Epidemiological impact and cost-effectiveness of varicella vaccination strategies in the United Kingdom (UK)

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Summary
A 2-dose universal varicella vaccination was demonstrated to be a cost-effective alternative to no vaccination. With comparable effectiveness as MSD varicella-containing vaccines (VCVs) at lower costs, GSK VCV may offer higher value for money.
Abstract

Background

Despite the burden of varicella, there is no universal varicella vaccination (UVV) programme in the United Kingdom (UK) due to concerns this could increase herpes zoster (HZ) incidence. This study assessed the cost-utility of a first-dose monovalent (V) or quadrivalent (MMRV) followed by a second-dose quadrivalent (MMRV) UVV programmes. GSK and MSD varicella-containing vaccines (VCVs) were considered.

Methods

A dynamic transmission and cost-effectiveness models were adapted to the UK. Outcomes measured included varicella and HZ incidences, the incremental cost-utility ratio (ICURs) over a lifetime horizon. The payer and societal perspectives were evaluated.

Results

The impact of V-MMRV and MMRV-MMRV UVV programmes on varicella incidence was comparable between both VCVs at equilibrium. HZ incidence increased by 1.6%-1.7% over seven years after UVV start, regardless of the strategies, then decreased by >95% at equilibrium. ICURs ranged from £5,665 (100 years) to £18,513 (20 years) per quality-adjusted life year (QALY) gained with V-MMRV; and from £9,220 to £27,101 per QALY gained with MMRV-MMRV (payer perspective). MMRV-MMRV was cost-effective in medium- and long-terms with GSK VCV, and only cost-effective at long-term with MSD VCV.
at £20,000 per QALY gained threshold. Without the exogenous boosting hypothesis, HZ incidence decreased through UVV implementation. ICURs were most sensitive to discount rates and MMRV price.

Conclusions

A 2-dose UVV was demonstrated to be a cost-effective alternative to no vaccination. With comparable effectiveness as MSD VCV at lower costs, GSK VCV may offer higher value for money.

Keywords: Cost-utility; vaccination strategies; varicella; United Kingdom
Introduction

Varicella (chickenpox) is a preventable disease predominant in childhood that is caused by the varicella-zoster virus (VZV). After a primary infection, VZV remains dormant in the dorsal root ganglion, and can reactivate at older ages, causing herpes zoster (HZ) with post-herpetic neuralgia as a possible complication. Usually, varicella incidence is highest in children less than 5 years old with a high primary care, hospitalisation and mortality burden [1-3]. Annual hospitalisation costs were recently estimated to be ≈ £7 million and indirect costs associated with parental off-work time indicated to contribute considerably to the economic impact of varicella [3, 4].

Live-attenuated varicella vaccines have a clinically acceptable profile and are effective in reducing varicella burden. Two monovalent varicella (V) vaccines are commonly used: the Oka-recombinant immunotoxin Varilrix (GSK, Belgium) and the Oka/Merck Varivax [MSD, United States of America (USA)]. Other varicella-containing vaccines (VCVs) formulations include quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines Priorix-Tetra (GSK, Belgium) and ProQuad (MSD, USA).

Both Varilrix and Varivax are licensed in the United Kingdom (UK). However, varicella vaccination is limited to specific high-risk groups (non-immune healthcare workers, close contacts of immunosuppressed individuals) [5]. In 2010, the Joint Committee on Vaccination and Immunisation (JCVI) did not recommend implementation of a 2-dose childhood universal varicella vaccination (UVV) [6]. This decision was notably driven by the model-predicted increase in HZ incidence in the first 30-50 years following UVV, which would make the programme cost-ineffective [7]. Brisson et al. also reported an increase in HZ incidence following 1-dose UVV, which would offset the benefits associated with vaccination [8]. The theoretical assumption behind these models is that UVV reduces circulating VZV, thereby limiting re-exposure to exogenous virus from varicella-infected individuals. Consequently, cell-mediated immunity (CMI) is not boosted and maintained above a threshold, which would increase the risk of HZ [9, 10]. Real world data have not confirmed these model predictions [11]. An increase in HZ incidence over the past decade was reported in countries without UVV, including the UK [12]. Unlike van Hoek et al. and Brisson et al., Poletti et al.
predicted a continuous decrease in HZ incidence in line with the progress of a 2-dose UVV in the UK [7, 13, 14]. They concluded that HZ incidence following UVV appeared to depend on the presence or absence of factors promoting a strong boosting intensity that may (or may not) be heavily affected by changes in varicella circulation due to UVV.

The question of UVV implementation in the UK is becoming increasingly important with Ogunjimi et al.’s immunological study demonstrating the limited protective effect of re-exposure to varicella, with boosting occurring in only 17-25% of grandparents who were exposed to varicella and lasting less than one year. Ethical concerns have also been raised regarding withholding the beneficial impact on mortality and morbidity of varicella vaccination in children, to protect adults from HZ, especially with the recent licensure of a highly efficacious recombinant HZ subunit vaccine [11, 15].

The implementation of a 2-dose UVV programme in the UK raises key questions about the age (12 or 13 months) at first dose vaccination -and implicitly the use of a monovalent or a quadrivalent varicella vaccine as first dose- given the crowded vaccination schedule at 12 months. Therefore, a dynamic transmission model was first used to evaluate the impact of UVV on varicella epidemiology. Cost-benefit and cost-utility analyses were performed to assess whether UVV could be recommended for implementation in the UK. Vaccination strategies using GSK or MSD VCV were compared to evaluate their impact on the epidemiology and economic burden of varicella.

Methods

Vaccination strategies

In this report, a hyphen indicates separation of the first dose from the second dose vaccine. Given the crowded vaccination schedule at 12 months of age (moa), the following strategies were considered:

1. **V-MMRV**: first dose monovalent at 13 moa (at 87% coverage) – based on the proportion of children who received first and second dose of MMR by their fifth birthday [16]. MMRV is assumed to replace the second dose MMR given at 3 years and 4 months at equivalent coverage. It is further hypothesized that a stand-alone varicella vaccine at 13 months would result in a lower coverage than
a scenario that uses the first dose MMR vaccination platform. Consequently, the coverage of the first and second doses were conservatively assumed to be similar.

2. **MMRV-MMRV**: first and second dose quadrivalent varicella vaccines. With this scenario, it is assumed that MMRV will replace MMR vaccines at equivalent coverages; with first- and second-dose ages of 12 months age (at 95% coverage), and 3 years and 4 months (at 87% coverage) respectively.

In additional scenario analysis, the exogenous boosting assumption was excluded from the **MMRV-MMRV** scenario; defining the **MMRV-MMRV (no boosting)** scenario. Vaccination strategies were compared to no varicella vaccination.

**Models**

The description of the dynamic and cost-utility models and associated inputs are provided in Table 1, Appendix Tables 1-3, and Appendix Figure 1. A stationary population was assumed (Appendix Figure 2) and the basic reproduction number computed by the next generation matrix method (Appendix Table 4). Economic model outcomes included the incremental cost utility ratio (ICUR) and the net monetary benefit (NMB). A willingness-to-pay (WTP) threshold of £20,000 per quality-adjusted life years (QALY) gained was considered, and results reported at 20-, 40- and 100-year post-UVV.

**Vaccine parameters**

Primary vaccine failure after one dose of varicella vaccine was based on similar seroconversion rates between GSK and MSD monovalent varicella vaccines [17-19].

With respect to vaccine efficacy, estimates of 67.2% and 95.4% after the first and the second dose were considered for GSK VCV, respectively [20]. Similarly, Kuter et al. reported values of 94.4% and 98.3% after the first and the second dose for MSD VCV, respectively [21]. However, vaccinees were 1 to 12 years old, which contrasts with the average age at vaccination of 14 months in GSK studies [20]. Chan et al. indicated a lower risk of VZV infection as age increases and calculated an efficacy of 78.0% in 1-dose Varivax
recipients aged 18 months old [22]. Consequently, MSD VCV first and second dose efficacies of 78.0% and 98.3% were considered. Sensitivity analyses on vaccine parameters were conducted (Appendix Tables 5-7).

Price information was not available for MMRV vaccines as currently not marketed in the UK. GSK and MSD MMRV prices of £56.4 and £62.6 per dose were assumed, respectively (see Appendix for details). Monovalent prices were £27.3 and £30.3 per dose for GSK and MSD VCVs, respectively [23].

Febrile seizure is a common adverse event of measles-containing vaccines. Based on Ma et al., we performed a random effects meta-analysis on the risk of febrile seizure associated with first-dose MMRV, considering a follow-up period of 42 days post-vaccination and excluding co-administration with other vaccines [24]. A first-dose pooled risk of 2.4‰ (95% CI: 1.2‰ – 3.6‰) and 2.7‰ (95% CI: 1.2‰ – 4.2‰) was estimated for GSK and MSD MMRV vaccines, respectively. GSK and MSD VCV associated injection site adverse events were 19.5% (95% CI: 14.2% – 25.7%) and 21.7% (95% CI: 16.2% – 28.0%), respectively [25].

**Results**

**Impact on varicella incidence**

Within five years following UVV implementation, the incidence of WT varicella was reduced by half – GSK VCV: from 12,565 to 5,944 and 5,900 per million with V-MMRV and MMRV-MMRV respectively; respective values for MSD VCV: from 12,565 to 5,884 and 5,862 per million. At equilibrium, the total (i.e. WT and BKT) incidence of varicella was reduced by 95.6% under MMRV-MMRV and by 91.0% under V-MMRV with GSK VCV (Figure 1A). Similarly, with MSD VCV, the total incidence of varicella was reduced by 96.9% and 93.8% under MMRV-MMRV and V-MMRV, respectively (Figure 1B). BKT varicella contributed to 46.2% and 69.2% of the total varicella incidence with GSK VCV compared to 38.0% and 63.7% with MSD VCV in V-MMRV and MMRV-MMRV, respectively.

**Impact on herpes zoster incidence**

The estimated pre-vaccination incidence of HZ was 7,469 per million. At equilibrium, the total incidence of HZ was reduced by 98.2% and 95.1% under MMRV-MMRV and V-MMRV with GSK VCV, respectively (Figure 1C). Similarly, the total incidence of HZ, using MSD VCV, decreased by 98.5% and 96.1% under MMRV-
MMRV and V-MMRV, respectively (Figure 1D). HZ in vaccinees represented 9.8% and 20.5% of all HZ cases in V-MMRV and MMRV-MMRV with GSK VCV. Comparatively, 7.0% and 16.2% of all HZ cases were predicted to occur in MSD VCV recipients under V-MMRV and MMRV-MMRV. With respect to the early effect of UVV on HZ, a maximum increase of 1.6% in the total incidence of HZ was predicted four and three years after UVV start with V-MMRV and MMRV-MMRV strategies using GSK VCV, respectively. Similarly, a maximum increase of 1.6% and 1.7% in HZ incidence were predicted with V-MMRV and MMRV-MMRV, four and three years after UVV start using MSD VCV, respectively. Overall, HZ incidence returned to levels below the pre-vaccination era as of the eighth year following UVV start.

Impact on the age at varicella and herpes zoster infection

Acknowledging a reduction in varicella cases in all ages following UVV, Figure 2A-B show that 42.2% (respectively 45.2%) of varicella cases are predicted to occur among individuals older than 14 years old at equilibrium compared to 9.0% in the same age group in the pre-vaccination era with GSK (respectively MSD) VCV under V-MMRV. Similarly, under MMRV-MMRV, 40.2% (respectively 43.2%) of varicella cases are predicted in those aged >14 years with GSK (respectively MSD) VCV at equilibrium (Figure 2C-D). Appendix Figure 3 shows that the age distribution of HZ cases at equilibrium was almost comparable to that of the pre-vaccination era and at peak.

Additional scenario analysis on vaccination

Figure 3 shows that the MMRV-MMRV (no boosting) scenario differed from MMRV-MMRV in predicting a continuous decrease in HZ incidence following UVV implementation. Additional analyses indicated that 1-dose UVV and targeted adolescent strategies were less effective in reducing varicella and HZ incidence compared to a 2-dose UVV, with the latter being the worst (e.g. varicella incidence reduction of 55.3% (respectively 62.2%) and 5.2% (respectively 5.9%) with GSK (respectively MSD) monovalent vaccines for infant and adolescent strategies, respectively – Appendix Figure 4). These scenarios were excluded in subsequent economic analyses.
Cost-utility and cost-benefit analyses

Table 2 summarises cumulative discounted costs and QALYs, ICURs and NMBs. The V-MMRV strategy using GSK or MSD VCV was cost-effective with ICURs less than £20,000 per QALY gained and positive NMBs increasing with the time horizon. The NMBs for strategies using GSK VCV were consistently higher than those using MSD VCV, indicating greater value for money independently of the vaccination strategy and time horizon. Of note, MMRV-MMRV was cost-effective with GSK VCV at medium- and long-terms; and only cost-effective in the long-term with MSD VCV.

From a societal perspective, V-MMRV was cost-effective at £20,000 per QALY gained in short-, medium- and long-terms with any vaccine, but dominant (i.e. less costly and more effective than no-vaccination) with GSK VCV in the long-term. Similarly, MMRV-MMRV demonstrated to be consistently cost-effective but cost-ineffective with MSD VCV in the short-term.

The cost effectiveness acceptability curve shows the likelihood of UVV strategies to be cost-effective at a WTP threshold. Figure 4A indicates that the probability of V-MMRV being cost-effective at £20,000 per QALY gained with GSK VCV was 88.7% at 20 years and 100.0% at other time horizons. Corresponding values for MSD VCV were 73.0% at 20 years, 99.6% at 40 years and 100.0% at 100 years. The probability of MMRV-MMRV being cost-effective at £20,000 per QALY gained, with GSK and MSD VCVs, was 9.6% and 2.5% at 20 years, 78.2% and 46.3% at 40 years, and 100% at 100 years, respectively (Figure 4B).

Sensitivity analyses on cost-utility outcomes and MMRV price

In one-way sensitivity analysis, discount rates and MMRV costs were identified as parameters that ICURs were most sensitive to (Appendix Figures 5 and 6). Using a discount rate of 1.5% for costs and QALYs increased absolute NMB values for V-MMRV and MMRV-MMRV (data not shown). On the other hand, cost-effectiveness results did not change, except that MSD VCV-based MMRV-MMRV turned to be cost-effective at 40 years. The direct medical break-even price was £74.2 and £71.1 for GSK and MSD MMRV after 20 years of UVV, respectively. MMRV price parity analysis showed that the cost-effectiveness probability of V-MMRV with MSD VCV increased to 87.2%, 100.0% and 100.0% at 20, 40 and 100 years at
£20,000 per QALY gained, respectively (Appendix Figure 7A). The same analysis under MMRV-MMRV reported cost-effectiveness probabilities of 10.4%, 77.0% and 100% at 20, 40 and 100 years at £20,000 per QALY gained, respectively (Appendix Figure 7B). This analysis further supports the comparable effectiveness of the vaccines and suggest that MMRV price would drive the cost-effective utilisation of GSK or MSD VCV in a UVV programme.

**Discussion**

This study evaluates the impact of 2-dose UVV on varicella epidemiology and associated cost-effectiveness estimates. The epidemiological model showed that although different in efficacy, GSK and MSD VCVs presented comparable impact on the total incidence of varicella and HZ. These results were further confirmed when assuming MMRV price parity in sensitivity analyses; and agreed with Marin et al.’s meta-analysis [26]. Additionally, we showed that the greater the coverage, the greater the reduction in varicella incidence (95.6%-96.9% with MMRV-MMRV compared to 91.0%-93.8% with V-MMRV at equilibrium). Holl et al. demonstrated that out of efficacy, number of doses, dosing intervals, and coverage, ensuring high coverage remains the critical success factor when implementing UVV [27]. Related to this outcome is the question of age at first dose vaccination. Adding a standalone monovalent varicella vaccine at 13 months to the national immunisation programme would pose a logistical challenge with an additional injection and visit, potentially hampering acceptance and vaccination coverage. The rationale for MMRV vaccines is to reduce the number of injections and vaccination visits, and to increase overall acceptance, compliance, and coverage of the varicella vaccine [28]. This argues for the implementation of first-dose MMRV at 12 moa in agreement with the vaccine product information. However, an approximately 2-fold increase in the risk of febrile seizure for 5-12 days after vaccination was reported in children aged 10-24 months who received a first dose MMRV compared with those who received a first dose MMR vaccine with or without varicella monovalent vaccine [24]. The approximately 2-fold increased risk could be translated into one extra febrile seizure per 2,300-2,600 MMRV doses. Therefore, it will be important that healthcare providers inform parents about the risk of fever and seizure associated with first-dose MMRV. In Europe, first-dose MMRV is
at 13 months in Italy [29]; with a second dose between 23 months and six years old depending on countries [30].

The 2010 JCVI recommendation to not implement UVV was largely motivated by a predicted increase in HZ in the first 30-50 years post UVV due to loss of exogenous boosting. The recommendation is based on model predictions assuming that exposure to VZV boosts immunity against HZ for 20 years and that 100% of HZ susceptibles become immune due to contact with varicella [7, 8]. Ogunjimi et al.’s immunological study aligned with an individual-based model for VZV that estimated the duration of boosting (DoB) to last for 1-2 years [31, 32]. Building further on that, Rafferty et al. estimated a 2-7-year DoB by simultaneously varying the DoB and the coefficient that determines the annual loss of protection based on VZV-CMI to ensure the best fit with epidemiological data [33]. In our study, a 2-year DoB was determined optimal based on calibration of VZV reactivation rates to best fit HZ empirical incidence data (see Supplementary information for further details on DoB selection and calibrations, Appendix Figure 8-12). Our estimated DoB aligns, therefore, with Ogunjimi et al.’s immunological assay results [31]. Consequently, only a 1.6%-1.7% marginal increase in HZ incidence compared to the pre-vaccination era was predicted for about seven years following UVV. These results contrast with van Hoek et al.’s predictions of 20% increase over 40-60 years in England [34] or 30-50 years in the UK [7]. Last but not least, real world data are inconsistent with model predictions of an increase in HZ incidence following UVV implementation [11, 35]. Overall, these contrasting results further highlight the complex interplay between UVV and HZ incidence. As expected, when considering no exogenous boosting, HZ incidence decreased from the start of UVV.

With respect to the long-term effect of UVV on HZ, our results aligned with the literature and showed a continuous decrease in HZ incidence. As a greater proportion of the population is vaccinated, the naturally-infected cohort is progressively replaced by the vaccinated cohort. As a result, and given the lower reactivation rate of vaccine strain compared to WT strain VZV [36], HZ incidence is expected to decrease. From the Humes et al. study, this cohort effect starts being visible with a lower rate of HZ hospitalisation in the 0-14 age group in the post-UVV era, compared to the equivalent age group in the pre-vaccination era.
Weinmann et al. also reported the benefit of UVV to prevent pediatric HZ with a 72% reduction in the HZ incidence among vaccinees aged 0-17 years old versus age-equivalent unvaccinees over 12 years [38]. This cohort effect, together with the predicted marginal increase in HZ cases explains the age distribution of HZ cases at long-term. The increase in HZ cases could be explained by the sudden decline in the force of boosting caused by the introduction of the vaccine, which is accompanied by an increased flow from a varicella recovered state to an HZ susceptible state.

Congruent with the literature, UVV is further predicted to result in an age-shift of varicella towards older age groups in the long-term, with lower incidence rates across all age groups [14, 27, 39]. Most of the predicted varicella cases in older age groups are mild BKT cases.

From the NHS perspective, V- MMRV using GSK or MSD VCV was cost-effective in short- to long-terms at £20,000 per QALY gained. With MMRV- MMRV, cost-ineffectiveness was demonstrated only in the short-term with GSK VCV and in both short- and medium-terms with MSD VCV at £20,000 per QALY gained. These results indicated that the cost-effective benefits of a V- MMRV programme would be visible in short to long horizons. With MMRV- MMRV, cost-effective benefits would be observed earlier with GSK than with MSD VCV. These differences between vaccines rest on vaccine prices. Under current MMRV price assumptions, GSK VCV appears to offer the higher value for money, independent of the vaccination strategy.

Among the study limitations, demographic changes were not modelled to facilitate comparison with previous studies and because the focus was on the relative impact of vaccination versus no vaccination [40]. Additionally, the complex interplay between varicella and HZ is poorly understood and model parameters for exogenous boosting are speculative and possibly over-simplified. For example, DoB is a determinant parameter of unknown value.

Next, the literature debates the range of seroprotection rates associated with MSD VCV [41-45]. To enable a straightforward comparison between GSK and MSD VCVs, seroconversion rates derived from clinical
studies using the same laboratory assays and cut-offs have been employed. Importantly, there is no correlate of protection against varicella.

In conclusion, the present study identified that GSK and MSD VCVs have similar impact on the incidence of varicella and HZ. A high-coverage 2-dose UVV appears to be the most effective strategy to reduce the burden associated with varicella. The early impact of UVV on the incidence of HZ is also predicted to be marginal. Cost-utility analyses show that 2-dose UVV with either GSK or MSD VCV will be a cost-effective alternative to no vaccination, with MMRV price and discount rates being key drivers.
NOTES

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Conflict of Interest

EIHA, MH and GC are employees of the GSK group of companies and hold shares in the GSK group of companies. OC is a consultant for Creativ-Beutical on behalf of GSK and received fees for performing project-related tasks.
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Tables

Table 1: Key model input parameters

| Parameters                                                                 | Value                                                                 | Source and comments |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------------|
| **Epidemiological and vaccine parameters**                                |                                                                       |                     |
| Duration of boosting (DoB) or CMI (i.e. number of years before protection returns to previous levels and recovered varicella to become HZ susceptible), $1/\delta$ | Values of $\delta$ tested in calibration: 1, 2, 5, 10 and 20 years. | Calibration         |
| % of effective varicella contacts that boost against HZ by age, $g$       | 0-49 yr: 75.0% 50-69 yr: 71.0% 70-79 yr: 57.0% 80+ yr: 32%            | [13]                |
| Varicella vaccine efficacy after the first dose, $T_1$                    | GSK: 67.2% (95% CI: 62.3% - 71.5%) MSD: 78.0% (95% CI: 76.6% - 79.4%) | GSK: [20]           |
| Varicella vaccine efficacy after the second dose, $T_{2nd}$               | GSK: 95.4% (95% CI: 94.0% - 96.4%) MSD: 98.3% (95% CI: 97.3% - 99.0%) | MSD: [21]           |
| % HZ cases with PHN                                                       | 0-14yr: 0.00% [0.00% – 0.38%] 15-44yr: 6.28% [5.18% – 7.62%] 45-64yr: 10.75% [8.76% – 12.94%] 65+yr: 18.80% [15.62% – 22.10%] | [46]                |
| Relative propensity* for BKT HZ cases with PHN                           | 0.01 [0.00 – 0.05]                                                    | [47]                |
| Risk of death associated with WT varicella                               | 0-14yr: 4.20E-07 [2.33E-07 – 6.53E-07] 15-44yr: 1.60E-07 [1.00E-07 – 2.20E-07] 45-64yr: 3.37E-07 [2.32E-07 – 4.40E-07] 65+yr: 8.70E-07 [6.30E-07 – 1.10E-06] | Calculated from [3] |
| Relative propensity* for BKT HZ to cause death                           | 0.01 [0.00 – 0.01]                                                    | Assumption          |
| % of WT varicella cases hospitalized                                      | 0-14yr: 0.39% [0.31% – 0.46%] 15-44yr: 0.80% [0.64% – 0.96%] 45-64yr: 1.90% [1.52% – 2.28%] 65+yr: 7.00% [5.60% – 8.40%] | Calculated from [7] |
| Relative propensity for BKT hospitalized varicella                        | 0.25 [0.16 – 0.35]                                                    | [48], [49]          |
| % of HZ cases hospitalized                                                | 0-14yr: 4.47% [3.57% – 5.36%] 15-44yr: 0.00% [0.00% – 0.00%] 45-64yr: 1.00% [0.80% – 1.20%] 65+yr: 2.52% [2.02% – 3.02%] | Calculated from [7] |
| QALY lost per case                                                       |                                                                       |                     |
| WT varicella                                                             | 0-14 yr: 0.0040 [0.0032 – 0.0048] 15+ yr: 0.0050 [0.0040 – 0.0060]   | [8]                 |
| BKT varicella                                                            | 0.0010 [0.0008 – 0.0012]                                               | [8]                 |
| WT or BKT HZ without PHN                                                 | 0-14yr: 0.0220 [0.0100 – 0.0715] 15-44yr: 0.0220 [0.0100 – 0.0715] 45-64yr: 0.0222 [0.0100 – 0.0715] 65+yr: 0.0238 [0.0117 – 0.0715] | [50]                |
| WT or BKT HZ with PHN                                                    | 0-14yr: 0.1892 [0.1060 – 0.3140] 15-44yr: 0.1892 [0.1060 – 0.3140] 45-64yr: 0.1897 [0.1060 – 0.3140] 65+yr: 0.2367 [0.1489 – 0.3140] | [50]                |

* Compared with WT disease

Note: extensive details on the model parameters are provided in Appendix Tables 1 and 2.

BKT, breakthrough; CMI, cell-mediated immunity; DoB, duration of boosting; GSK, GlaxoSmithKline; HZ, herpes zoster; MSD, Merck Sharp & Dohme; PHN, post-herpetic neuralgia; QALY, quality-adjusted life years; SD, standard deviation; WT, wild-type or natural disease; yr, year.
### Table 2: Cost-utility and cost-benefit results

|                      | Total direct costs (£) | Total indirect costs (£) | QALYs loss | ICUR (total direct, £ per QALY gained) | ICUR (total direct and indirect, £ per QALY gained) | NMB (direct, £) |
|----------------------|------------------------|--------------------------|------------|----------------------------------------|-------------------------------------------------|----------------|
| **V-MMRV, short-term time horizon: 20 years** |                        |                          |            |                                        |                                                 |                |
| No vaccination       | 2,290,273,101           | 1,639,488,089            | 414,965    | -                                      | -                                              | -              |
| GSK VCV             | 2,890,794,348           | 1,411,523,084            | 378,361    | 16,678                                 | 10,353                                          | 131,551,596    |
| MSD VCV             | 2,964,774,791           | 1,416,879,723            | 377,941    | 12,174                                 | 12,174                                          | 65,819,225     |

| **V-MMRV, medium-term time horizon: 40 years** |                        |                          |            |                                        |                                                 |                |
| No vaccination       | 3,365,623,421           | 2,409,275,779            | 609,808    | -                                      | -                                              | -              |
| GSK VCV             | 4,249,272,900           | 1,944,223,034            | 536,150    | 12,181                                 | 5,769                                           | 589,216,311    |
| MSD VCV             | 4,367,659,099           | 1,945,479,596            | 535,443    | 7,185                                  | 7,185                                           | 484,942,641    |

| **V-MMRV, equilibrium: 100 years** |                        |                          |            |                                        |                                                 |                |
| No vaccination       | 3,360,155,452           | 2,438,989,448            | 606,634    | -                                      | -                                              | -              |
| GSK VCV             | 4,708,266,138           | 1,917,708,532            | 530,617    | 24,301                                 | 17,932                                          | -147,857,617   |
| MSD VCV             | 4,896,529,651           | 1,926,935,075            | 530,225    | 27,101                                 | 20,714                                          | -253,653,534   |

**MMRVE-MMV, short-term time horizon: 20 years**

| No vaccination       | 2,286,552,203           | 1,652,903,043            | 607,808    | -                                      | -                                              | -              |
| GSK VCV             | 3,191,078,916           | 1,415,800,543            | 374,975    | 24,301                                 | 17,932                                          | -147,857,617   |
| MSD VCV             | 3,310,753,431           | 1,410,061,211            | 374,462    | 20,714                                 | 20,714                                          | -253,653,534   |

**MMRVE-MMV, medium-term time horizon: 40 years**

| No vaccination       | 3,360,155,452           | 2,438,989,448            | 606,634    | -                                      | -                                              | -              |
| GSK VCV             | 4,708,266,138           | 1,917,708,532            | 530,617    | 24,301                                 | 17,932                                          | -147,857,617   |
| MSD VCV             | 4,896,529,651           | 1,926,935,075            | 530,225    | 27,101                                 | 20,714                                          | -253,653,534   |

**MMRVE-MMV, equilibrium: 100 years**

| No vaccination       | 4,307,151,525           | 3,113,554,046            | 777,602    | -                                      | -                                              | -              |
| GSK VCV             | 5,781,037,871           | 2,118,158,312            | 615,335    | 9,220                                  | 2,994                                           | 1,771,454,409  |
| MSD VCV             | 6,027,578,648           | 2,097,842,784            | 614,787    | 10,642                                 | 4,345                                           | 1,542,711,358  |

Cost-utility and cost-benefit results for the monovalent and quadrivalent varicella vaccines (V-MMRV) strategy and the quadrivalent and quadrivalent varicella vaccines (MMRVE-MMV) strategy considering the National Health Service and the societal perspectives. Direct costs consisted of general practitioner visits, hospitalisation associated costs and vaccination costs. Indirect costs were determined by the number of days off from work secondary to varicella or herpes zoster (HZ), multiplied by the mean income. Cumulative discounted costs and outcomes are reported. Cost-utility and cost-benefit results were expressed as incremental cost utility ratio (ICUR) and net monetary benefits (NMB) estimates, respectively. Evaluations were performed at short-term (20 years), medium-term (40 years) and long-term (100 years) time horizons. Discount rates of 3.5% were used for both costs and quality adjusted life years (QALYs). Vaccination versus no vaccination strategies were run independently for GlaxoSmithKline (GSK) and Merck Sharp & Dohme (MSD) varicella-containing vaccines (VCVs); and values for the no vaccination strategy were from the GSK VCV based scenarios. Additionally, for every analysis, a new Monte Carlo simulation was performed, resulting in values for the ‘No vaccination’ strategy being slightly different for the same time horizon.
Figure legends

Figure 1: Total incidence of varicella and herpes zoster

Top row. Yearly total incidence of varicella using GlaxoSmithKline (GSK) (A) or Merck Sharp & Dohme (MSD) (B) varicella-containing vaccine (VCV) per million. Bottom row. Yearly total incidence of herpes zoster (HZ) using GSK (C) or MSD (D) VCV. In black is the monovalent-quadrivalent varicella vaccines (V-\textit{MMRV}) strategy corresponding to a first dose of monovalent varicella vaccine administered at 13 months (at 87% coverage) followed by a second dose of quadrivalent varicella vaccine administered at 3 years and 4 months (at 87% coverage). In purple is the quadrivalent-quadrivalent varicella vaccines (\textit{MMRV-\textit{MMRV}}) strategy corresponding to a quadrivalent varicella vaccine administered as first and second dose at 12 months (at 95% coverage) and 3 years and 4 months (at 87% coverage) of age.

Figure 2: Age distribution of WT varicella infection

Age distribution of varicella cases among individuals aged 0-14 (red), 15-44 (blue), 45-64 (orange) and 65+ (green) years old (yr) as estimated for the monovalent-quadrivalent varicella vaccines (\textit{V-\textit{MMRV}}) strategy (top row) and the quadrivalent-quadrivalent varicella vaccines (\textit{MMRV-\textit{MMRV}}) strategy (bottom row) using GlaxoSmithKline (GSK) (left column) or Merck Sharp & Dohme (MSD) (right column) varicella-containing vaccines. Results were reported at the pre-vaccination era and at equilibrium (i.e. 100 years following UVV implementation corresponding to a new steady states). The numbers above the bars indicate the wild-type annual incidence of varicella at the pre-vaccination era and at equilibrium.

Figure 3: Scenario analysis on the exogenous boosting hypothesis

Yearly total incidence of varicella using GlaxoSmithKline (GSK) (A) or Merck Sharp & Dohme (MSD) (B) varicella-containing vaccine (VCV) per million considering or not (no boosting) exogenous boosting. In green is the quadrivalent-quadrivalent varicella vaccines (\textit{MMRV-\textit{MMRV}}) strategy that included the exogenous boosting hypothesis with a duration of boosting or cell-mediated immunity of two years. In red is the equivalent varicella vaccination strategy, excluding the exogenous boosting hypothesis. At
equilibrium, the incidence of herpes zoster (HZ) was reduced by 98.3% (respectively 98.2%) and 98.6%
(respectively 98.5%) with GSK and MSD VCVs when no boosting (respectively boosting) was assumed,
respectively. At the third year following universal varicella vaccination implementation, whilst the peak in
HZ incidence was predicted under the exogenous boosting hypothesis, a 0.4% reduction in HZ incidence
was predicted under the no boosting hypothesis for both GSK and MSD VCV.

**Figure 4: Cost-effectiveness acceptability curves for base-case immunisations**

Cost-effectiveness acceptability curves (CEAC) showing the probability of the monovalent-quadrivalent
varicella vaccines (V-MMRV) strategy (left column) and the quadrivalent-quadrivalent varicella vaccines
(MMRV-MMRV) strategy (right column) to be cost-effective using GlaxoSmithKline (GSK; magenta) or
Merck Sharp & Dohme (MSD; brown) varicella-containing vaccines (VCVs) compared to no vaccination for a
range of willingness to pay (WTP) thresholds. Results are reported at short (20 years), medium (40 years)
and long-term (100 years) time horizons. The vertical line represents the WTP threshold of £20,000 per
quality-adjusted life years (QALY) gained. yr, year.
Figure 3

A) Total incidence of HZ, GSK VCV

B) Total incidence of HZ, MSD VCV

Incidence (per million)

Years after vaccination

MMRV-MMRV
MMRV-MMRV (no boosting)
Figure 4

A) CEAC, V-MMRV

B) CEAC, MMRV-MMRV