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Assessing optimal use of the standard dose adjuvanted trivalent seasonal influenza vaccine in the elderly

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ABSTRACT

Background: Despite a long-standing vaccination programme, seasonal influenza remains a major public health problem in England, in particular for the elderly where a significant disease burden remains despite vaccine coverage approaching the WHO target of 75%. The recently licensed adjuvanted trivalent vaccines (TIV-ADJ) have been shown to offer greater protection for the elderly compared to the standard-dose non-adjuvanted trivalent vaccines (TIV), particularly for those individuals 75 years old and above for whom the TIV has limited effectiveness. We assessed the cost-effectiveness of the TIV-ADJ for use in the elderly.

Methods: We used a dynamic SEIR-type transmission model coupled with an economic evaluation framework, estimating the reduction in GP consultations, hospitalisations and influenza-attributable mortality. We assessed the optimal use of the TIV-ADJ by estimating the cost-effectiveness of programmes that used this vaccine in the 65+ and 75+ age groups.

Findings: The use of TIV-ADJ is highly cost-effective for both target age cohorts with incremental cost-effectiveness ratios well below the £20,000 per quality-adjusted life year (QALY) with over 90% probability that the vaccine is cost-effective at a cost-effectiveness threshold of £30,000 per QALY.

Interpretation: The increased protection provided across all three influenza vaccine sub-types makes TIV-ADJ a more attractive option than TIV from the perspective of the healthcare provider, driven by the increased efficacy against A(H3N2). When deciding on the optimal use of the newly available vaccine it is important to consider the fact that TIV has very limited effectiveness for the 75+ age group, who would therefore get the greatest benefit from a more effective vaccine.

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1. Introduction

Seasonal influenza causes a substantial health and economic burden every year in England. It is estimated that on average 10% of all respiratory admissions and deaths can be attributed to influenza annually. This burden is not homogenous with the highest admission rates for influenza A and influenza B attributable disease in children under five years of age and the greatest influenza-attributable deaths occur in individuals 65 years or older with comorbidities [1]. Furthermore, the burden of disease within the elderly population is also heterogeneously-distributed, with an individual of age 75+ years on average seven times more likely to die from influenza than a 65–74 year old [2].

The national influenza vaccination programme in England is a long-established programme of annual influenza vaccination for several population groups: the elderly and individuals with comorbidities that increase the risk of influenza complications and more recently the incremental introduction of the offer of vaccination ultimately to healthy children aged 2–16 years old.

The elderly though are recognised to still have an important burden of disease attributable to influenza despite uptake levels approaching 75% with the currently available non-adjuvanted, standard dose influenza vaccines for this target group in the UK

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[3]. The reasons for the lower effectiveness in the elderly for influenza vaccines particularly against A(H3N2) are likely to be multifactorial.

Manufacturers have developed new vaccines to increase the immune response, and thus vaccine efficacy, in this group. The trivalent inactivated adjuvanted vaccine (TIV-ADJ) containing the MF59 oil-in-water emulsion of squalene oil has demonstrated superiority over trivalent standard-dose vaccines (TIV) in protecting elderly individuals from laboratory-confirmed influenza infection [4]. TIV-ADJ has been available in some EU countries since 1997 [5] and has been shown to be cost-effective for adult individuals in receipt of haemodyalysis [6], though its cost-effectiveness for the general elderly population has yet to be assessed. In August 2017 the Department of Health approved the NHS list price for the TIV-ADJ, set at £9.79. The decision to set a list price follows the decision by the Medicines and Healthcare products Regulatory Agency in early August 2017 to license TIV-ADJ for adults of age 65 years and older.

Adjusted vaccine effectiveness data from the UK amalgamating influenza surveillance data sources for all seasons from 2010 through 2017 show that the effectiveness of TIV declines with age, with little-to-no evidence of effectiveness for individuals of age 75 years and older against the influenza A strains on average [2]. A comparative analysis of TIV-ADJ and TIV for elderly individuals reported that TIV-ADJ was significantly protective with estimated effectiveness of 58%, compared to TIV for which there was no evidence of significant effectiveness [4]. Crucially, of 282 individuals in the study population 81.6% were of age 75 years or older. In view of the lack of apparent protection offered by TIV to this age group, preferential use of TIV-ADJ may be beneficial to this group.

This analysis considers the cost-effectiveness of a seasonal influenza vaccination programme that uses TIV-ADJ for individuals in the 75+ years age group.

2. Methods

We adapted the fluEvidenceSynthesis SEIR-type mathematical model [7] from [8] and [9] that was used to recommend the introduction of the paediatric seasonal influenza vaccination programme in the United Kingdom (see Table 1). This model synthesises data from a variety of surveillance systems within a Bayesian inference framework to estimate the potential burden of disease for the study population stratified by age and risk status. By modelling at least two scenarios, one for each potential intervention strategy, the model assesses the incremental cost-effectiveness of each intervention, using the ratio of incremental costs to incremental health benefits measured in quality-adjusted life years (QALY), reporting the result in terms of the incremental cost-effectiveness ratio (ICER). The original model simulated seasonal influenza outbreaks in seven age groups (<1 year, 1–4, 5–14, 15–24, 25–44, 45–64 and 65+ years) and two at-risk groups (low risk, clinical risk) over 14 influenza seasons.

Table 1
Descriptions of the three vaccination programmes assessed in the cost-effectiveness analysis.

Programme	Vaccine used for 65–74 age group	Vaccine used for 75+ age group
Baseline	Inactivated standard-dose non-adjuvanted trivalent (TIV)	Inactivated standard-dose non-adjuvanted trivalent (TIV)
1st alternative	Inactivated standard-dose non-adjuvanted trivalent (TIV)	Inactivated standard-dose non-adjuvanted trivalent (TIV-ADJ)
2nd alternative	Inactivated standard-dose adjuvanted trivalent (TIV-ADJ)	Inactivated standard-dose adjuvanted trivalent (TIV-ADJ)

For this analysis we divided the 65+ years age group into two age groups, delineating between the 65–74 years and 75+ years groups. We inferred the model parameters for three vaccine subtypes of seasonal influenza (A/H1N1pdm09, A/H3N2 and B) over the 14 seasons using an MCMC-approach to obtain 1000 samples after a 500,000 burn-in and thinning the chain by 1000.

Social contact patterns are a key determinant of age-assortative infectious disease burdens, so we analysed the social contact data for elderly individuals in Great Britain in the POLYMOD study [10] to determine the extent of our knowledge of social interactions in the elderly population and their impact on the burden of seasonal influenza.

2.1. Modelled vaccination programmes

We simulated three vaccination programmes, varying the vaccine that was used for the two age groups in the elderly population. In all three programmes we assumed that the childhood programme had been successfully rolled-out to all children attending primary schools (2–11 years old) and that these children would receive a quadrivalent vaccine (the live-attenuated QLAIV for children without contraindications and the inactivated QIV otherwise). We assumed that the Department of Health was prepared to pay for the unadjuvanted vaccines and was not considering withdrawal of influenza vaccines for the elderly.

2.2. Model parameters

Model parameters were taken from the literature including a recently published analysis of pooled VE results for the elderly in the UK and matched to those parameters used by Baguelin et al. 2015 [8] where possible to maintain a consistent modelling approach (see Table 1 and Table 2). Estimated healthcare resource use such as the number of general practice (GP) consultations, influenza-attributable hospitalisations and influenza-attributable mortality in hospitals were taken from Cromer et al. 2014 [1]. Economic parameters such as the cost of GP consultations and inpatient admissions were adjusted for inflation. Vaccination coverage data were taken from monthly influenza vaccine coverage data published by Public Health England [11]. The unit costs of both vaccines were the list price plus VAT at 20%. We assumed that vaccine administration costs would be equivalent for both vaccines therefore we excluded these from the incremental cost-effectiveness analyses.

Limited data describing the use of healthcare resources within the 65+ age group exist. To conduct this analysis we assumed that any reduction in the number of GP consultations, hospitalisation and deaths in this age group occurred exclusively in the 75+ age group for programme 2 (TIV-ADJ for 75+ only). When assessing the incremental cost-effectiveness of programme 3 we assumed that any incremental reductions occurred exclusively in the 65–74 years age group.

A recent analysis of vaccine effectiveness data from the UK for all seasons from 2010 through 2017 shows the reduced effectiveness of TIV in the 75+ years age group for all three strains in the vaccines used [2]. Adjusted vaccine effectiveness against A (H1N1) was 60.5% in the 65–74 age group versus 0% in the 75+ age group, whilst against the A(H3N2) and B strains the adjusted effectiveness was 24.2% versus 0% and 53.3% versus 48.8% respectively.

A 2016 systematic review on the efficacy of influenza vaccines for each influenza strain was used to parameterise the model for the trivalent vaccine efficacy [12]. For eligible children, the efficacy of QLAIV and QIV against the influenza B strains was assumed to

Table 2
Parameters used in the disease transmission and economic models.

Parameter	Value	Source
Vaccine coverage		
Season-end coverage for low-risk < 5 yrs	28.1%	[3]
Season-end coverage for low-risk 5–14 yrs	38.5%	[3]
Season-end coverage for clinical risk 1–64 yrs	48.6%	[3]
Season-end coverage for 65–74 yrs	68.0%	[3]
Season-end coverage for 75 + yrs	80.0%	[3]
TIV efficacy		
A(H1N1) < 15 yrs	69.0%	[11]
A(H1N1) 15–64 yrs	73.0%	[11]
A(H1N1) 65–74 yrs	60.5%	[2]
A(H1N1) 75 + yrs	0.0%	[2]
A(H3N2) < 15 yrs	43.0%	[11]
A(H3N2) 15–64 yrs	35.0%	[11]
A(H3N2) 65–74 yrs	24.2%	[2]
A(H3N2) 75+ yrs	0.0%	[2]
B < 15 yrs	69.0%	[11]
B 15–64 yrs	54.0%	[11]
B 65–74 yrs	53.3%	[2]
B 75+ yrs	48.8%	[2]
Efficacy of TIV-ADJ		
Additive efficacy for each strain	20.0%	Assumption
GP consultation costs		
<1 years	£88.11	[14]
1–4 years	£64.54	[14]
5–14 years	£54.32	[14]
15–44 years	£84.78	[14]
45–64 years	£100.72	[14]
65+ years	£100.72	[14]
Hospital admission costs		
<1 years	£1606	[14]
1–4 years	£1606	[14]
5–14 years	£1606	[14]
15–44 years	£1662	[14]
45–64 years	£1983	[14]
65+ years	£5354	[14]
Per-dose vaccine costs		
Non-adjuvanted TIV	£9.05	List price (inc. VAT)
Adjuvanted TIV	£11.75	List price (inc. VAT)

match the top-end of the 95% confidence intervals for the efficacy of the trivalent vaccine against influenza B. The comparative analysis of TIV-ADJ and TIV reported VE of 58% (95% CI 5–82%) [4], but we assumed a more conservative 20% additional VE as a first approach. In a sensitivity analysis we assessed the impact of this assumption on the ICER of both modelled programmes as well as an assumption that TIV offers no protection against influenza B for the 75+ age group, in line with the reported protection against A(H1N1pdm09) and A(H3N2) for this age group. Finally, we conducted a threshold analysis to determine the additional VE across all three strains at which TIV-ADJ is cost-effective by decreasing the additional VE at 1% increments from 20%.

3. Results

Both modelled vaccination programmes would result in large reductions in healthcare resource use and clinical outcomes arising from influenza infection (Table 3, originally published online [13]). Using the TIV-ADJ for the 75+ years age group would reduce the burden of influenza disease in terms of GP consultations by a median of 12,689 (interquartile range, IQR:13,815); hospitalisations by a median of 878 (IQR:770); and deaths by 299 (IQR: 321). Further reductions are likely if eligibility for the TIV-ADJ is extended to the 65–74 years age group.

Table 3
Incremental reductions of health outcomes of both proposed programmes and results from the economic evaluation. Values in parentheses are the interquartile range.

Programme	Adjuvant for 75 + only vs. baseline	Adjuvant for all 65 + vs. Adj 75+
Healthcare resource use		
Median reduction: GP consultations (IQR)	12,689 (13,815)	18,913 (14,767)
Median reduction: hospitalisations (IQR)	878 (7 7 0)	1152 (7 0 9)
Median reduction: deaths (IQR)	299 (3 2 1)	380 (2 9 3)
Economic evaluation		
Median incremental cost (IQR)	£6.2 m (2.4)	£4.2 m (2.4)
Median incremental QALYs saved (IQR)	5549 (7260)	7430 (6257)
Median ICER (IQR)	£852 (1290)	£469 (5 1 5)
Simulations below £30 k/QALY WTP	90%	91%

Both programmes would be highly cost-effective with median ICERs below the £30,000 per QALY willingness-to-pay (WTP) threshold and more than 90% of all simulations below that WTP threshold (Fig. 1). The programme targeting the 75+ years age group has a median ICER of £852 (IQR: 1290) and 90% of the 1000 simulations also resulting in ICERs below the WTP threshold. The median net incremental cost of the programme was £6.2 m (IQR: 2.4, Fig. 2). Increasing eligibility for the TIV-ADJ programme to the 65–74 years age group incurs further median net costs of £4.2 m (IQR: 2.4, Fig. 2) with 91% of simulations below the WTP threshold.

There was variation in the ICERs reported for each vaccination programme, with 1.2% of simulations for the 75+ programme and 0.1% of simulations for the 65–74 years programme above the WTP threshold. Additionally, 8.9% of simulations for the 75+ programme and 8.6% of simulations for the extension to the 65–74 years age group had ICERs below the £0 per QALY threshold. For 27% of the simulations for the 75+ programme with negative ICERs (24/89) the new programme was cost-saving (i.e. the negative ICERs were a result of fewer costs compared to the baseline), and for 81% of the simulations for the 65–74 years programme with negative ICERs (70/86) the new programme was cost-saving.

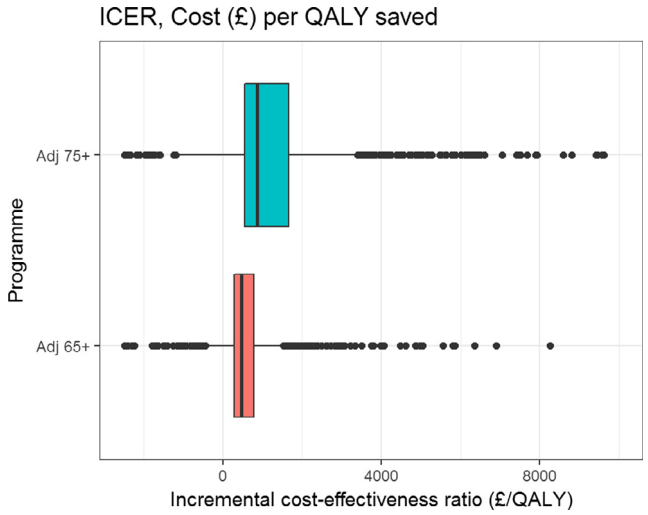

Fig. 1. The incremental cost-effectiveness ratios of both proposed programmes. The TIV-ADJ programme in the 75+ age group is compared to the TIV baseline, whilst the TIV-ADJ programme in the 65+ age group is compared to the TIV-ADJ programme for the 75+ age group.

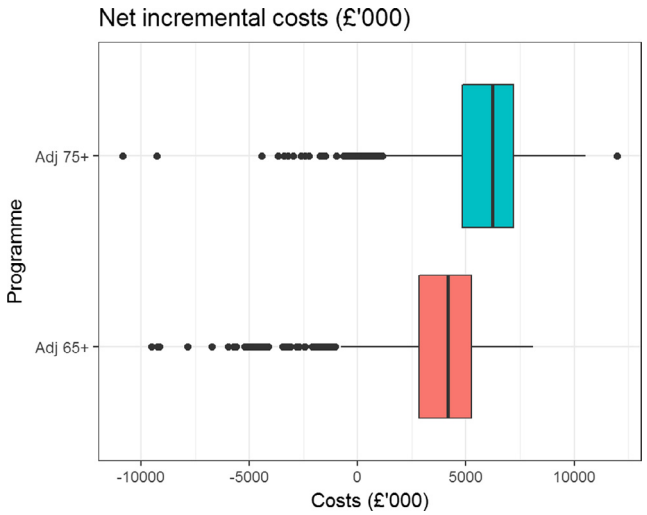

Fig. 2. The incremental costs of both proposed programmes. The TIV-ADJ programme in the 75+ age group is compared to the TIV baseline, whilst the TIV-ADJ programme in the 65+ age group is compared to the TIV-ADJ programme.

3.1. Sensitivity analysis

Both programmes remain highly cost-effective even with only 10% additional efficacy over the TIV (Table 4), though with only 76% of simulations below the WTP threshold for the 75 + age group and 83% of simulations below the WTP threshold for the subsequent extension to the 65–74 years age group (see Table S1 in the supplementary material). If the assumed incremental efficacy is increased above the 20% used in the main analysis then the vaccine becomes more cost-effective. If TIV for the 75+ age group offered no protection against the influenza B strains, along with the A(H1N1pdm09) and A(H3N2) strains, the TIV-ADJ would be cost-effective for both age groups with median ICERs of £923 (IQR: 1299) and £459 (IQR: 508) respectively.

3.2. Threshold analysis

Lower estimates of additional VE for both age groups reduces the probability that each programme meets the criteria of cost-effectiveness, as the percentage of all simulations with ICERs below the WTP threshold reduced as the additional VE was decreased from 20% (see Table S1 in the supplementary material). Indeed, 5% additional VE has a favourable median ICER of £1294 for the 75 + programme, but the IQR is much larger at £6085 with only 59% of simulations below the WTP threshold. The larger IQR means there is more uncertainty in the overall cost-effectiveness of this vaccination programme if the additional VE of the adjuvanted vaccine is only 5%.

Table 4
Sensitivity analysis on selected parameter inputs.

Parameter	Median ICER of Adj75+ (IQR)	Median ICER of Adj65+ (IQR)
1. 5% additional efficacy across all three strains	£1294 (6085)	£1193 (4165)
2. 10% additional efficacy across all three strains	£1336 (3141)	£1052 (1780)
3. 30% additional efficacy across all three strains	£496 (5 5 2)	£193 (2 6 6)
4. 40% additional efficacy across all three strains	£270 (3 1 2)	£56 (1 9 7)
5. No efficacy against B in the baseline, 20% uplift across all three	£923 (1,299)	£459 (5 0 8)

4. Discussion

Our analysis demonstrates that the standard-dose adjuvanted trivalent vaccine for seasonal influenza would be cost-effective if given to elderly individuals 75 years old and above, as well as to elderly individuals 65 years old and above instead of the current non-adjuvanted influenza vaccine. Our results also demonstrated that both programmes could be cost-saving compared to their respective baselines, but for 2.4% and 7.0% of simulations for both programmes respectively. We assumed that the adjuvanted vaccine offers only 20% additional protection in absolute terms, far below the 58% additional efficacy reported from a study on this issue [4], yet based on this assumption the introduction of the vaccine to the seasonal influenza vaccination programme for the elderly would reduce further the burden of seasonal influenza in primary care by a median of 12,689 (IQR:13,815) consultations if given to the 75+ age group and by a further 18,913 (IQR:14,767) if also given to the 65–74 years age group. We also estimate substantial reductions in influenza-attributable hospitalisations and influenza-attributable mortality in hospitals for both proposed programmes. Results from the sensitivity analysis suggest that both programmes with the adjuvanted vaccine remain cost-effective if the incremental efficacy of TIV-ADJ is less than the 20% figure we used, becoming more cost-effective if the efficacy of the vaccine approaches that reported by Van Buynder et al. [4].

The sensitivity analysis demonstrated that the vaccination programmes proposed may be cost-effective at lower additional VE estimates, but the threshold analysis demonstrated that the uncertainty in the cost-effectiveness estimates reduces as the additional VE decreases from the assumed 20%, as the IQR around the estimated median ICERs widens and the percentage of simulations below the WTP threshold reduces. Although the reported comparative effectiveness estimate was 58%, there was considerable uncertainty in this estimate, with the 95% confidence intervals extending from 5% to 82%. Our analysis shows that at the lower end of the estimated additional VE the adjuvanted vaccine programmes are less likely to be cost-effective, but even with our conservative choice of just 20% additional VE both programmes would meet the criteria for cost-effectiveness.

The main question under consideration by policy makers is whether to change the elderly vaccination programme for seasonal influenza for all individuals aged 65 years and above with preferential use of the TIV-ADJ, or to consider preferential use in subgroup of this elderly population. Although a programme to include all individuals aged 65 years and above would be cost-effective and would result in a reduced burden of influenza in the elderly, it is important to assess the costs and benefits of this programme in context with the current vaccination programme. There is little-to-no evidence of effectiveness of TIV in individuals of age 75 years and older against the influenza A strains on average, yet it still demonstrates some effectiveness in the 65–74 years age group. A seasonal influenza vaccination programme with preferential use of the TIV-ADJ for individuals of age 75 years and older would be £4.2 m less costly (net, median) than a programme that also included the 65–74 years age group, whilst still ensuring that the 65–74 years age group has access to an effective vaccine in the non-adjuvanted TIV.

4.1. Strengths and weaknesses of this study

This study uses a dynamic disease transmission model fitted to 14 years of surveillance data from a variety of sources in the healthcare system of England, coupled with an economic evaluation framework that has been used to assess the cost-effectiveness of the influenza vaccination programme for children

[8]; the elderly population [15]; and the use of standard-dose quadrivalent vaccines for all target cohorts [16]. Our modelling approach was to maintain consistency in the parameters and data sources used where applicable.

Our economic evaluation of the different vaccines followed the guidelines recommended by the National Institute for Health and Clinical Excellence (NICE) [17]. We considered vaccination programmes with at least 90% of all simulations below the WTP threshold as cost-effective, with a WTP threshold of £30,000 per QALY as recommended by NICE.

There are several limitations in our analysis. First, the data used to parameterize the transmission model is based on the period up to the 2009 pandemic. Although this covers a large number of seasons, there may have been changes in the epidemiology of influenza since then. Second, the effectiveness estimates for adjuvanted influenza vaccine are based on relatively limited data, which results in some uncertainty for the findings. Further work is planned to incorporate this uncertainty into the model. Third, we assumed that the rates of local or systemic adverse events was the same between TIV-ADJ and TIV, but evidence suggests that a localised pain at the site of injection is more common for recipients of TIV-ADJ [18], therefore we may have excluded the additional health disutility associated with pain at the site of injection for the adjuvanted vaccine. However, to our knowledge these health utilities have not been measured nor published in the literature, and their inclusion is unlikely to affect the overall result of our analysis given that the health disutility would be minor in comparison to the substantial reduction in healthcare resource use attributable to the adjuvanted vaccine. Finally, our use of the contact matrix derived from the POLYMOD survey conducted in Great Britain [10]. The survey recorded daily contact information from only five individuals in the 75+ years age group from a total of 1012 participants, though 81 participants recorded at least one contact with someone in the 75+ years age group (Figs. S1–S3). A lack of participants in the POLYMOD study in this age group limits our knowledge of social interaction in our studied population.

5. Research in context

5.1. Evidence before this study

Decision analytic models report that TIV-ADJ can be cost-effective compared to TIV for adult haemodialysis patients depending on the incremental vaccine cost and increased vaccine efficacy. The TIV-ADJ offers more protection from influenza for elderly individuals than the TIV, for which individuals aged 75+ years receive little benefit.

5.2. Added value of this study

This is the first cost effectiveness analyses that compares TIV and TIV-ADJ for a general elderly population, and also the first cost-effectiveness analyses of TIV-ADJ that estimates the burden of influenza using a dynamic transmission model for two separate age groups within the elderly population.

5.3. Implications of all the available evidence

TIV-ADJ would be more cost-effective for elderly individuals in England than existing TIV. It is likely that individuals aged 75+ years would receive the greatest benefit given the lack of efficacy of the TIV in this age group.

Availability of data and material

The mathematical model is available for use at https://github.com/MJomaba/flu-evidence-synthesis.

Authors' contributions

Conception of work: DT, RP, MB. Established the modelling framework: DT, EvL, MB. Conducted the modelling: DT. Analysed the data: DT. Wrote the first draft of the manuscript: DT. Contributed to the final draft of the manuscript: DT, EvL, MR, RP, MB.

Competing interests

The authors declare no competing interests exist.

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The views expressed are those of the author (s) and not necessarily those of the NHS, the NIHR, the London School of Hygiene & Tropical Medicine, the Department of Health or Public Health England.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.03.002.

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