



Review

Inclusion of the value of herd immunity in economic evaluations of vaccines. A systematic review of methods used



Liv S. Nymark^{a,b,c,*}, Tarang Sharma^{d,e}, Alexander Miller^f, Ulrika Enemark^{a,b}, Ulla Kou Griffiths^{g,h}

^a Department of Public Health, Aarhus University, Bartholins Allé 2, DK-8000 Aarhus C, Denmark

^b Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serums Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark

^c Department of Health Services Research & Policy, London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK

^d Nordic Cochrane Centre, Rigshospitalet, Blegdamsvej 9, DK- 2100 Copenhagen Ø, Denmark

^e Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 København N, Denmark

^f Independent Researcher, London, UK

^g Department of Global Health and Development, London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK

^h UNICEF, 3 UN Plaza, New York, NY 10007, USA

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ABSTRACT

Objective: The objectives of this review were to identify vaccine economic evaluations that include herd immunity and describe the methodological approaches used.

Methods: We used Kim and Goldie's search strategy from a systematic review (1976–2007) of modelling approaches used in vaccine economic evaluations and additionally searched PubMed/MEDLINE and Embase for 2007–2015. Studies were classified according to modelling approach used. Methods for estimating herd immunity effects were described, in particular for the static models.

Results: We identified 625 economic evaluations of vaccines against human-transmissible diseases from 1976 to 2015. Of these, 172 (28%) included herd immunity. While 4% of studies included herd immunity in 2001, 53% of those published in 2015 did this. Pneumococcal, human papilloma and rotavirus vaccines represented the majority of studies (63%) considering herd immunity. Ninety-five of the 172 studies utilised a static model, 59 applied a dynamic model, eight a hybrid model and ten did not clearly state which method was used. Relatively crude methods and assumptions were used in the majority of the static model studies.

Conclusion: The proportion of economic evaluations using a dynamic model has increased in recent years. However, 55% of the included studies used a static model for estimating herd immunity. Values from a static model can only be considered reliable if high quality surveillance data are incorporated into the analysis. Without this, the results are questionable and they should only be included in sensitivity analysis.

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* Corresponding author at: Department of Public Health, University of Aarhus, Bartholins Allé 2, DK-8000 Aarhus C, Denmark.

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1. Introduction

Vaccination confers both direct and indirect effects. The direct effect implies protection against disease in vaccinated individuals [1]. Indirect protection is when susceptible individuals avoid infection because the people who surround them are immunized [2]. The magnitude of indirect effects is a function of transmissibility of the infectious agent, population mixing patterns, distribution of vaccine, and distribution of immunity in the population [3]. ‘Herd immunity’ refers to population-scale immunity. The herd immunity threshold is defined as the proportion of a population that need to be immune in order to halt the spread of a communicable disease. The key parameter defining the herd immunity threshold is R_0 , which is the number of new infections generated by the first infectious individual in a completely susceptible population [2]. R_0 is affected by duration of infectivity of infected patients, infectiousness of the organism, and the number of susceptible people the infectious carrier is in contact with [3]. Measles is known to have a relatively high R_0 while diseases like Haemophilus influenza type b and polio spread less easily from person to person [4].

The natural disease mechanisms associated with communicable diseases require a dynamic model structure to simulate pathogen transmission among individuals. A dynamic approach captures both direct and indirect effects by modelling mixing patterns and risks of infection between vaccinated and unvaccinated individuals. Conversely, static models assume constant risk of infection and are therefore unable to account for disease transmission in populations. Hence, these are less likely to accurately estimate the full value of vaccination [5]. Compared to static models, dynamic models tend to show more favorable incremental cost-effectiveness ratios [6]. The exception to this is for vaccines where herd immunity can have a negative impact. This can be due to an upward shift in the age of the susceptible population or due to serotype replacement. Rubella has for instance substantially more severe consequences in the first trimester of pregnancy than in infants and the currently used pneumococcal vaccines lead to serotype replacement, which decreases the overall health impact of vaccinations. In such situations, a dynamic model would lead to a less favorable cost-effectiveness ratio than a static model.

In best practice guidelines on economic evaluation of vaccines, a dynamic model is recommended when the rate at which susceptible individuals acquire infection is reduced due to vaccination or when it is not possible to obtain a conservative estimate with a static model [7,8]. To our knowledge, a systematic review has not yet assessed to what extent economic evaluations of vaccines consider herd immunity and if so, which model approach is employed for this. The objectives of this review were to identify economic evaluations of vaccines that include herd immunity and assess which model properties were used.

2. Methods

2.1. Search strategy and data extraction

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [9]. We

searched PubMed/MEDLINE and Embase. Kim and Goldie conducted a systematic review detailing the modelling approaches used in cost-effectiveness analyses (CEAs) of vaccines from 1 st January 1976 to 31 st May 2007 [10]. We adopted their search to identify CEAs of vaccines from 1 st June 2007 to 31 st July 2015, and we searched for the same monovalent and multivalent vaccines (Table S1 in the supplement). Kim and Goldie used free text and MeSH terms, such as vaccin*, economic evaluat*, humans, and they limited the search to English language. A detailed description of the search process using rotavirus vaccine as an example is presented in Table S2. English-language, human vaccine CEAs were eligible for inclusion if the analysis had an explicit comparator, included both costs and health effects and presented a decision-analytic model. Two reviewers independently screened titles and abstracts and reviewed full-texts to determine inclusion of herd immunity in either the main analysis (base case) or sensitivity analysis. Kim & Goldie included 275 CEAs of vaccines in their review and we also screened these for inclusion of herd immunity. Vaccination will not induce herd immunity where human transmission (including via a vector) is non-existent. Humans are the end of the transmission cycle for rabies, Q Fever, Japanese Encephalitis and Lyme disease and tetanus does not have a transmission cycle. We therefore excluded CEAs of these vaccines.

2.2. Data analysis

Four main categories were used to classify CEA models: Static (type 1), dynamic (type 2), hybrid (type 3) and ‘model not clearly stated’ (type 4) (Table 1). Types 1 and 2 were based on Kim and Goldie’s framework for modelling approaches while type 3 was defined based on literature, which describes the hybrid model as combining characteristics of both dynamic and static models [11,12]. The number of type 1–4 models and associated subtypes were counted. For each vaccine type, the methods used to estimate herd immunity were described. We focused this description on the static models as it is especially for these that the methods are debatable and not well established. Dynamic models are in contrast primarily developed to account for herd immunity. For vaccine types with only few studies that included herd immunity, we also described the methods used in the dynamic models. We counted the number of CEAs that included herd immunity in their main analysis versus how many did so in the sensitivity analysis only (including scenario analyses). We extracted data on time horizon used and compared this between static and dynamic models. Main health outcomes measures were identified and counted.

Table 1
Classification of model types.

Model types
Type 1: Static (e.g. flow tree, cohort, Markov)
Type 2: Dynamic (e.g. transmission dynamic, SIR, SEIR)
Type 3: Hybrid (e.g. Markov and transmission dynamic)
Type 4: Not clearly stated (classification of model was not possible due to incomplete description)

Abbreviations: SIR = Susceptible-Infected-Recovered, SEIR = Susceptible-Exposed-Infected-Recovered.

2.3. Quality appraisal of included CEAs

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement consisting of 24 requirements was used [13]. Due to the importance of model choice to accurately predict herd immunity effects, we focused on item 15, which contains requirements for modelling: (1) clear description of model, (2) justification for choice of decision-analytical model, and (3) figure illustrating model structure provided. Data on the remaining 23 items in CHEERS were also extracted, such as the choice of health outcomes, measure of effectiveness, and estimation of resources and costs. For each of the 24 items we assigned a yes/no judgement and then calculated the total number of confirming items ('yes') to assess the overall quality of each study. Quality was assessed by two authors independently with disagreements resolved through discussion.

3. Results

3.1. Paper selection

The PubMed/MEDLINE and Embase databases searches from 2007 to 2015 returned 2215 papers after removing duplicates (Fig. 1). We screened 640 full-text articles, of which 285 did not meet the inclusion criteria. Commentaries, methods papers, reviews and abstracts totalled 195 records, 51 papers focused on non-vaccine outcomes, such as breastfeeding, stockpiling and reimbursement, 14 articles were on non-human transmission, ten articles did not combine costs and effects, eight studies failed to report on health effects, no model was presented in five articles, one article was in Czech, and one article was on rabies vaccination in dogs. We screened 355 CEAs for inclusion of herd immunity and 134 of these were included. Of the 275 articles included in the

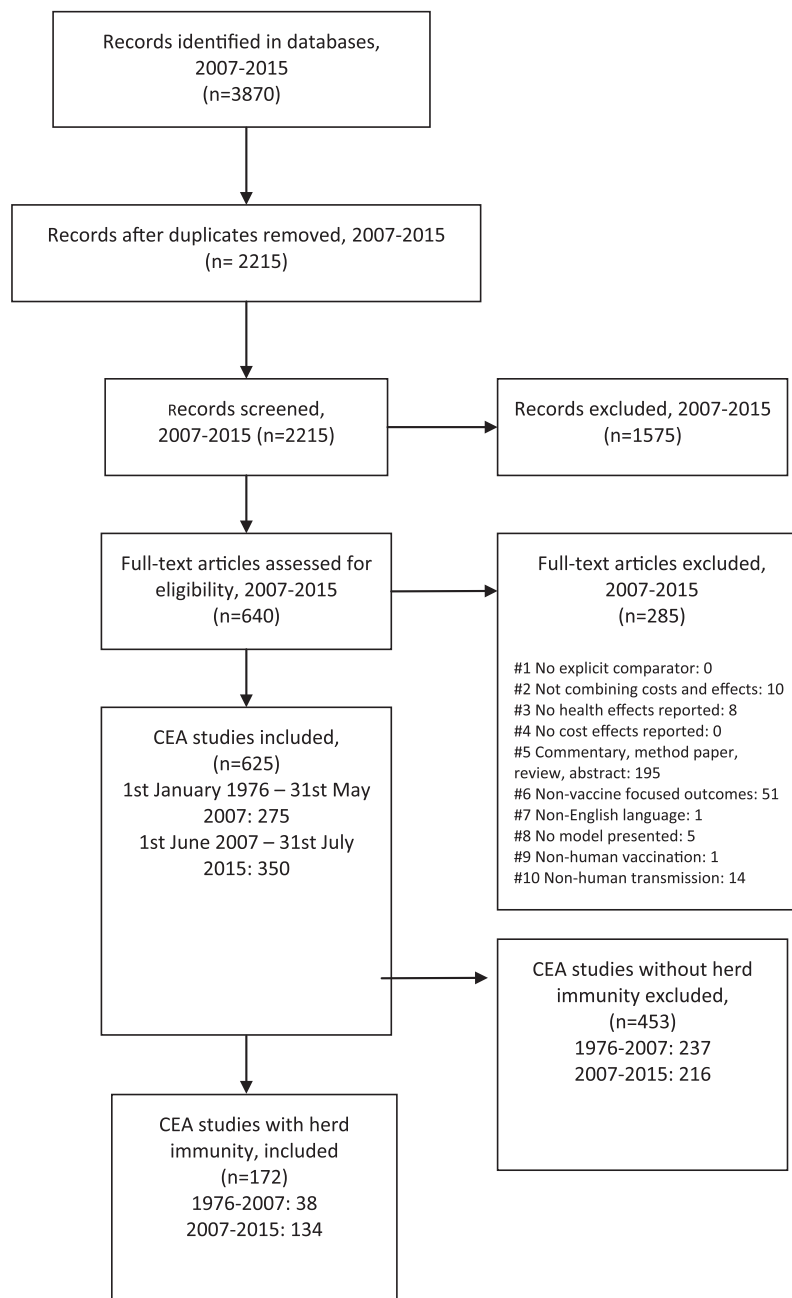


Fig. 1. PRISMA flowchart.

Table 2
Summary of study characteristics (1976–2015).

First author (publication year), by vaccine	Model subtype	Analysis with herd immunity		Primary outcome measure	Time horizon (years)
		Main	Sensitivity		
<i>Cholera</i>					
Jeuiland [125]	NS	Yes	Yes	DALY	15
Schaetti [126]	NS	Yes	Yes	DALY	3
<i>Hepatitis A</i>					
Armstrong [127]	Cohort	Yes	Yes	QALY	Lifetime
Lopez [128]	SIR	Yes	Yes	LY	100
Dhankhar [129]	TD	Yes	Yes	QALY	100
<i>Hepatitis B</i>					
Fenn [130]	Markov	Yes	No	LY	25
Williams [131]	TD	Yes	No	Cases	Lifetime
<i>Hib</i>					
Miller [15]	NS	Yes	No	DALY	Unclear
Jimenez [18]	NS	No	Yes	Cases	5
Miller ¹ [16]	NS	Yes	No	DALY	Unclear
Zhou [14]	Flow tree	Yes	No	QALY	5
Akumu [19]	NS	No	Yes	DALY	5
Broughton [17]	Flow tree	Yes	Yes	QALY	Lifetime
Griffiths [20]	Cohort	No	Yes	DALY	6
Clark [21]	Flow tree	No	Yes	DALY	Lifetime
<i>HPV</i>					
Taira [25]	TD, Cohort	Yes	No	QALY	Lifetime
Elbasha [138,139]	TD	Yes	Yes	QALY	Lifetime
Goldie [140]	TD, Cohort	No	Yes	LY	Various
Insinga [141]	TD	Yes	Yes	QALY	3
Kim [142]	TD	Yes	Yes	LY	Lifetime
Chesson [26]	TD, Cohort	Yes	Yes	QALY	Various
Dasbach [143]	TD	Yes	Yes	QALY	Various
Goldhaber-Fiebert [22]	Markov	No	Yes	QALY	Various
Jit [144]	TD	Yes	Yes	QALY	100
Kim [145]	TD	Yes	Yes	QALY	Various
Usher [146]	TD	Yes	No	LY	70
Anonychuk [24]	Markov	Yes	Yes	QALY	Lifetime
Kim [147]	TD	Yes	No	QALY	100
Zechmeister [148]	TD	Yes	Yes	LY	80
Olsen [149]	TD	Yes	No	QALY	62
Vanagas [150]	TD	Yes	No	LY	90
Bogaards [151]	TD	Yes	Yes	QALY	Various
Chesson [152]	TD	Yes	Yes	QALY	100
Schobert [153]	TD	Yes	No	QALY	Lifetime
Vanni [154]	TD	Yes	No	QALY	Various
Brisson [155]	TD	Yes	No	QALY	70
Uusküla [156]	TD	Yes	No	QALY	100
Burger [157]	TD	Yes	Yes	QALY	Lifetime
Laprise [158]	TD	Yes	No	QALY	70
Pearson [23]	Markov	Yes	Yes	QALY	Various
Burger [159]	TD	Yes	Yes	QALY	Lifetime
Jit [160]	TD	Yes	Yes	QALY	100
<i>Influenza</i>					
Patriarca [161]	Flow tree	Yes	No	Cases	1
Pradas-Velasco [28]	SIR, Flow tree	Yes	No	Cases	1
Baguelin [162]	SEIR	Yes	No	QALY	Lifetime
Sander [29]	SIR, Regression analysis	No	Yes	QALY	Lifetime
Clements [27]	Flow tree	No	Yes	QALY	Lifetime
Fisman [163]	TD	Yes	No	QALY	10
Baguelin [164]	TD	Yes	Yes	QALY	1
Giglio [165]	TD	Yes	No	QALY	Lifetime
Newall [166]	SEIR	Yes	Yes	QALY	1
Pitman [167]	TD	Yes	Yes	QALY	150–200
Meeyai [168]	TD	Yes	No	DALY	1
<i>Measles</i>					
Zwanziger [132]	NS	Yes	No	QALY	Lifetime
Levin [133]	TD	Yes	No	DALY	100
<i>Meningococcal</i>					
Bovier [30]	Markov	Yes	Yes	LY	30
De Wals [34]	Cohort	Yes	No	QALY	Lifetime
Rancourt [31]	NS	Yes	No	Cases	5
Welte [36]	Cohort	No	Yes	QALY	77
Trotter [186]	TD	Yes	Yes	QALY	100
De Wals [32]	Markov	Yes	Yes	QALY	Lifetime

(continued on next page)

Table 2 (continued)

First author (publication year), by vaccine	Model subtype	Analysis with herd immunity		Primary outcome measure	Time horizon (years)
		Main	Sensitivity		
Christensen [34]	TD, Cohort	Yes	No	QALY	100
Hepkema [35]	Flow tree	Yes	Yes	QALY	99
Christensen [169]	SIS	Yes	Yes	QALY	100
Tu [33]	Markov	No	Yes	QALY	Lifetime
<i>Pertussis</i>					
Tormans [43]	Markov	No	Yes	Cases	6
Beutels [42]	Markov	Yes	Yes	QALY	6
Edmunds [170]	TD	Yes	Yes	LY	Lifetime
Stevenson [41]	Markov	Yes	Yes	QALY	5
Caro [40]	Cohort	Yes	Yes	QALY	Lifetime
Lee [37]	Markov	No	Yes	QALY	Lifetime
Lee [38]	Markov	No	Yes	QALY	Lifetime
Lee [39]	Markov	Yes	Yes	QALY	Lifetime
Coudeville [171]	TD	Yes	Yes	LY	100
de Greeff [172]	NS	Yes	No	QALY	Various
de Vries [173]	TD	Yes	Yes	QALY	25
Greer [174]	TD, Markov	Yes	No	QALY	10
Rozenbaum [175]	TD	Yes	Yes	QALY	25
McGarry [176]	TD	Yes	No	QALY	1
<i>Pneumococcal</i>					
Melegaro [44]	Cohort	Yes	Yes	QALY	Lifetime
McIntosh [177]	Cohort	Yes	Yes	LY	10
Ray [45]	Flow tree	Yes	Yes	LY	5
Wisloff [178]	Markov	Yes	Yes	QALY	Lifetime
Hubben [46]	Flow tree	Yes	Yes	QALY	10
Bergman [47]	Markov	Yes	No	LY	100
Lloyd [48]	Cohort	Yes	Yes	QALY	Lifetime
Tilson [49]	Cohort	Yes	Yes	LY	5
Claes [50]	Markov	Yes	Yes	QALY	5
Lee [51]	Flow tree	Yes	Yes	LY	10
Poirier [52]	NS	Yes	Yes	QALY	5
Ray [53]	Flow tree	Yes	Yes	LY	5
Silfverdal [54]	Cohort	Yes	Yes	LY	10
Vespa [55]	Flow tree	Yes	Yes	DALY	10
Chuck [56]	Flow tree	Yes	Yes	QALY	1
Giglio [57]	Markov	Yes	Yes	LY	76
Kim [83]	Markov	Yes	Yes	DALY	5
Rozenbaum [84]	Flow tree	Yes	Yes	QALY	5
Rozenbaum [85]	Flow tree	Yes	Yes	QALY	5
Rozenbaum [58]	Flow tree	Yes	Yes	QALY	5
Rubin [59]	Markov	Yes	Yes	QALY	1
Rubin [60]	Markov	Yes	Yes	QALY	10
Aljunid [61]	Cohort	Yes	Yes	LY	10
Nakamura [62]	Flow tree	Yes	Yes	DALY	Lifetime
Newall [63]	Markov	Yes	No	QALY	100
Robberstad [86]	Markov	Yes	Yes	QALY	94
Tyo [64]	Markov	Yes	Yes	QALY	5
Uruena ² [96]	Flow tree	Yes	Yes	DALY	5
Bin-Chia Wu [65]	TD	Yes	Yes	LY	10
Blank [87]	Flow tree	Yes	No	QALY	10
Earnshaw [88]	Flow tree	No	Yes	QALY	Lifetime
Grzesiowski [66]	Markov	No	Yes	QALY	35
Hoshi [90]	Markov	No	Yes	QALY	5
Knerer [67]	Markov	Yes	No	QALY	94
Kuhlmann [68]	Markov	Yes	Yes	LY	1
Rozenbaum [179]	Cohort	Yes	Yes	QALY	100
Smith [75]	Markov	Yes	Yes	QALY	Lifetime
Strutton [70]	Flow tree	Yes	Yes	QALY	1
Van Hoek [95]	TD	Yes	No	QALY	30
Weycker [71]	Markov	Yes	Yes	Cases	Lifetime
Ayieko [72]	Flow tree	No	Yes	DALY	10
Gomez [73]	Markov	No	Yes	QALY	Lifetime
Hoshi [89]	Markov	Yes	Yes	QALY	5
Klok [91]	Flow tree	Yes	Yes	QALY	1
Kulpeng [74]	Markov	Yes	Yes	QALY	Lifetime
Lee [92]	Flow tree	Yes	No	QALY	10
Marti [93]	Flow tree	No	Yes	QALY	Lifetime
Smith [75]	Markov	Yes	Yes	QALY	15
Smith et al. [76]	Markov	Yes	Yes	QALY	Lifetime
Wu [77]	Flow tree	Yes	Yes	LY	10
Che [78]	Flow tree	Yes	Yes	QALY	Lifetime
Hu [76]	Flow tree	Yes	Yes	QALY	1

Table 2 (continued)

First author (publication year), by vaccine	Model subtype	Analysis with herd immunity		Primary outcome measure	Time horizon (years)
		Main	Sensitivity		
Jiang [79]	Markov	Yes	Yes	QALY	100
Vemer [80]	Flow tree	Yes	Yes	QALY	5
Caldwell [81]	Flow tree	Yes	Yes	QALY	1
Kieninger ³ [97]	Flow tree	Yes	Yes	DALY	5
Komakhidze ⁴ [98]	Flow tree	Yes	Yes	DALY	10
Mezones-Hilguin ⁵ [99]	Flow tree	Yes	Yes	DALY	5
Ordonez [82]	Flow tree	Yes	No	LY	5
Sibak ⁶ [100]	Flow tree	Yes	Yes	DALY	10
Vucina ⁷ [101]	Flow tree	Yes	Yes	DALY	20
<i>Polio</i>					
Thompson [134]	TD	Yes	No	Cases	60
Duintjer Tebbens [135]	TD	Yes	Yes	DALY	50
<i>Rotavirus</i>					
Jit [180]	Cohort	Yes	No	QALY	5
Shim [181]	TD	Yes	Yes	QALY	20
Mangen [182]	TD, Cohort	Yes	Yes	DALY	20
Rozenbaum [107]	Cohort	Yes	No	QALY	5
Syriopoulou [109]	Cohort	Yes	No	Cases	5
Atherly [110]	Cohort	No	Yes	DALY	5
Atkins [111]	TD	Yes	Yes	QALY	50
Bakir [183]	Markov	Yes	No	QALY	5
Bruijning-Verhagen [184]	Cohort	No	Yes	QALY	20
Tu [108]	Cohort	Yes	No	QALY	25
Aidelsburger [112]	Markov	No	Yes	QALY	5
de Blasio [185]	TD	Yes	No	LY	20
Ahmeti ⁸ [101]	Flow tree	Yes	No	DALY	Lifetime
Diop ⁹ [103]	Flow tree	Yes	Yes	DALY	5
Javanbakht ¹⁰ [104]	Flow tree	No	Yes	DALY	20
Sigei ¹¹ [105]	Flow tree	Yes	Yes	DALY	5
Uruena ¹² [106]	Flow tree	No	Yes	DALY	5
<i>Varicella</i>					
Brisson [113]	TD	Yes	Yes	QALY	30
Banz [117]	TD	Yes	Yes	Cases	30
Brisson [114]	TD	Yes	Yes	QALY	80
Coudeville [121]	TD	Yes	Yes	QALY	50
Coudeville [122]	TD	Yes	Yes	QALY	50
Lenne [119]	TD	Yes	Yes	Cases	50
Hammerschmidt ¹³ [120]	TD	Yes	No	Cases	30
Bonanni ¹⁴ [124]	TD	Yes	No	QALY	30
Valentim [123]	TD	Yes	No	LY	30
Banz ¹⁵ [118]	TD	Yes	No	Cases	30
Van Hoek [116]	TD	Yes	Yes	QALY	Infinite
Bilcke [115]	TD	Yes	No	QALY	Various
<i>Yellow Fever</i>					
Monath [136]	TD	Yes	Yes	Cases	35

Abbreviations: Hib = *Haemophilus influenzae* type b, HPV = Human papillomavirus, DALY = Disability-adjusted life year, QALY = Quality-adjusted life year, LY = Life-year, SIR = Susceptible-Infected-Recovered, NS = Not explicitly stated, TD = Transmission dynamic, SEIR = Susceptible Exposed Infectious Recovered model, SIS = susceptible-infected-susceptible model.

¹ Hib, Hepatitis B, Pneumococcal and Rotavirus vaccines in national immunization schedules.

^{2–12} The TRIVAC model which is classified as a flow tree was used in these cost-effectiveness analyses [187].

^{13–15} The Economic Varicella Vaccination Tool for Analysis model (EVITA) which is classified as a transmission dynamic model is used in these cost-effectiveness analyses [188].

1976–2007 review by Kim and Goldie, 38 included herd immunity. Hence, a total of 172 papers were included in the analysis. These are summarized in Table 2.

3.2. Number of cost-effectiveness analyses including herd immunity 1976–2015

Between 1976 and July 2015 a total of 625 CEAs were published on vaccines against human-transmissible diseases. Of these, 172 (28%) included herd immunity. In 1993, 2000, 2001 and 2003 less than 10% of CEAs published in each year incorporated herd immunity (Fig. 2). The highest proportion of CEAs including herd immunity was 53% in 2015. Both the total number of CEAs published and those including herd immunity increased from 2007 onwards compared to earlier years; 80% of the included stud-

ies were published between 2007 and July 2015. One-fifth of the CEAs that excluded herd immunity mentioned the aspect in their introduction, methods or discussion section, providing a rationale for why it was not included, listing it as a limitation or arguing that modified (more favorable) results would be expected if herd immunity had been incorporated.

3.3. Number of cost-effectiveness analyses including herd immunity by vaccine type

Fig. 3 shows the number of CEAs including herd immunity by vaccine type. Four percent of hepatitis B vaccine, 11% of hepatitis A and measles vaccines each, 14% of influenza vaccine, 21% of rotavirus vaccine, 22% of varicella and cholera vaccines each, and 29% of polio vaccine CEAs included herd immunity. For human papillo-

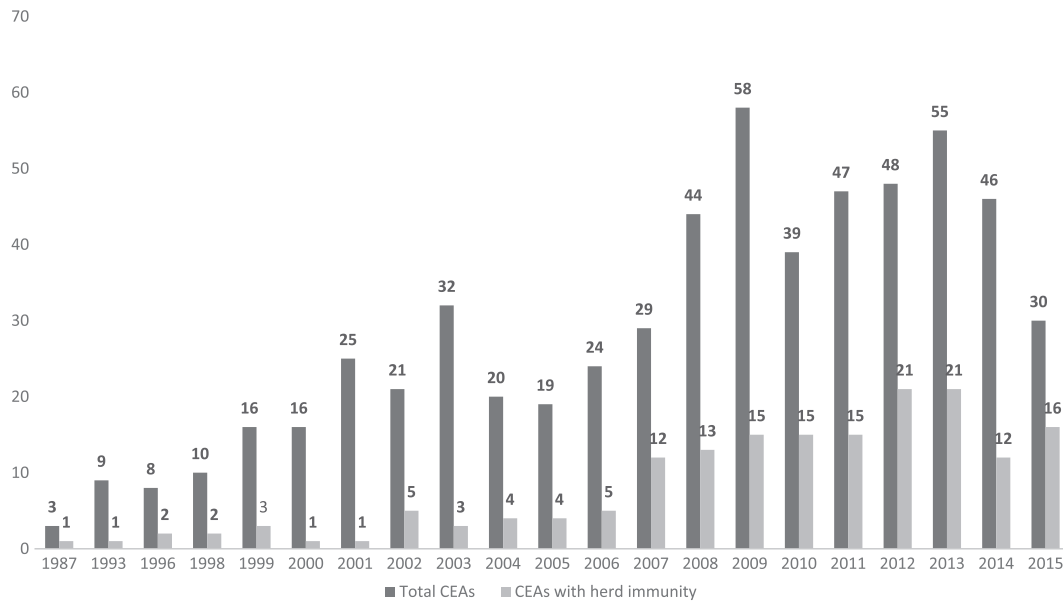


Fig. 2. Number of vaccine cost-effectiveness analyses including herd immunity, by year 1976–2015 (N = 625).

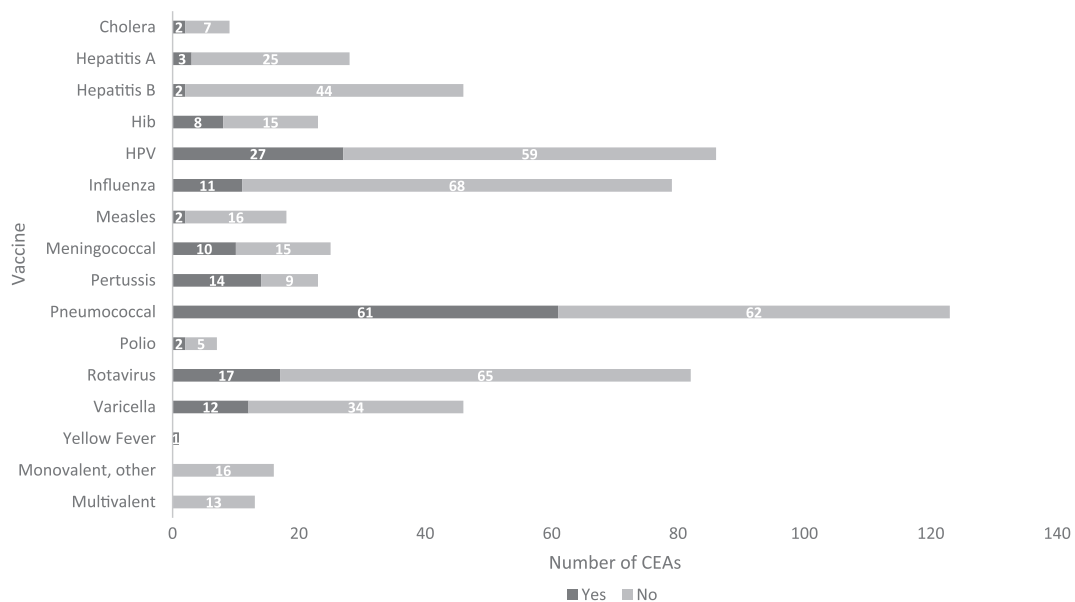


Fig. 3. Number of cost-effectiveness analyses (CEAs) including herd immunity, by vaccine type (N = 625). Abbreviations: BCG = Bacillus Calmette–Guérin; DTP = diphtheria-tetanus-pertussis; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; MMR: measles-mumps-rubella. Monovalent, other: Adenovirus, BCG, Typhoid, Rubella, Mumps. Multivalent: DTP, MMR, Hepatitis A-Hepatitis B, Pneumococcal-Influenza, Pneumococcal-Meningococcal.

mavirus (HPV), *Haemophilus influenzae* type b (Hib), and meningococcal vaccines, herd immunity was presented in 31%, 35% and 40% of the CEAs, respectively. Nearly half of the CEAs of pneumococcal vaccine analysed herd immunity while a majority of pertussis CEAs (61%) considered it. One CEA on yellow fever vaccination was identified and it considered herd immunity.

3.4. Summary characteristics of cost-effectiveness analyses including herd immunity

Most CEAs (55%) adopted static models utilising cohort, flow tree and Markov models (Table 3). The second most commonly used approach was a transmission dynamic model (34%). Five per cent were classified as hybrid CEAs and 6% did not clearly state which type of model was used. The majority of the CEAs that

included herd immunity did so in the main analysis (86%) and 58% of these varied it in the sensitivity analysis. Fourteen per cent included herd immunity in the sensitivity/scenario analysis only. Quality-adjusted life years was the most reported primary outcome measure (62%), followed by disability-adjusted life years (16%), life-years (15%) and cases (7%).

Time horizons used varied from one year to lifetime. While 87% of the dynamic models used a time horizon longer than 20 years, this was done in 45% of the static analyses. A lifetime horizon was used in 38% and 52% of static and dynamic models, respectively. None of the dynamic models used a 5-year time horizon while this was the case for 32% of the static models. A 1-year time horizon was used in 8% and 7% of static and dynamic models, respectively. The 1-year time horizon was for influenza studies (n = 5), pertussis (n = 1) and pneumococcal (n = 7).

Table 3
Characteristics of cost-effectiveness analyses including herd immunity (N = 172).

Characteristics	N
<i>Model type</i>	
Dynamic	59
Static	95
Hybrid	8
Not stated	10
<i>Model subtypes</i>	
Transmission dynamic	54
SEIR	2
SIR	1
SIS	1
Cohort	17
Epidemiological	1
Flow tree	40
Markov	36
SIR, Flow tree	2
SIR, Regression	1
TD, Cohort	4
TD, Markov	3
Not stated	10
<i>Herd immunity</i>	
Herd immunity in main analysis	148
Herd immunity only in sensitivity analysis	24
Proportion varying herd immunity in sensitivity analysis	99
<i>Primary outcome measure</i>	
DALY	27
QALY	106
LY	25
Cases	14

Abbreviations: DALY = Disability-adjusted life year, LY = Life-year, QALY = Quality-adjusted life year, SEIR = Susceptible Exposed Infectious Recovered model, SIS = Susceptible-Infected-Susceptible Model, SIR = Susceptible-Infected-Recovered, TD = Transmission Dynamic.

3.5. Model approaches for herd immunity

Hib (*Haemophilus influenzae* type b): Eight CEAs of Hib vaccine included herd immunity; four in the base case analysis and four only in scenario analysis. All eight studies used static models. In the US study by Zhou et al., herd immunity was captured from surveillance data before and after vaccine introduction [14]. This was possible because the study was undertaken nine years after Hib vaccine was introduced. In the 1998 and 2000 papers by Miller [15,16], herd immunity was reportedly included, but the methods were not explained and no decision analytic models were presented. The methods used by Broughton were similarly unclear [17]. Relatively crude methods were used in the four studies that only included herd immunity in scenario analyses. Akumu et al. and Jimenez et al. assumed Hib disease elimination in the long run [18,19]. Clark et al. and Griffiths et al. assumed that herd immunity would increase impact by 20% [20,21]. None of these four studies gave references for the assumptions.

HPV: Of the 27 HPV studies that included herd immunity, 24 did so in the main analysis and three only in the sensitivity analysis. The majority used a disease transmission dynamic approach to account for herd immunity (78%), with only three studies using a static model. In the static models used by Goldhaber-Fiebert et al. (in the sensitivity analysis only) and Pearson et al. (both main and sensitivity analysis), herd immunity effects were based on incidence rates derived from previously published dynamic transmission models [22,23]. Similarly, Anonychuk et al. used a Markov model and attempted to incorporate a conservative estimate of herd immunity effects in the main and sensitivity analysis by approximating equations used in a previously published susceptible-infectious-recovered (SIR) dynamic model [24]. Taira et al., and Chesson et al. used hybrid models [25,26]. Taira et al. used a

transmission model to simulate the incidence of HPV infection in the US population of males and females 12–50 years old. The HPV infection rates predicted by this model were then incorporated into a probabilistic flow tree model for calculation of HPV vaccine cost-effectiveness. In a dynamic model, Chesson et al. estimated herd immunity effects for non-vaccinated individuals and a reduction in genital warts in men as a spill-over effect of female HPV vaccination. The impact estimates were linked to costs in a cohort model.

Influenza: We identified 11 influenza vaccine CEAs with herd immunity, of which nine included it in the base case and two in the sensitivity analysis only. Dynamic models were commonly used (63%). Clements et al. presented a flow tree model and reported that they incorporated herd immunity in the scenario analysis as disease reduction among unvaccinated persons, but no additional details on methods were provided [27]. Both Pradas-Velasco et al. and Sanders et al. used two models; one static and one dynamic. Pradas-Velasco et al. reported on the results with and without herd immunity effects, but provided little detail regarding methods used [28]. In their SIR model, Sander et al. derived herd immunity as the projected reduction factor for the change in vaccine coverage estimates from the literature [29].

Meningococcal: Ten meningococcal vaccine CEAs included herd immunity. Eight of these considered herd immunity in the main analysis and two only in the sensitivity analysis. Six used static models. Bovier et al. used a Markov model and reported herd immunity effects in both the main and sensitivity analysis, but the approach was unclear [30]. In other papers, herd immunity effects were captured by assuming an increase in vaccine effectiveness [31], reduction in age-specific attack rates in a cohort model [32], and increase in strain coverage in a Markov model [33]. De Wals and Erickson undertook a population based cohort study that enabled them to measure herd immunity directly by comparing incidence rates in unvaccinated people before and after a mass immunization campaign [34]. Hepkema et al. used a flow tree model and herd-immunity effects were obtained by comparing the serogroup C incidence of 2001 with the average serogroup C incidence of 2007–2011 [35]. Welte et al. quantified the impact of herd immunity in the sensitivity analysis in a cohort model by assuming 50% protection of the unvaccinated [36].

Pertussis: Fourteen CEAs on pertussis vaccine included herd immunity; 11 in the main and three only in the sensitivity analysis. Half of the studies applied a static model. In the three CEAs by Lee et al., Markov models were used and herd immunity was derived from a published model of transmission dynamics of pertussis and from published studies of sources of infection of young infants [37–39]. In the sensitivity analysis, disease reduction from herd immunity was assumed to depend on vaccination rates in the adult population and time since last vaccination of the cohort. Based on assumptions, Caro et al. varied herd immunity effects in infants from 5% to 35% in a cohort model (with varying effects by age groups). Due to lack of data on herd immunity, assumptions were based on expert opinions from the Global Pertussis Initiative and broad ranges were applied [40]. Stevenson et al. calculated the probability of infection to vary proportionately to the number infected within the community [41]. Beutels et al. assumed that 10% of the susceptible part of the population would be indirectly protected at 70% coverage, whereas at 80% and 90% coverage this was assumed to be 30% and 70%, respectively [42]. Tormans et al. used a Markov model and included herd immunity in the sensitivity analysis only. This was done by assuming that with 45% vaccination coverage, 85–99% of unvaccinated, susceptible children would be indirectly protected [43].

Pneumococcal: We identified 61 pneumococcal CEAs considering herd immunity. Fifty-five CEAs included herd immunity in the base case while six did so in the sensitivity analysis only. These

mainly used static models (95%). The majority of the studies (38 studies; 62%) estimated herd immunity from US surveillance data in unvaccinated persons for different age groups [44–82]. Ayieko et al. also used the US surveillance data to predict the impact of serotype replacement in Kenyan children. This was done by assuming that children less than 5 years were 1.21 times more likely to get non-vaccine type disease after PCV introduction [72]. Assumptions about the reduction of incidence of invasive pneumococcal diseases were used to account for herd immunity in 15 CEA studies [76,83–95]; 12 tested assumptions in sensitivity analyses and 12 derived estimates of herd immunity effects from published literature. In the CEAs by Uruena et al., Kieninger et al., Komakhidze et al., Mezones-Hilguin et al., Sibak et al., and Vucina et al. a simple multiplier was used to calculate a percentage increase in health benefits due to herd immunity effects [96–101].

Rotavirus: 17 rotavirus vaccine CEAs included herd immunity; 12 in the main analysis and five only in sensitivity analysis. Seventy-six percent used static models. Ahmeti et al., Diop et al., Javanbakht et al., Sigei et al., and Uruena et al. crudely accounted for herd immunity effects in the static TRIVAC model using a multiplier and inflating health benefits to 120% of direct effects in children <5 years of age [102–106]. In cohort models, Rozenbaum et al. and Tu et al. presumed herd protection for those not yet protected by the vaccine and the non-vaccinated, assuming protection would be as effective as vaccination would be after completing all doses [107,108]. The implications of this assumption were, however, not clear. Syriopoulou et al. incorporated herd immunity effects (from 5% to 10%) into a flow tree model by extending vaccine efficacy [109]. In a scenario analysis, Atherly et al. assumed that unvaccinated children would receive 15% protection at 50% vaccination coverage [110]. In a transmission dynamic model, Atkins et al. predicted herd immunity effects to be a 45% reduction in the probability of infection in unvaccinated individuals at 80% coverage [111]. Aidelburger et al. used Atkins et al.'s estimate in their sensitivity analysis in a Markov model [112].

Varicella: 12 varicella vaccine CEAs included herd immunity and they all used dynamic models. All CEAs included herd immunity in the main analysis. Papers from 2002 and 2003 by Brisson and Edmunds considered herd immunity effects as post-immunization shifts in the age of infection in a transmission dynamic model [113,114]. Bilcke et al. adapted Brisson's original model in their 2011 analysis of varicella-zoster vaccination in Belgium [115]. Van Hoek et al. similarly adopted Brisson's model in their analysis of varicella vaccination programmes in the UK [116]. The models used by Banz et al. [117] for Germany, by Banz et al. [119] for Switzerland, and by Lenne et al. [118] were similarly age-structured deterministic models based on a set of differential equations [117–119]. Hammerschmidt et al. (2007) used Banz's model to analyse the cost-effectiveness of a two-dose varicella vaccine schedule in Germany [120]. In the transmission dynamic models by Coudeville et al., Valentim et al. and Bonnani et al., transition probabilities based on time, age of individuals and potential age shift were used to account for herd immunity [121–124].

Other vaccines: Two CEAs on cholera vaccine with herd immunity were identified; both included it in the main as well as sensitivity analysis. However, neither of the two studies clearly stated their model type. In the 2009 paper by Jeuland et al., a mathematical equation linked oral cholera vaccine effectiveness to varying coverage rates in the study population [125]. Schaetti et al. calculated herd immunity effects by multiplying the annual incidence of cases without vaccination with protective efficacy among unvaccinated people [126].

Three hepatitis A vaccine CEAs accounted for herd immunity in both the main and sensitivity analysis. Using a cohort model, Armstrong estimated herd immunity from a previously published analysis of the relationship between vaccination coverage and declines

in hepatitis A incidence [127]. Lopez et al. simulated herd immunity effects in a SIR model by calculating the reduction in force of infection [128]. Dhankhar et al. used a deterministic, age-structured transmission dynamic model in which exposure to hepatitis A infection were age and time dependent. Contact patterns between individuals were governed by a conditional probability mixing matrix [129].

Two hepatitis B vaccine CEAs included herd immunity in the main, but not in sensitivity analysis. Using a static model, Fenn et al. assumed a linear relationship between incidence of infection and prevalence of chronic carriers, which subsequently reduced infection rates in the non-vaccinated population (herd immunity effects). The basis for the assumed parameters was not clear [130]. Williams et al. used an age-structured deterministic model for analysing hepatitis B virus transmission through sexual contact and at birth. Targeted versus universal infant vaccination was assessed on its ability to break the chain of transmission, (referred to as herd immunity effects) as measured by reduction in chronic carrier prevalence [131].

Two measles vaccine CEAs considered herd immunity in the base case, but not in sensitivity analysis. Instead of modelling measles transmission, Zwanziger et al. [132] used empirical U.S. data to determine the relationship between measles incidence and vaccination coverage. The authors assumed that the herd immunity threshold would be reached with 90% measles vaccine coverage. Levin et al. [133] evaluated the cost-effectiveness of measles eradication using a global transmission dynamic model. The population was stratified by age and infection status of susceptible, exposed, infectious or recovered. Transmission rates varied seasonally and were based on a matrix of age-specific contact rates related to household size.

Two polio vaccine CEAs by Thompson and Tebbens [134] and Duintjer et al. [135] used dynamic transmission models and included herd immunity in the main, but not in the sensitivity analysis.

A dynamic model was utilised by Monath and Nasidi [136] in the CEA of yellow fever vaccine and herd immunity effects estimated from incidence rates were included in both the main and sensitivity analysis [136].

3.6. Quality assessment

The majority of the 172 included studies (77%) met 20 or more of the 24 CHEERS checklist criteria. Ten studies satisfied all 24 items, 42 met 23 criteria, 31 conformed to 22 criteria, 29 met 21 criteria, and 20 satisfied 20 items. The mean number across the 172 CEAs was 21 with a range between 12 and 24 items. A complete overview of non-conforming items for individual CEAs is available in Table S3.

A total of 125 studies (73%) failed to conform to all three components in item 15 regarding the choice of model. Thirteen CEAs failed to provide sufficient description regarding the model used. Eighty-five CEAs (49%) did not include a graphic figure of the model structure. Inadequate justification of the model choice was given in 108 of the 172 CEAs (63%). Forty-six of these studies justified the choice by using a previously published model. This can however not be considered an adequate justification; it is necessary to explain why this exact model is considered valuable to answer the study question.

4. Discussion

There has been an exponential growth in economic evaluations of vaccines during the past two decades [137]. We found that this development was mirrored by considerably more studies of newer

vaccines compared to traditional vaccines. The proportion of studies that included herd immunity has increased in recent years in line with the growth in economic evaluation studies in general. Herd immunity effects were not considered in 72% of vaccine CEAs published between 1976 and 2015. However, the number of CEAs including herd immunity has increased nearly fourfold since 2007, with 80% of included studies being published during 2007–2015. We identified a total of 172 vaccine CEAs that included herd immunity.

This is the first review to evaluate the inclusion of herd immunity for all published vaccine CEAs. We however only included English language articles in our search and we acknowledge this as a limitation. There are numerous vaccine specific reviews available and some of these have assessed the inclusion of herd immunity.

We found marked differences among vaccine types with regard to the total number of studies and the likelihood of herd immunity being included. From a technical viewpoint, the importance of including herd immunity should depend on (i) whether the rate at which susceptible individuals acquire infection is reduced due to vaccination and/or (ii) whether it is not possible to obtain a conservative estimate with a static model [7,8]. The effective reproductive rate depends on contact patterns between susceptible, vaccinated, and infectious individuals, and coverage rates. Vaccination targeted at a specific risk group, such as hepatitis A in travellers, will for instance not alter the reproductive rate. Herd immunity will on the other hand always occur when vaccination targets an epidemiologically influential subgroup, though infants are only an important subgroup for certain infections (e.g. pneumococcus). Hence, while the first principle is a valid reason for exclusion of herd immunity, incorporation of herd immunity effects would in no doubt be warranted in the large majority of studies following the second principle.

We believe that the inclusion of herd immunity is driven by four main factors: (1) Growth in dynamic modelling expertise is an important reason for the rise in inclusion of herd immunity since 2007, including the availability of computer simulation power. However, infectious disease modelling is still a highly-specialized field and this capacity is not available to the majority of health economic researchers, (2) The extent to which herd immunity is understood also influences the decision to include these effects. The link between carriage and Hib disease is for instance not well established, which explains why there are no Hib CEAs using dynamic models. Similarly, herd immunity protection from rotavirus was not recognized until post-marketing data became available, (3) If uncertainty concerning the cost-effectiveness of the vaccine exists, herd immunity may not be included. Pneumococcal vaccine may for instance only be cost-effective if indirect effects on the elderly are included, and (4) The availability of funding will likely matter since building a transmission dynamic model is a substantially greater undertaking than a static model, costs will be higher and sufficient funding is essential.

We showed that 55% of the 172 studies used a static model for estimating herd immunity. There are no recommended methods available for incorporating herd immunity using a static model and the reliability of these results is questionable. We found that the static models incorporated herd immunity in four different ways: (1) By assuming a percentage increase in vaccine impact, (2) by increasing the vaccine efficacy value, (3) by using herd immunity impact published by dynamic models and (4) by estimating herd immunity impact from surveillance data or population-based cohort studies. Among the methods identified for static models only the use of high quality surveillance data is defensible.

Results produced by static models must be interpreted with caveats unless high quality surveillance data are available, in

which case uncertainty is reduced. For each study, researchers need to assess whether the additional benefits of a dynamic model outweigh the additional costs and efforts needed to build it. The additional benefits of including herd immunity effects by way of a dynamic model are likely higher in the absence of good surveillance data and when a more accurate/comprehensive analysis could potentially affect decision-making. The latter could be the case when cost-effectiveness considering only direct effects is in doubt or when competition between producers of vaccines is high and any additional benefit counts.

Since the uncertainty about long term impacts are inherently greater when indirect effects are not implicitly included in the model, it is warranted that substantially shorter time horizons were used in the static compared to the dynamic models. Static models are not able to predict the potential long term increase in herpes zoster incidence in the elderly following introduction of varicella vaccination for children. Brisson et al. showed that although the overall burden of varicella would be significantly reduced in the UK following infant vaccination, these benefits will be offset by a rise in zoster morbidity, which would last more than 60 years [138,139]. Hence, a dynamic model is especially required for a disease like varicella where a vaccine can lead to long term negative impacts.

Nearly two-thirds of the CEAs lacked sufficient justification for model choice scored according to the CHEERS guideline. This indicate that further attention is still required to ensure that guideline standards are adhered to. The lack of clear reporting on reasons for model choice impedes our ability to understand if herd immunity effects have been accounted for accurately.

5. Conclusion

Only 28% of the CEAs of vaccines in this review included herd immunity effects. 55% of the CEAs used static models, which cannot accurately predict herd immunity. Crude methods and assumptions were used in the static models to get a rough estimate of herd immunity.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2017.10.024>.

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