Supplementary material

Example search strategy

1 Influenza, Human/
2 influenza/
3 flu/
4 influenza virus/
5 seasonal flu/
6 1 or 2 or 3 or 4 or 5
7 Vaccination/
8 vaccine/
9 7 or 8
10 Economics/
11 exp "costs and cost analysis"/
12 Economics, Dental/
13 exp economics, hospital/
14 Economics, Medical/
15 Economics, Nursing/
16 Economics, Pharmaceutical/
17 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
18 (expenditure$ not energy).ti,ab.
19 value for money.ti,ab.
20 budget$.ti,ab.
21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 ((energy or oxygen) adj cost).ti,ab.
23 (metabolic adj cost).ti,ab.
24 ((energy or oxygen) adj expenditure).ti,ab.
25 22 or 23 or 24
26 6 and 9 and 21
27 26 not 25
28 letter.pt.
29 editorial.pt.
30 historical article.pt.
31 28 or 29 or 30
32 27 not 31
33 exp animals/ not humans/
34 32 not 33
35 limit 34 to yr="2014 -Current"

Blank data extraction form: key study attributes and critical appraisal

Subject of the study	
Health technology	
Disease	
Type of intervention	
Hypothesis and/or study question	
Key elements of the study	
Economic study type	
Study population	
Modelling and statistical extrapolation	
Setting	
Dates to which data relate	
Link between effectiveness and cost data	
Clinical evidence	
Clinical and epidemiological data	
Parameter value	
Data sources	
Methods to obtain data	
Economic analysis	
Summary measure of health benefit reported	
Type of measure of health benefit	
Utility or WTP benefit measures - method of valuation	
Discount rate for utility or WTP	
Economic analysis	
Whose direct cost	
Which direct costs	
Source of resource use	
How prices estimated	
Costs discounted	

Date of price data	
Marginal or average costs	
Resource use separately reported	
Costs adjusted for inflation and how	
Costs excluded	
Adjustments to costs	
Budget impact (yes or no)	
Currency	
Economic analysis	
Why include/exclude productivity costs	
Source of cost and quantity data	
Were costs and quantities separately reported	
When resources measured	
Discounted? Why? Relevant?	
Statistical analysis cost	
Point estimates used (yes or no)	
Descriptive statistics used	
Statistical tests used	
Parameters tested	
Study powered to detect differences?	
Analysis uncertainty	
Parameter uncertainty investigated (yes or no)	
How parameter uncertainty investigated	
Uncertainty investigated all parameters (yes or no)	
If not all parameters, which investigated	
Methods or rationale for deterministic analysis	
Probabilistic analysis were distributions defined	
Was structural uncertainty assessed	
Was variability in data investigated	

Estimated benefits	
Total benefits for each intervention	
Duration of benefits	
Were side effects/adverse events included	
Net (incremental benefit) of intervention-comparator	
Statistical test of differences in benefit	
Sensitivity analysis of benefits only	
Cost results	
Net (incremental) cost) of intervention-comparator	
Statistical test of differences in cost	
Sensitivity analysis of costs only	
Results of any currency conversion	
Synthesis	
Was synthesis reported (yes or no)	
If no, was rationale for no synthesis reported	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Sub-group analysis or sensitivity analysis (yes or no)	
Type of sub group or parameters varied in sensitivity analysis	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Authors conclusions	
Conclusions	
Choice of comparators	
Was the choice of intervention explicitly justified (yes or no)	

Was the choice of intervention implicitly justified (yes or no)	
Key reasons for choice of intervention	
Was the choice of comparator explicitly justified (yes or no)	
Does the choice of intervention or comparator affect the	
Modelling	
Model structure/technique clearly reported	
Input data clearly reported	
Input data sources clearly reported	
Uncertainty investigated (yes or no)	
Methods used to assess uncertainty	
Results of uncertainty assessments clear (yes or no)	
Other positive or negative comments on model	
Assessment of validity of model - robust? - biased?	
Validity effectiveness	
Sources of data for model parameters	
Were data combined to estimate parameters (yes or no)	
If yes, were methods clearly reported (yes or no)	
If yes, what methods used to combine data	
How were data identified for inclusion	
What inclusion criteria	
Justification for choice of data (yes or no)	
If yes, what was justification	
What was quality of evidence used to derive parameter estimates	
Validity of health benefit	
Summary measure of benefit (yes or no)	
If yes, how derived	
How were utility values measured or identified	
To what extent does the measure of benefit cover all relevant	
Overview of costs	

Were all relevant costs included for perspective (yes or no)	
If no, what omitted	
For each cost category, were all relevant cost items included (yes	
If no, what omitted	
Do any omissions affect results or authors conclusions (yes or no)	
Cost details	
Sources of resource use, price and cost data	
Price adjustments (yes or no)	
If yes, what price adjustments	
Costs discounted (yes or no)	
If no, appropriate	
Were any resource use, price or cost data stochastic (yes or no)	
If yes, any statistical analysis	
Cost data adequately reported yes/no	
If no, why	
Other cost issues	
Costs valid (unbiased) (yes or no)	
If no, why	
Costs generalisable (yes or no)	
If no, why	
Other issues	
Comparisons with other studies (yes or no)	
If yes, results of comparison	
Generalisability addressed (yes or no)	
If yes, how	
Selective reporting of results (yes or no)	
If yes, in what ways	
Conclusions reflect scope/data	
Authors report the limitations (yes or no)	

If yes, what	
Any other shortcomings yes/no	
If yes, what	
Implications	
Authors recommendations	
Recommendations suggested by abstractor	
Implications reported by authors	
Implications suggested by abstractor	
Related publications	
Related publications	
Important to review for model	
Important to review for systematic review paper	
Focus on key model attributes	
Static or dynamic	
Stochastic or deterministic	
Aggregate or individual	
Discrete or continuous	
Key: ICER, incremental cost-effectiveness ratio; WTP, willingness to pay threshold.	

Adapted from: [22,23]

Table summary of critical appraisal

Study	**Studies reporting clearly**
Research question	100% [26–33]
Study design	25% [29,30]
Perspective	87.5% [26–28,30–33]
Intervention	100% [26–33]
Comparators	100% [26–33]
Study population	100% [26–33]
Method of economic evaluation	87.5% [26–33]
Data collection	
Source(s) of effectiveness estimates	87.5% [26,28,30–33]
Methods of synthesis used to source effectiveness estimates (if applicable)	37.5% [26,30,33]
Methods used to value health states and benefits	87.5% [26,28–33]
Quantities of resource use and costs reported separately	62.5% [26,28,29,31,33]
Methods for resource use and unit costs	87.5% [26,28,29,31,33]
Price year	62.5% [28–33]
Price adjustments for inflation or currency conversion	12.5% [29]
Analysis and interpretation of results	
Time horizon	87.5% [26,28–33]
Discount rate (if applicable)	100% [28–33]
Explanation given if cost or benefits were not discounted (if applicable)	100% [26,27]
Statistical test(s) and confidence intervals given for stochastic	12.5% [26]
Sensitivity analysis methods	100% [26–33]
Choice of variables for sensitivity analysis	87.5% [26,28–33]
Ranges used in sensitivity analysis	100% [26–33]
Appropriate comparisons	100% [26–33]
Incremental analysis reported	100% [26–33]
Outcomes presented disaggregated and aggregated	25% [28,33]
Study question answered	100% [26–33]
Conclusions relevant to study	100% [26–33]
Limitations	62.5% [26,28–30,33]
Generalisability issues	25% [28,29]

Comparisons to other studies	37.5% [26,28,30]

Summary of sensitivity analysis

Study	Description	Key results (€, 2014)
Allsup et al (2004)	• One-way sensitivity analyses conducted on: target coverage, hospitalisation risk, mortality risk, vaccine efficacy, incident rates, promotion costs, hospitalisation costs and life expectancy	• Vaccination was judged to be not cost effective under any scenario when compared with no intervention. • The most influential parameters were vaccine efficacy, influenza hospitalisation and the risk of complications. • ICER ranged from €73,342 to €2,646,693 (life-year)
Baio et al (2006)	• The use of an object-oriented influence model Bayesian network model accounts for uncertainty implicitly.	• Pairwise comparisons demonstrated that the adjuvanted vaccine was over 90% likely to be cost-effective versus standard vaccine at a willingness to pay threshold of €0. At the same threshold adjuvanted was over 75% cost-effective versus no vaccination and standard vaccine was over 80% cost-effective versus no vaccination.
Brydak et al (2012)	• One-way sensitivity analysis (all parameters except vaccine price) • Probabilistic sensitivity analysis	• One-way sensitivity analysis stated that all scenarios (for reimbursed vaccination versus no intervention) were cost effective (below a WTPT 3 GDP per capita). • Probabilistic sensitivity analysis concluded that reimbursed vaccination was 79.93% likely to be cost effective (below the threshold of 3 GDP per capita). • The most influential parameters were vaccine efficacy against death, population utilities, outcome discount rate and the influenza attack rate. • ICER ranged from €9,070 to €21,107 (QALY).
Lugner et al (2012)	• One-way sensitivity analysis was conducted on vaccination cost, influenza transmissibility, coverage and pre-existing immunity	• The vast majority of tested scenarios had ICERs below €15,000 for vaccination versus no intervention. The least cost effective scenario occurred when there was high pre-existing immunity, low transmissibility, direct costs alone were considered and there was a higher vaccine cost. • The most influential parameter was the pandemic scenario (which influences transmissibility/incidence). The other main influential parameters differed according to country.

		• ICER ranged from dominated to €43,006.
Meier et al (2015)	• One-way sensitivity analysis was conducted on the discount rate, vaccine efficacy (degree of matching), influenza incidence and influenza complication rates • Probabilistic sensitivity analysis	• All scenarios indicated that vaccination would be cost-effective under a threshold of £30,000/QALY. • Probabilistic sensitivity analysis concluded that a total of 68% of the simulations were below a threshold of £20,000/QALY, and 87% were below a threshold of £30,000/QALY. • The most influential parameters were circulation of influenza A and the degree of matching between the trivalent vaccine and the circulating influenza B lineages. • ICER ranged from dominant to €25,483 (QALY).
Piercy et al (2004)	• One-way sensitivity analysis was conducted on the discount rate, life expectancy and the influenza incidence rate	• The adjuvanted vaccination was judged to be cost effective (versus standard vaccination) under all scenarios tested. • ICER ranged from dominated to €26,383 (life-year).
Postma et al (1999)	• One-way sensitivity analysis was conducted on pneumonia related hospitalisation rates, mortality risk and hospitalisation bed days, vaccine efficacy and the discount rate	• All tested scenarios resulted in cost effectiveness results (below €12,500 ICER per life-year gained). • The most influential parameters for the net cost were risk of complications (hospitalisation and mortality). • Broken down ICER results were not provided for sensitivity analysis.
Scuffham and West (2002)	• One-way sensitivity analysis was conducted on vaccination effectiveness, side effects, vaccine price, years per life lost, discount rate, coverage and the attack rate	• The majority of tested scenarios were cost saving when vaccination was compared to no intervention. With the exception of a vaccination price increase. • The most influential parameters were vaccine price, vaccine effectiveness and the discount rate for outcomes. • Broken down ICER results were not provided for sensitivity analysis (only net costs).
Key: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year; WTPT, willingness to pay threshold.		