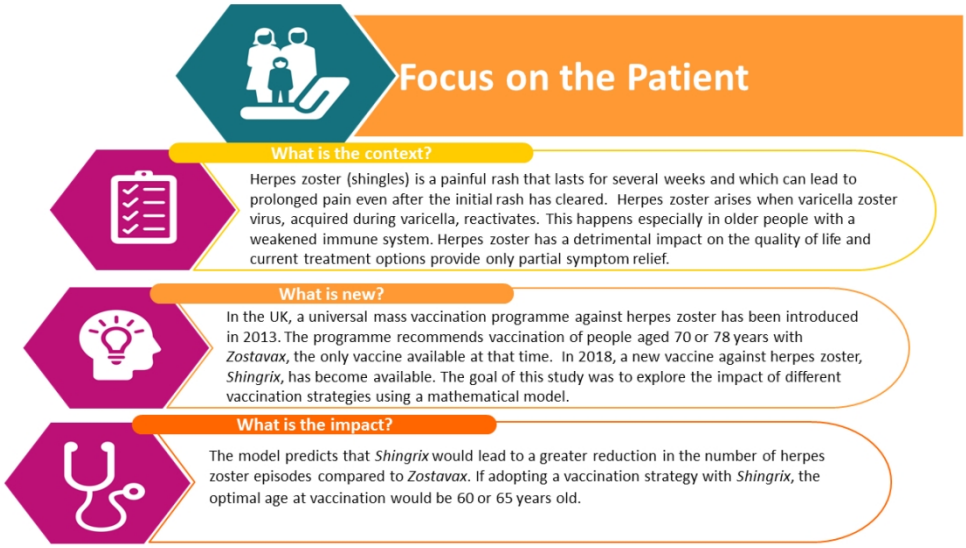


Lay language summary of the study

108x60mm (300 x 300 DPI)

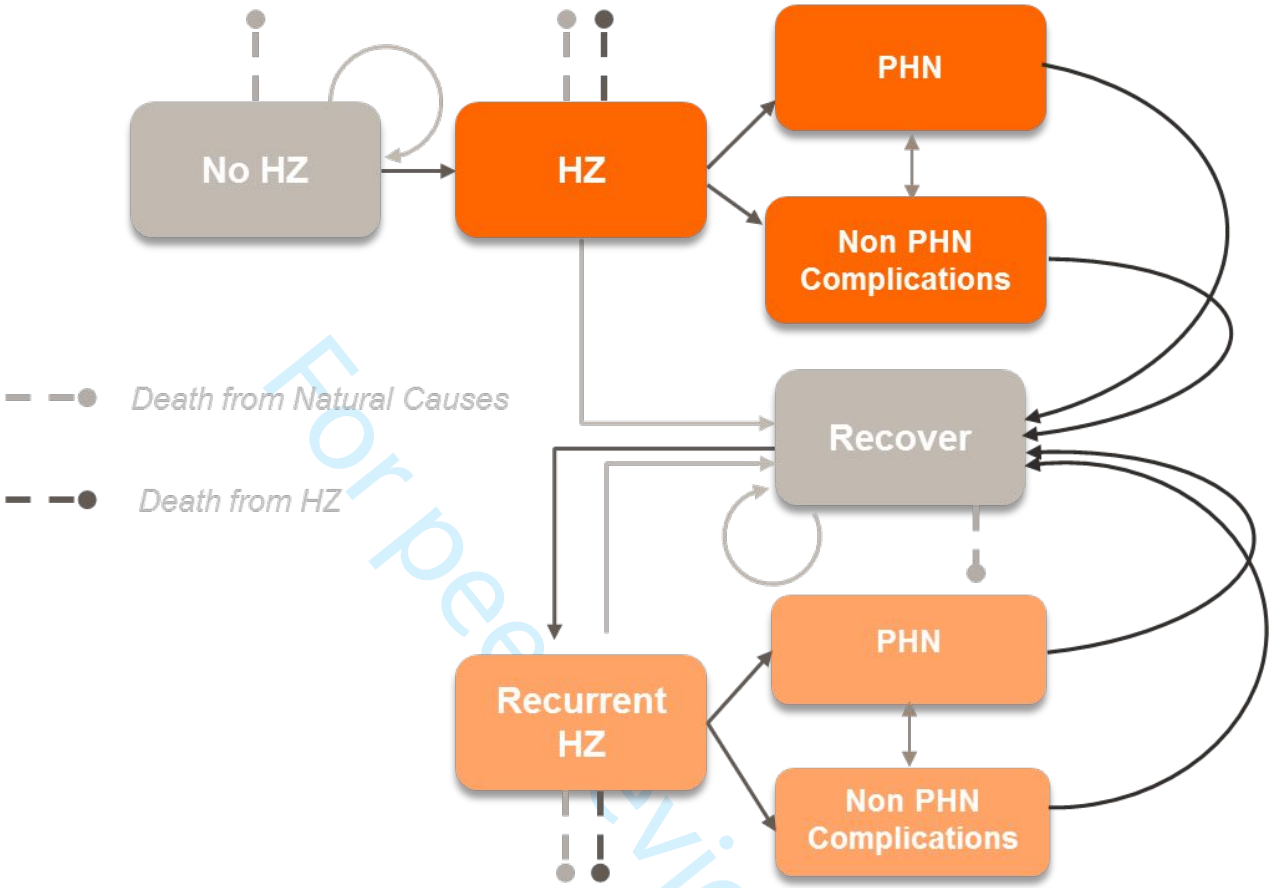
Supplementary Material

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 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	ALL	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

	ZVL			RZV – 2-dose			RZV – 1-dose		
Age (YOA)	**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

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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

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 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