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ORIGINAL RESEARCH



Cost-effectiveness of high dose versus adjuvanted trivalent influenza vaccines in England and Wales

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ABSTRACT

Aims: High dose trivalent influenza vaccine (HD TIV) and adjuvant TIV (aTIV) have been developed specifically for adults aged 65 and older (65+) who are at high risk of life-threatening complications. However, there is a scarcity of evidence comparing the clinical and cost-effectiveness of HD TIV and aTIV. The aim of this study was to determine the cost-effectiveness of HD TIV versus aTIV in the England and Wales 65+ population.

Methods: A cost-utility analysis was conducted using a decision tree with two influenza related outcomes: Laboratory confirmed cases that could result in GP consultation, and hospitalizations that may result in premature mortality. Due to a lack of comparative evidence, the effectiveness of HD TIV versus aTIV was calculated indirectly, based on relative effectiveness estimates for each vaccine versus a common comparator, standard dose (SD) TIV. The primary analysis included hospitalizations explicitly due to influenza/pneumonia. Cost-effectiveness was established for three scenarios applying differing relative effectiveness estimates for aTIV versus SD TIV. Uncertainty was analysed in one-way deterministic sensitivity analyses. A secondary analysis included hospitalizations due to any respiratory illness.

Results: The minimum population impact of vaccination with HD TIV rather than aTIV was 13,092 fewer influenza cases, 1,109 fewer influenza related deaths, 4,673 fewer hospitalizations, and 3,245 fewer GP appointments. HD TIV was cost-effective versus aTIV for all three effectiveness scenarios, with incremental cost-effectiveness ratios (ICER) equal to £1,932, £4,181, and £8,767 per quality adjusted life year. Results were consistent across the secondary analysis and deterministic sensitivity analyses.

Limitations: The analysis was limited by a lack of robust and consistent effectiveness data for aTIV.

Conclusion: HD TIV is cost-effective versus aTIV in people aged 65+ in England and Wales. Use of HD TIV over aTIV could increase clinical benefits and reduce the public health and economic burden of influenza.

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Introduction

Influenza vaccination programmes are a public health priority, particularly for older adult populations who are at higher risk of complications including lower respiratory tract infection, hospitalization, and death¹. Seasonal flu epidemics are typically caused by influenza type A (subtypes H1N1 and H3N2) and different type B viruses². Consequently, the World Health Organization (WHO) currently recommend vaccines containing multiple type A and B antigens, for example inactivated trivalent (TIV) and quadrivalent influenza vaccines (QIV)³. The standard dose influenza vaccination typically contains 15 µg of antigen per strain. In a meta-analysis of 10 randomized controlled trials (RCTs), standard dose trivalent vaccines (SD TIV, Fluzone[®], Sanofi Pasteur) had an

effectiveness in healthy adults of around 59%, which varied substantially across influenza seasons and subtypes⁴.

The effectiveness of standard dose vaccines is diminished in older populations likely due to immune system functionality and antibody response which declines naturally with advancing age⁵. To address issues of reduced effectiveness, specific vaccine formulations have been developed in adults 65 years of age and older, herein referred to as 65+. A high dose trivalent influenza vaccine (HD TIV, Fluzone[®] High-Dose, Sanofi Pasteur), which contains 60 µg of haemagglutinin (HA) antigen per strain, generates higher antibody responses and greater effectiveness than SD influenza vaccines^{6,7}: Evidence from a phase IIIb–IV, multi-centre, double blinded RCT demonstrated that HD TIV is more efficacious versus SD TIV in adults 65+⁸, a finding which has been consistently

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supported by multiple observational studies^{9–18} and a meta-analysis covering over 12 million HD TIV recipients across nine influenza seasons^{6,19}. Furthermore, standard dose vaccines are not recommended by the Joint Committee on Vaccination and Immunization (JCVI). Instead, high dose and adjuvanted vaccines are recommended for adults 65+²⁰.

Adjuvant TIV (aTIV, Flaud, Seqirus) contains 15 µg HA antigen per strain with the addition of MF59 oil-in-water emulsion of squalene oil²¹. There is a scarcity of data comparing aTIV with active vaccines in RCTs and moreover there is inconsistency in observational study findings published in the literature. Four out of six observational studies included in a systematic review did not identify statistically significant differences between aTIV and other SD influenza vaccines²²; and a recent case control study in the UK did not identify significant benefits for aTIV versus non-adjuvant vaccines for the 2018/19 influenza season²³. Furthermore, a systematic literature review by the European Centre for Disease Prevention and Control found no statistical difference in relative effectiveness between aTIV and non-adjuvanted TIV and QIV vaccines in adult populations²⁴. Therefore, the *in vivo* benefits of aTIV remain uncertain. Furthermore, a recent randomized clinical trial found that aQIVs failed to demonstrate superiority versus a non-influenza vaccine in older adults during seasons with high amounts of vaccine strain mismatch²⁵.

The respective difference in the evidence profiles for HD TIV and aTIV is reflected in assessments made by the National Advisory Committee on Immunization in Canada (NACI). In a literature review, NACI states that there is good quality, “grade A”, evidence indicating superiority for high dose vaccines versus SD TIV, whereas the effectiveness evidence for adjuvant vaccines versus unadjuvanted vaccines is “insufficient”²⁶. A retrospective cohort study on more than 12 million fee-for-service US Medicare beneficiaries found high-dose egg-based vaccines were not significantly different to adjuvanted egg-based vaccines, which was 7.5% more effective than standard (i.e. nonadjuvanted) vaccines¹². A second retrospective cohort study of over 2 million people aged 65+ in the USA indicates HD TIV may be up to 12% more effective than aTIV in preventing respiratory related hospitalizations²⁷.

If HD TIV is effective over aTIV, its preferential use in the 65+ population could reduce the impact of influenza and may have public health implications, particularly by reducing hospitalizations and early mortality which are key contributors to the overall economic burden of influenza²⁸.

Aims and objectives

The main objective of this analysis was to determine the cost-effectiveness of HD TIV versus aTIV for adults 65+ in England and Wales from a UK healthcare perspective by utilizing the best available evidence to date. A further objective was to explore cost-effectiveness results across several deterministic scenarios, thus accounting for uncertainty in the effectiveness evidence for aTIV. In addition, we established the cost-effectiveness of HD TIV versus aTIV for (i) a primary analysis which defined hospitalizations explicitly due to

influenza/pneumonia and (ii) a secondary analysis which included all hospitalizations due to any lower respiratory infection.

Methods

Model perspective and structure

This was a cost-utility analysis, adopting a UK healthcare perspective including costs incurred by the NHS and Prescribed Specialized Services (PSS) and health benefits as quality adjusted life years (QALYs). The analysis estimated the incremental cost-effectiveness ratio (ICER) of HD TIV versus aTIV, assuming a cost-effectiveness threshold (CE threshold) between £20,000 and £30,000 per QALY, as stipulated in the NICE reference case²⁹.

We constructed a decision tree to compare the cost-effectiveness of HD TIV with aTIV over a single influenza season. The decision tree included two disease pathways following vaccination: (i) Laboratory confirmed influenza (LCI) cases that could result in a general practitioner (GP) visit and (ii) hospital stays which could lead to premature death (Figure 1). The primary analysis defined hospitalizations specifically due to influenza or pneumonia which was expanded to include all respiratory related hospitalizations in a secondary analysis. The two disease pathways were not mutually exclusive,¹ meaning populations could enter one, both, or neither following vaccination. The model was conducted over a single average influenza season. A lifetime horizon for QALYs was adopted by establishing life expectancies for populations who were discharged from hospital and to a third non-disease pathway who were neither LCI cases nor hospital attendees. To avoid double counting we included influenza related mortality as an outcome on the hospitalization, but not the LCI, disease pathway.

Target population

The target population included adults 65+ in England and Wales stratified into three groups according to their age and risk of influenza-related complications: (i) People aged 65–74 with chronic respiratory disease or chronic heart disease, who are defined as “high risk” as their underlying condition predisposes them to influenza related complications; (ii) people aged 65–74 without underlying medical conditions who are at relatively lower risk of complications; and (iii) all people aged 75 and over including both low and high-risk groups. Age groups were analysed separately due to differences in vaccination coverage, vaccination effectiveness, and the likelihood of GP or hospital attendance if infected. Due to limitations in available data it was only possible to differentiate the age 65–74 risk groups by likelihood of GP attendance. Mean costs and QALYs were calculated independently for each of the three populations. Cost-effectiveness results were pooled across the full population of over 65s by calculating a weighted average across the stratified age and risk groups. We also report cost-effectiveness results separately for the 65–74 (pooled across high and low risk) and 75+ age

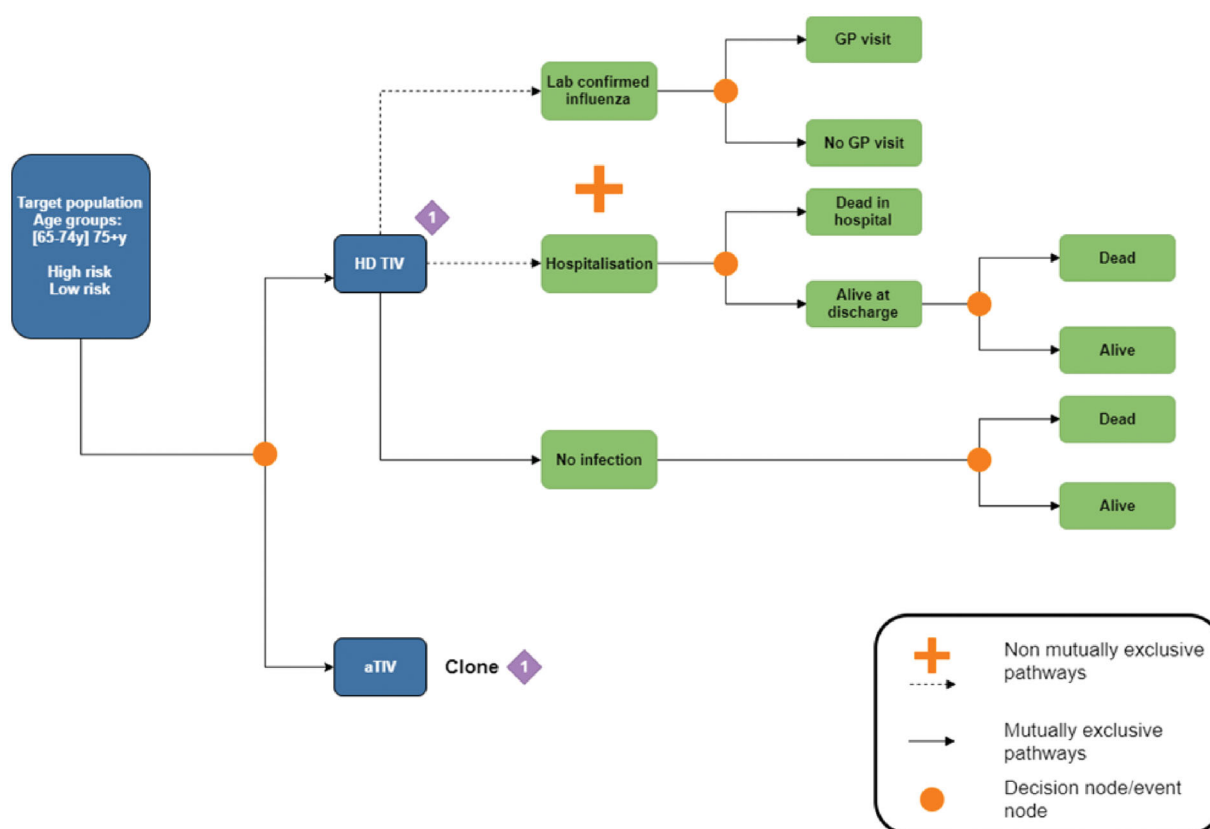


Figure 1. Structure of the decision tree. #Laboratory confirmed cases of influenza. * Pneumonia/influenza related hospitalizations (primary analysis), hospitalizations due to any respiratory cause (secondary analysis).

Table 1. Model input parameters by age and risk group.

Parameter	Input value			Source
	Age 65–74 (low risk)	Age 65–74 (high risk)	Age 75+ (all risk)	
Population parameters:				
Population size	3,171,289	2,594,691	4,751,498	ONS ⁵⁵
Vaccination coverage rate	62.7%	62.7%	80.0%	Public Health England ⁵⁶
Influenza attack rate (unvaccinated) ^a	7.5%	7.5%	7.5%	Assumption based on WHO ³¹
Hospitalization rate per 100,000 (SD TIV)	190.65	190.65	898.29	Observational study ³²
Clinical outcomes probabilities				
GP Visit Influenza diagnosis	20.2%	30.4%	24.8%	UK burden of illness study ⁴⁰
Death hospitalization	13.0%	13.0%	26.0%	UK Observational Study ⁴¹
Death no hospitalization	1.4%	1.4%	5.2%	ONS life tables ⁴²

^aInfluenza attack rate obtained for all adult population (i.e. not specific for populations aged 65+).

groups. Population parameters by age and risk group are reported in Table 1.

Model parameters

Vaccination coverage

The model included both vaccinated and unvaccinated populations. The probability of vaccination was estimated for each age and risk group separately. To establish the percentage of the population receiving the HD TIV and aTIV vaccination we applied typical coverage rates as described in Public Health England Annual Flu reports³⁰, equal to 62.7% in people aged 65–74 (for both low and high and risk groups), and 80% in the 75+ age group.

Probability of lab confirmed influenza

To calculate the probability of LCI in the unvaccinated cohort, we applied a baseline influenza attack rate of 7.50%, this being the mid-point of global influenza attack rates (between 5% and 10%) reported by the World Health Organization for all adult populations, that is, not specific for populations aged 65+³¹. Probabilities for the vaccinated cohort were calculated by multiplying the baseline influenza attack rate for the unvaccinated cohort by the vaccine effectiveness (VE) of HD TIV and aTIV versus no vaccination.

Probability of hospitalization

The probability of hospitalization was calculated using age stratified rates for pneumonia and influenza related

hospitalizations, defined as ICD10 codes J09-J18, from a longitudinal study³². We applied a single baseline probability for hospitalization across both the vaccinated and unvaccinated cohorts as the original study³² utilized Clinical Practice Research Database (CPRD) and Hospital Episode Statistics (HES) data, therefore establishing rates in a UK population where SD TIV was available. Probabilities for the vaccinated cohort were then adjusted based on VE for HD TIV and aTIV versus no vaccination.

Vaccination effectiveness

The key inputs into the economic model were: (i) VE, which measures the proportion reduction in cases among vaccinated versus unvaccinated populations; and (ii) relative vaccine effectiveness (rVE), which measures the proportion reduction in cases for populations vaccinated with one vaccine relative to another vaccine. Due to restrictions in data availability, VE for both HD TIV and aTIV (versus no vaccination) were estimated *indirectly* by rearranging rVE estimates for HD TIV and aTIV versus SD TIV and VE estimates for SD TIV (versus no vaccination).ⁱⁱ

We calculated the VE for SD TIV on LCI cases as a weighted average across influenza A, matched B, and mismatched B. The VE for influenza type A and matched B were both equal to 46% based on a pooled estimate across both lineages in observational evidence across the 2005–2008 UK influenza seasons³³. The mismatched status of influenza B was defined as a poor match between the vaccine and the circulating strain. Consequently, mismatched influenza B was assigned a reduced VE of 28% based on a published cost-effectiveness study³⁴. To pool VE for SD TIV, we estimated the mean percentage of circulating influenza virus from annual Public Health England (2010–2017) influenza reports as equal to 78% for influenza A, 10.7% for matched influenza B, and 11.3% for mismatched influenza B³⁰. The VE for SD TIV on hospitalizations could not be disaggregated and was set equal to 28% across all strains and subtypes based on a published cost-effectiveness study³⁴.

The rVE against lab-confirmed influenza of HD TIV versus SD TIV for the LCI pathway was sourced from a phase 3b/IV

randomized efficacy trial and equal to 24.2%⁸. Meanwhile, the rVE for HD TIV versus SD TIV on hospitalization endpoints was equal to 24.3%, this being obtained from a meta-analysis informed by two RCTs and three observational studies and covering multiple influenza seasons⁶. The rVE estimates indicate that for every 100 influenza cases in populations vaccinated with SD TIV, there would be roughly 76 cases in populations vaccinated with HD TIV (i.e. a 24% reduction).

Despite large observational studies being conducted to evaluate the effectiveness of influenza vaccines¹², due to inconsistent results from season to season²², randomized clinical trials (RCTs) remain the gold standard when assessing vaccine efficacy. Therefore, the economic model used values from RCTs whenever available.

The 2021 Ständige Impfkommision (STIKO) guideline systematic review and the 2020 European Centre for Disease Prevention and Control (ECDC) systematic review both identified one RCT reporting on rVE of HD-TIV compared with conventional vaccination in LCI. The rVE of aTIV in preventing LCI was compared only with unvaccinated populations or standard dose vaccines in non-randomized studies^{35,36}. No RCTs or observational studies compared aTIV and HD-TIV directly^{35,36}. Due to this scarcity of trial-based evidence and heterogeneous findings from observational studies, three different rVE scenarios were investigated for aTIV versus SD TIV. The base case (scenario 1) applied an rVE of 0% on both LCI and hospitalization endpoints reflecting NACI evidence assessments and the non-significant differences identified between aTIV and SD TIV in multiple observational studies^{22,23,26}. The second scenario applied an rVE of 6% on LCI endpoints based on a non-significant effect size from a Spanish observational study³⁷, and assumed an rVE of 10% on hospitalization endpoints.ⁱⁱⁱ Finally, scenario 3 applied the largest rVE effectiveness estimates of 12% on LCI and 20% on hospitalization endpoints: The former estimate was informed by an observational study in an Italian population³⁸ which has been challenged for its academic quality by NACI²⁶; the latter estimate mirrored an assumption in a published economic model assessing the cost-effectiveness of aTIV versus SD TIV, however this was not based on either

Table 2. Vaccine effectiveness/relative vaccine effectiveness.

Vaccine	Input parameter	Input value			Source
		Base case (scenario 1)	Scenario 2	Scenario 3	
HD TIV	rVE vs SD TIV (LCI)	24.2%	24.2%	24.2%	RCT ⁸
	rVE vs SD TIV (hospitalization)	24.3%	24.3%	24.3%	Meta-Analysis ⁶
aTIV	rVE vs SD TIV (LCI)	0%	10%	20%	See below ^a
	rVE vs SD TIV (hospitalizations)	0%	6%	12%	See below ^b
SD TIV ^c	VE (matched LCI) ^d	46%	46%	46%	Public Health England (PHE) economic model ³⁴
	VE (mismatched LCI) ^e	28%	28%	28%	Public Health England (PHE) economic model ³⁴
	VE (hospitalizations) ^f	28%	28%	28%	Public Health England (PHE) economic model ³⁴

^aaTIV rVE versus LCI: S1 assumed based on non-significant effects from observational evidence²²; S2 mid-point assumption based on no clinical or observational evidence; S3 assumption mirroring estimate applied in cost-effectiveness study based on no clinical or observational evidence³⁹.

^baTIV rVE versus pneumonia hospitalization: S1: Assumed based on non-significant effects from observational evidence²²; S2: Assumption from an observational study³⁷, the outcome was non-significant rVE versus influenza hospitalization (actual trial endpoint did not specify pneumonia); S3: Observational study³⁸ outcome non-significant rVE for the full influenza season.

^cAll VE for SD TIV is versus no vaccination.

^dVE for SD TIV versus no vaccination for matched influenza type A and type B.

^eVE for SD TIV versus no vaccination for mismatched influenza type B.

^fVE for SD TIV versus no vaccination on hospitalizations endpoint. Actual endpoint is “influenza complications”, not specifying pneumonia hospitalizations, but such data is not available.

RCT or observational data³⁹. All VE and rVE for the base case and scenario analyses are summarized in Table 2.

Probability of general practitioner visits

We calculated the probability of GP attendance following LCI separately for the 65–74 and 75+ age groups by dividing the total number of GP attendances due to influenza by the total number of people in the population with influenza (i.e. influenza attack rate multiplied by total population size). Data for the numerator were sourced from a published linear regression analysis estimating the total number of people in England and Wales who attended influenza related GP appointments. This was stratified by age in a database utilizing Hospital Episode Statistics (HES)⁴⁰.

Probability of mortality

The probability of premature mortality following hospitalization was obtained directly from published literature which used HES data to estimate the percentage of patients who died following hospitalization for influenza or pneumonia by age group, defining cases by ICD-10 code (J09-18^{iv})⁴¹. We obtained age-group specific absolute risks of mortality due to any cause from age- and gender-weighted life tables published by the Office for National Statistics⁴².

Quality adjusted life years

We calculated gender weighted life expectancies by age group using the mortality data from UK life tables to establish the expected remaining life years for subjects who survived the influenza season⁴². Total quality adjusted life years (QALYs) were then calculated by aggregating health utilities across subjects' remaining life years whilst incorporating utility reductions for any LCI cases or hospitalizations. Baseline utility values by age group are reported in Table 3 and were obtained from the published literature based on self-reported UK EQ-5D scores⁴³. We applied utility reductions per LCI case using influenza specific utility values from an HTA report⁴⁴ and assuming a duration of infection equal to 6 days. The total disutility per influenza related hospitalization was obtained from a published cost-effectiveness analysis which reported summed QALY detriments for hospital patients with uncomplicated influenza like illness and

pneumococcal pneumonia³⁴. All QALYs occurring after 12-months were discounted at 3.5%.

Unit costs

All unit costs are reported in Table 3. Vaccination costs for HD TIV and aTIV were obtained from Sanofi/Seqirus list prices and applied to the proportion of the population who received the vaccination (i.e. the vaccination coverage rate). All administration costs were excluded as this was an incremental analysis and both vaccination procedures and coverage rates were assumed to be equivalent. GP consultation costs were obtained from a published UK based cost-effectiveness analysis which reported the mean primary care staff and prescription costs (2008 GB£) per influenza episode utilizing the General Practice Research Database⁴⁵. Costs (2008 GB£) per hospitalisation were taken from the same cost-effectiveness study, which calculated the mean length of stay for all LCI hospitalizations (ICD code J10) by daily NHS reference costs (tariff DZ11B for lobar, atypical or viral pneumonia without complications)⁴⁵. All unit costs from published literature were inflated to 2018 values using the Hospital and Community Services Pay and Prices index⁴⁶. Discounting was not required for costs as these occurred across a single influenza season, within a year of vaccination.

Uncertainty analysis

Uncertainty was investigated for the primary analysis using one-way deterministic sensitivity analyses (DSA) which individually varied input parameters and recalculated ICERs according to the altered values. The DSA was limited to the scenario with the highest efficacy rates for aTIV. A Tornado plot was generated with parameter ranges equal to 95% confidence intervals or $\pm 15\%$ of the mean if confidence intervals were not available. The DSA included scenarios which reduced the rVE of HD TIV versus SD TIV from (i) 24.3% to 17% for influenza related hospitalizations, and (ii) 24.2% to 9.70% for LCI cases. In addition, we investigated uncertainty around HD TIV vaccination costs by identifying the economically justifiable price (EJP). We calculated the EJP by identifying the maximum price at which HD TIV remained cost-effective, that is, achieved an ICER below the CE threshold of £20,000 and £30,000 per QALY.

Table 3. Unit costs (2018 GB£) and QALYs.

Parameter	Input value	Source
Costs		
Cost per aTIV vaccine	£9.79	List Prices
Cost per HD TIV vaccine	£20.00	List Prices
Cost per GP consultation	£103.9	CE Analysis ⁴⁵
Cost per hospitalization	£5,633.53	CE Analysis ⁴⁵
Quality adjusted life years		
Utility general population (65–74 only)	0.773	Published self-report EQ-5D scores ⁴³
Utility general population (75+ only)	0.703	Published self-report EQ-5D scores ⁴³
Utility (influenza)	0.2947	HTA report ⁴⁴
Disutility (hospitalization)	0.018	CE Analysis ³⁴
Mean influenza duration (days)	6	Assumption
Mean life expectancy (year)		
Age 64–75	80.8	Calculation based on ONS UK Life Tables ⁴²
Age 75+	88.3	

Table 4. Model inputs used in the secondary analysis (all respiratory hospitalizations).

Parameter	Input	Source
Hospitalization rates per 100,000		
65–74 years	1,638	HES 2015–2018 ⁵⁷
75+ years	4,577	
Vaccine effectiveness (versus respiratory hospitalizations)		
TIV SD	30%	Assumption
rVE TIV HD vs TIV SD	27%	Correspondence with authors of RCT ⁸
rVE TIV HD vs aTIV	12%	Observational study ²⁷
Cost per hospitalization (2018, GB£)	£2,920	Analysis using HES 2017/2018 data (unpublished)

Table 5. Cost-effectiveness results for HD TIV versus aTIV (2018 GB£).

	Primary analysis ^a (influenza/pneumonia hospitalizations)			Secondary analysis (respiratory hospitalizations)
	Base case (scenario 1)	Scenario 2	Scenario 3	
Incremental costs (population)	£22,144,118	£35,700,436	£49,256,755	£13,685,101
Incremental QALYs (population)	11,460	8,539	5,618	4,888
ICER (£/QALY)	£1,932	£4,181	£8,767	£2,800
Total hospitalizations avoided	9,161	6,899	4,637	21,128
Cost per hospitalization avoided	£2,417	£5,175	£10,622	£647

^aResults aggregated across all population groups aged 65+ (65–74 low risk; 65–74 high risk; 75+ all risk).

Table 6. Net population impact of HD TIV and aTIV for one influenza season (2018 GB£).

	aTIV			HD TIV
	Base case (scenario 1)	Scenario 2	Scenario 3	
Vaccination costs	£72,607,220	£72,607,220	£72,607,220	£148,329,357
Prescription costs	£168,614	£158,958	£149,301	£145,245
Cost of GP visits	£14,026,024	£13,222,753	£12,419,482	£12,082,108
Hospitalization costs*	£302,380,130	£289,636,739	£276,893,347	£250,769,395
Total healthcare costs	£389,181,989	£375,625,670	£362,069,351	£411,326,107
Influenza cases	544,292	513,120	481,949	468,857
GP visits	134,892	127,166	119,441	116,196
Hospitalizations	53,675	51,413	49,151	44,514
Influenza related deaths	12,526	11,985	11,444	10,335

A secondary analysis was also conducted which expanded the influenza and pneumonia hospitalizations outcome to include hospitalizations due to any lower respiratory infection. Whilst providing a less specific endpoint for influenza, the outcome was selected for the secondary analysis to include data from a retrospective observational study which directly compared the rVE of HD TIV and aTIV²⁷. For the secondary analysis, we estimated rates of hospitalization by age group using HES databases including all non-elective admissions with primary respiratory diagnosis (defined as ICD10 codes J00–J99) in four November–May influenza seasons between 2015 and 2018⁴⁷. Vaccine efficacy rates for HD TIV and aTIV (versus no vaccination) were calculated by rearranging equations for rVE of HD TIV versus aTIV and VE for SD TIV (Table 4).^v

Results

Primary analysis: pneumonia/influenza hospitalizations

High dose TIV was found to be cost-effective in adults aged 65+ in England and Wales when compared with aTIV, assuming the lower CE threshold estimate equal to £20,000 (Table 5). The results for the primary analysis were robust across all three aTIV influenza/pneumonia hospitalization effectiveness scenarios with ICERs equal to £1,932 per QALY

for the base case (scenario 1), £4,181 per QALY for scenario 2, and £8,767 per QALY for scenario 3.^{vi}

The net impact of HD TIV versus aTIV on population health and NHS costs is displayed in Table 6. Across a single influenza season, HD TIV was predicted to result in substantially fewer cases of laboratory confirmed influenza, hospitalizations, and influenza-related deaths when compared with populations vaccinated with aTIV. Across the lifetime, HD TIV achieved 11,460 (scenario 1), 8,539 (scenario 2), and 5,618 (scenario 3) additional QALYs when compared with aTIV. Populations who received HD TIV had a higher total cost burden, with incremental population costs versus aTIV equal to £22,144,118 (scenario 1), £35,700,436 (scenario 2), and £49,256,755 (scenario 3). Differences in healthcare costs were driven by higher vaccination costs for HD TIV, which exceeded cost savings attributable to reductions in primary and secondary healthcare resources required for influenza treatment (Table 6).

The EJP analysis indicated that uncertainty in the price of HD TIV was not likely to impact on the cost-effectiveness findings. The price of HD TIV could be increased from £20.00 (list price) to £47.91 (scenario 1), £38.21 (scenario 2), and £28.50 (scenario 3) whilst remaining cost-effective versus aTIV at a CE threshold of £20,000 per QALY. When applying a CE threshold of £30,000 per QALY, the EJP of HD TIV increased to £63.37 (scenario 1), £49.72 (scenario 2), and £36.08 (scenario 3).

Table 7. Cost-effectiveness results by age group: HD TIV versus aTIV (2018 GB£).

	Primary analysis (Influenza/Pneumonia hospitalizations)		
	Base case (scenario 1)	Scenario 2	Scenario 3
Age 65–74			
Hospitalizations avoided (population)	1,463	1,102	740
Incremental costs (population)	£27,712,717	£30,143,609	£32,574,500
Incremental QALYs (population)	1,955	1,424	893
ICER (£/QALY)	£14,175	£21,165	£36,460
Age 75+			
Hospitalizations avoided (population)	7,699	5,798	3,897
Incremental costs (population)	–£5,568,600	£5,556,828	£16,682,255
Incremental QALYs (population)	9,505	7,115	4,724.79
ICER (£/QALY)	Dominant	£781	£3,533

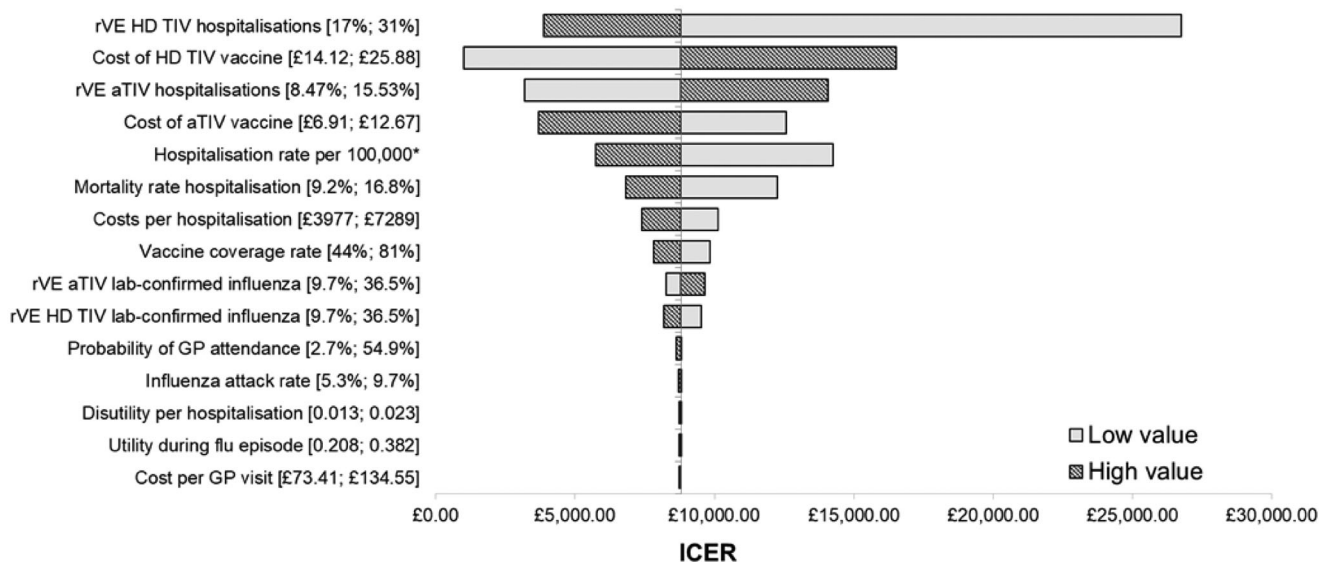


Figure 2. Tornado plot illustrating DSA results for aTIV Scenario 3. * Hospitalization rates varied simultaneously for different age groups: Age 65–74 (low value = 135; high value = 247); age 70+ (low value = 634; high value = 1162).

Age group specific results (primary analysis, base case scenario)

Results for the primary analysis and base case rVE for aTIV differed when stratifying populations by age group. The ICER for HD TIV versus aTIV decreased when populations were restricted to those aged 75 years and older, therefore remaining cost-effective at CE thresholds <£20,000 for all scenarios. In contrast, the ICERs increased when populations were limited to those aged 65–74: HD TIV remained cost-effective for the rVE aTIV effectiveness assumption in scenarios 1 and 2 but was not cost-effective for scenario 3 where ICERs exceeded the upper CE threshold of £30,000. The difference in results across age groups was driven by higher rates of hospitalization for people aged over 75 resulting in substantially more hospitalizations avoided for populations who received HD TIV (Table 7).

Secondary analysis (all respiratory hospitalizations)

Cost-effectiveness results were robust for the secondary analysis, which used direct rVE evidence for HD TIV versus aTIV on expanded endpoints including all respiratory hospitalizations. The ICER for HD TIV versus aTIV was equal to £2,800,

with incremental population costs equal to £13,685,101 and incremental lifetime population QALYs equal to 4,888. The economic analysis estimated 21,128 respiratory related hospitalizations per influenza season would be avoided if adults 65+ were vaccinated with HD TIV rather than aTIV.

Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted for aTIV scenario 3 as this was the most uncertain scenario with an ICER closest to the CE threshold. Results were robust with HD TIV remaining cost-effective versus aTIV for all DSA scenarios when applying a £30,000 per QALY CE threshold and all but one DSA scenario when applying the £20,000 per QALY CE threshold (Figure 2). The DSA identified the rVE of HD TIV on hospitalization outcomes as an important area of uncertainty as reducing parameter values from 24.2% (base case) to 17.17% (DSA low value) increased the ICER to £26,707. In contrast, the DSA which reduced the rVE of HD TIV on LCI cases from 24.3% (base case) to 9.70% (DSA low value) had a minimal impact only increasing the ICER slightly to £9,562. The DSA identified vaccination costs and hospitalization rates as drivers of the cost-effectiveness, meanwhile

varying epidemiological utility had a relatively minor impact on the ICER (Figure 2).

Discussion

This cost-utility analysis using the best available evidence to date identified HD TIV as cost-effective versus aTIV in populations aged 65+, when adopting a healthcare payer perspective and assuming a CE threshold of £20,000 per QALY. The additional vaccination costs associated with HD TIV were outweighed by substantial benefits achieved through preventing cases of influenza and subsequent reductions to health morbidity, mortality, and primary and secondary healthcare costs. Our results are informed by rVE and rely on a positive VE for SD TIV. The VE for SD TIV may be substantially reduced if there is a poor match between the vaccine and circulating influenza strains⁴. Therefore, our results are most applicable to future influenza seasons with similar levels of influenza (78% influenza A, 11% for matched influenza B, and 11% mismatched B) and VE for SD TIV (46% influenza A, 46% influenza B, 28% mismatched B).

The results of the uncertainty analysis showed the cost-effectiveness of HD TIV was robust to changes in the majority of parameter values. Due to the model assumptions, the rVE of HD TIV versus SD TIV on hospitalizations was a key driver of cost-effectiveness. However, even when using an rVE parameter value equal to the lower 95% confidence interval (as reported in the multi-season influenza meta-analysis⁶) the resultant ICER was less than the upper CE threshold of £30,000 per QALY recommended in the NICE reference case²⁹. Reductions in the number of hospitalizations are likely to be an important outcome for healthcare providers, particularly during busy winter seasons when demand for healthcare and hospital bed days often exceeds resource supply⁴⁸.

This is the first economic analysis to compare the cost-effectiveness of HD TIV with aTIV. Findings from this analysis could be used to inform future UK vaccination recommendations which require both clinical and cost-effectiveness evidence. We estimate a substantial reduction in the number of influenza cases, influenza-related hospitalizations, and influenza-related deaths with a relatively modest increase in vaccination costs in adults 65+ who are offered HD TIV rather than aTIV.

Our model estimated around 500,000 cases of influenza occur in adults 65+ during a single influenza season in England and Wales, costing the NHS roughly £400 million and resulting in 50,000 hospitalizations and over 10,000 deaths. Roughly 70% of the cost burden and over 85% of influenza related deaths occurred in populations aged 75 and over, despite this age group only containing around 45% of the total population in the model. The increasing health burden of influenza with age explains results from the scenario analysis where ICERs for HD TIV versus aTIV were decreased (i.e. increased cost-effectiveness) when populations were restricted to the 75 years and older age group. Based on findings from the published literature we assumed rates of pneumonia/influenza related hospitalizations are

over four times higher in those aged over 75s when compared with 65–74³², with the older population also twice as likely to die following hospitalization⁴¹.

The population impact of influenza is slightly higher in our analysis than annual estimates from published burden of illness studies. Green et al.⁴⁹ estimated mortality for adults 65+ in England and Wales ranged from 4,000 to 13,000 across six influenza seasons. Matias et al.⁴¹ estimated mean UK influenza deaths and hospitalizations for adults 65+ of 6,270 and 15,214, respectively. Meanwhile, Moss et al.⁵⁰ calculated UK 18+ hospitalizations due to influenza equal to 46,215 (2017/18) and 39,670 (2018/19). The primary driver of population outcomes in our model were the influenza attack rate and hospitalization rate. For HD TIV the DSA applying the lower attack rate reduced total influenza cases from 468,857 to 312,571 and the DSA applying the lower hospitalization rate reduced influenza deaths to 7,297 and hospitalizations to 31,439. Neither the attack rate nor hospitalization rate were key drivers of cost-effectiveness as both DSAs resulted in an ICER below £20,000 per QALY.

This analysis is subject to several limitations. Firstly, our literature review did not identify any clinical trial which directly established the rVE of HD TIV versus aTIV on influenza and pneumonia hospitalizations, the adopted primary endpoints. This gap is confirmed by the ECDC and STIKO systematic reviews that did not find head-to-head studies comparing aTIV and HD-TIV^{35,36}. Furthermore, both reviews concur on the scarcity of robust trial data and inconsistency of published evidence to inform rVE estimates of aTIV versus SD TIV; hence we could not identify nor conduct a robust indirect treatment comparison or network meta-analysis. This was in-line with the STIKO and ECDC guidelines, which only reported on one RCT estimating efficacy against LCI with HD-TIV compared with SD-TIV^{35,36} that we used for model inputs. Conversely, neither of these groups used observational studies to assess the impact of HD-TIV against LCI, and the ECDC guidelines noted that “pooled analyses of effectiveness data comparing adjuvant with non-adjuvanted vaccines was restricted by limited study numbers and statistical and clinical heterogeneity”³⁵. Consequently, vaccine benefits were estimated using the best available rVE estimates for HD TIV and aTIV versus a common comparator, SD TIV. The results from the primary analysis were supported by the secondary analysis which incorporated direct evidence for HD TIV versus aTIV on all respiratory hospitalization outcomes. It should be noted that the ECDC systematic review did identify observational studies to derive rVE estimates. However, the cost-effectiveness model in this study used RCT derived inputs where possible and assessed their uncertainty through sensitivity analysis. This is a limitation of the parameter inclusion criteria used as part of this study. Future studies are required to explore the estimated cost-effectiveness of influenza vaccines if observational studies were also included to derive rVE estimates.

Secondly, quadrivalent vaccines (both HD QIV and aQIV) were not modelled due to a lack of data. However, there is no reason to assume the comparative findings of HD TIV versus aTIV should differ from HD QIV versus aQIV. Essink

et al.⁵¹ found that aQIV induces a similar immune response as aTIV and has a comparable reactogenicity and safety profile. Adjuvant QIV has shown superior immunogenicity over aTIV against the additional B strain. Similarly, HD QIV is comparable to HD TIV in terms of reactogenicity and safety profile, but has a superior induced immune-response to HD TIV⁵². Given that the quadrivalent vaccine shows similar improvements over both the HD TIV and aTIV, it is likely that what applies for aTIV versus HD TIV will also apply to aQIV versus HD QIV.

Next, to account for underlying uncertainty in aTIV rVE parameter values, results were obtained for three effectiveness scenarios informed through an assumption in the published literature³⁹ and using observational study data^{37,38}. A scenario analysis in one of the observational studies by Mannino et al.³⁸ reported a higher aTIV rVE estimate (equal to 25%) than for the one for HD TIV, issued from an RCT. Whilst it is possible that the rVE of aTIV exceeds HD TIV, concurrent appraisals suggest it unlikely as: there is direct evidence of increased effectiveness for HD TIV versus aTIV on a wider outcome including all respiratory hospitalizations; the scenario analysis by Mannino et al.³⁸ was limited to the weeks with peak circulating influenza virus which may overstate effectiveness when compared with the studies conducted over a full influenza season⁶; and a systematic review found that only two out of six observational studies identified statistically significant increases in rVE for aTIV versus SD TIV²²; NACI and ECDC systematic reviews concluded on a lack of consistent evidence for aTIV superior to SD-TIV.

We were not able to combine GP attendance and hospitalization within a single influenza pathway due to differences in case definitions from the underlying evidence. Therefore, our decision model was structured to include non-mutually exclusive pathways where populations could contract both LCI and attend hospital due to influenza/pneumonia. Both pathways were included to avoid underestimating the cost-effectiveness of HD TIV as both GP visits and hospitalization are key contributors to the overall health and economic burden of influenza^{39,45}. We avoided double counting effects on life years by restricting mortality effects to the hospitalization pathway. Minimal double counting of influenza related disutility may have occurred if people had both LCI and a hospital attendance, however disutility was not shown to impact cost-effectiveness in the DSA. Our decision model may underestimate cost-effectiveness for HD TIV as it does not model influenza population transmission. Herd effects could have been included using a dynamic transmission model, however, this type of modelling was not selected given the disparity between data requirements and data availability.

Due to a lack of available data, vaccine related adverse events (AEs) were not included in the analysis, but this is not likely to impact the findings given the strong safety profiles for both HD TIV⁵² and aTIV. Furthermore, a recent study has shown there to be similar safety profiles between both vaccines in those aged 65 years and older⁵³. Limited data also meant the age 65–74 risk groups were only differentiated by the likelihood of a GP visit following infection. Higher risk

populations may have increased vaccine coverage, hospitalization, and mortality rates and therefore grouping parameter values may have underestimated the cost-effectiveness of HD TIV in this sub-population. Furthermore, the HD TIV cost-effectiveness may have been underestimated for all risk and age groups as influenza is likely to be linked to several cardiorespiratory complications that were not included within the influenza related hospitalization endpoint.

Additionally, the high-risk group was defined as those with respiratory and heart diseases as these individuals are likely to experience the biggest impacts of influenza. The high-risk group could be expanded in future studies to also include those with diabetes, renal diseases, immunocompromised and other chronic conditions, providing there is sufficient data available to allow for their inclusion in the analysis.

COVID-19

It should be noted that the inputs collected to feed the cost-effectiveness model were based on data prior to the COVID-19 pandemic, and therefore they may change in the forthcoming years. On one hand, it is possible that public health measures (e.g. masks, social distancing, and lockdowns) would decrease the spread of respiratory viruses and result in higher ICERs (i.e. HD TIV less cost-effective). Furthermore, by missing two influenza seasons, unpredicted mutations may result in vaccines that are less effective in general. On the other hand, due to this absence of influenza virus circulation, a strong epidemic rebound may occur⁵⁴ that would decrease the ICERs (i.e. HD TIV more cost-effective). Moreover, in light of the COVID-19 pandemic, influenza vaccine coverage increase (e.g. people more likely to get the influenza vaccine, and/or co-administration of influenza and COVID-19 booster) would result in further reduction of ICERs. Finally, the impact of COVID-19 on future government overall spending on immunization – and its prioritization – is currently unknown, as well as how the broader benefits of vaccination could be considered when assessing vaccines' value for the society. Future work is required to update parameter values and reassess cost-effectiveness when relevant data becomes available regarding the impact of the COVID-19 pandemic.

Conclusion

This is the first study to establish the cost-effectiveness of HD TIV versus aTIV in a population aged over 65. In the UK, vaccination with HD TIV instead of aTIV substantially reduced influenza related GP visits, hospitalizations, and mortality. The analysis was limited by a lack of robust and consistent effectiveness data for aTIV, which should be a priority area for future research.

Notes

- i. Further discussion of the non-mutually exclusive pathways is provided in the Limitations section.

- ii. See [Supplementary Material A](#) for detailed methodology.
- iii. The rVE estimate of 10% on hospitalization endpoints was applied as this is the mid-point between the lower and upper values applied in the base case scenario (0%) and scenario 3 (20%). The proportional increase in rVE estimates for aTIV on hospitalization endpoints is consistent with the proportional increase on LCI endpoints across each scenario (0%, 6%, 12%).
- iv. Mortality estimates for the scenario analysis were obtained from published study by Matias et al. (2016)⁴¹, who defined hospitalization due to any respiratory disease using ICD codes J00-99.
- v. See [Supplementary Material B](#) for full details.
- vi. See [Table 2](#) for rVE of aTIV per scenario.

Transparency

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Declaration of financial/other relationships

IG, NL, FPA and SC are employees of Sanofi Pasteur, which manufactures HD-TIV and may/may not hold shares in the company.

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