ARTICLE IN PRESS

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Cost of illness due to pertussis in adults ≥50 years of age in the United Kingdom

Jan-Willem Versteeg [a], Nicolas Jamet [b,*], Ken Redekop [a]

[a] Erasmus School of Health Policy & Management, Rotterdam, the Netherlands
[b] GSK, Wavre, Belgium

ARTICLE INFO

*Keywords:*
Adults
Economic burden
Pertussis
United Kingdom
Clinical practice research datalink
Cost-of-illness

ABSTRACT

*Background:* Pertussis is an endemic respiratory tract infection caused by *Bordetella pertussis* that may affect all individuals from infants to older adults. Pertussis incidence in adults is often underreported and in various countries, including the United Kingdom (UK), there are evidence gaps on pertussis-associated economic burden in the older adult population. We aimed to quantify the economic burden of pertussis in adults aged ≥50 years in the UK.
*Methods:* A cost-of-illness study was conducted to estimate the cost of pertussis from a societal perspective. We utilized a sum diagnosis cost approach in which costs related to infection with pertussis were included. Medical, patient, and indirect costs were calculated individually and combined to calculate total costs. A framework was developed to assess costs for consecutive age groups from 50–54 years of age to ≥85 years of age. Sensitivity and scenario analyses were used to assess analysis uncertainty.
*Results:* The base-case analysis estimated the total annual economic burden of pertussis to be approximately £238 million (M). This comprised approximately £159 M in indirect costs, £66 M in medical costs, and £13 M in patient costs. Costs for the age group 55–59 years had the highest impact on the economic burden, with approximately £79 M in total annual costs. Visits to general practitioners and nurses were the largest contributors to medical costs (~£37 M) followed by inpatient visits (~£21 M). Transportation costs (~£10 M) were the major patient costs. Productivity loss (~£71 M) and leisure time loss (~£72 M) had comparable contributions to annual indirect costs. Sensitivity and scenario analyses suggested that incidence rates, indirect costs, and underreporting estimates had the highest impact on outcomes.
*Conclusion:* Total cost of pertussis in the UK among adults ≥50 years of age is substantial and highest for adults 55–59 years of age. Indirect costs were the main contributors to the economic burden.

## 1. Introduction

Pertussis is a respiratory tract infection caused by the pathogen *Bordetella pertussis* [1]. The disease is highly infectious and is transmitted by close contact with an infected person via airborne droplets [2]. The most common symptoms include paroxysmal coughing and vomiting. These symptoms can persist for up to eight weeks, followed by a convalescent stage, which could last for months [1,2]. Typically, antibiotics are recommended to prevent infection from spreading to other individuals if initiated within 7–14 days of disease onset [3,4].

Pertussis is endemic worldwide. In 2018, the World Health Organization (WHO) reported more than 151,000 cases globally [5]. Although it is commonly presumed to affect only children, it can affect all age groups [1]. With universal pertussis vaccination in infants, which was introduced in the 1940s, pertussis disease incidence decreased in young children. However, in some countries the incidence of pertussis has increased in adolescents and adults due to several reasons. These included waning of immunity acquired through natural infection or vaccination, increased surveillance, improved diagnostics, and an antigenic shift of *B. pertussis*. The incidence of pertussis disease has increased in adolescents and adults in recent years [6,7]. Moreover, the incidence of pertussis among adults is often underreported. Hence, the real incidence (as based on seroprevalence data) is estimated to be considerably higher than the reported rate [8,9]. While morbidity and mortality due to pertussis are highest among infants, adults ≥50 years are at an increased risk of severe disease and hospitalization [10,11]. In the UK, a

* Corresponding author at: Av. Fleming 20, 1300 Wavre, Belgium.
*E-mail address:* nicolas.x.jamet@gsk.com (N. Jamet).

https://doi.org/10.1016/j.vaccine.2023.10.010
Received 28 April 2023; Received in revised form 4 October 2023; Accepted 4 October 2023
Available online 14 October 2023

real-world evidence database analysis conducted among adults 50 years and over by Harrington et al. [12] found an average incidence rate of 5.8 per 100,000 person-years (95 % CI: 5.5–6.0) between 2009 and 2018. The highest rates were found among the 50–54 age group (8.9 per 100,000), and the lowest among 85 + age-group (1.4 per 100,000). In Scotland, the pre-pandemic incidence ranged from approximately 25 per 100,000 for the 50–59 age group in 2016, to approximately 5 per 100,000 for 70 + age groups in 2017 and 2018, with high heterogeneity amongst age-groups and years. In Wales, available data from Public Health Wales show that the pre-pandemic pertussis incidence rates among adults 50 + were of 4.5 in 2018 and 5.2 in 2019 [13]. Unvaccinated or partially vaccinated infants and older adults also experience a higher frequency of severe disease presentation and a higher risk of complications and hospitalization than the general population [8,14].

Presently, only a few studies have assessed the economic burden of pertussis among older adults. These include three studies from the United States (US) [15–17] and one study from Canada [18]. All four studies concluded that the economic burden of pertussis in older adults was substantial [8]. To our knowledge, no such study has been conducted regarding adults over 50 years of age in the United Kingdom (UK). The objective of this study was therefore to increase pertussis awareness in the UK by describing the total economic burden of the disease among adults ≥50 years of age in the UK.

## 2. Methods

### 2.1. Study design and population

We conducted a cost-of-illness study to estimate the economic burden of pertussis among adults ≥50 years of age in the UK from a societal perspective. The study used a "sum diagnosis specific" cost approach [19,20], where only costs related to infection with *B. pertussis* were included. *Microsoft Excel* was used to perform all the analysis.

Population data for 2019 were collected from the Office for National Statistics (**Annex I, Table S1**) [21]. The population was divided into 5-year age groups, ranging from "50–54 years" to "85 years and older". Pertussis incidence data from 2009 to 2018 were retrieved from the publication by Harrington et al. (**Annex I, Table S1**) [12]. Incidence was defined as event rate per 100 patients/year of follow-up. The rate of underreported data for each age group was referenced from a previously published prospective study from Poland, including patients that first had a pertussis symptoms-based diagnosis, followed by a lab-confirmation (**Annex I, Table S1**) [9].

A framework was developed to assess the overall costs associated with pertussis for different age groups (Fig. 1). The number of patients in each age group was based on age-specific incidence data and under-reporting factors. For each age group the medical costs, patient costs, and indirect costs were calculated separately. These costs were combined to estimate the total annual economic burden for the population ≥50 years of age. Costs were adjusted to 2020 Pound Sterling (£) value using UK inflation rates (**Annex I, Table S2**) [22].

### 2.2. Medical costs

Total medical costs were calculated as the sum of diagnostic and medical care costs.

Different diagnostic methods were analysed to calculate diagnostic costs based on 2017–2019 data published by the UK Government (see

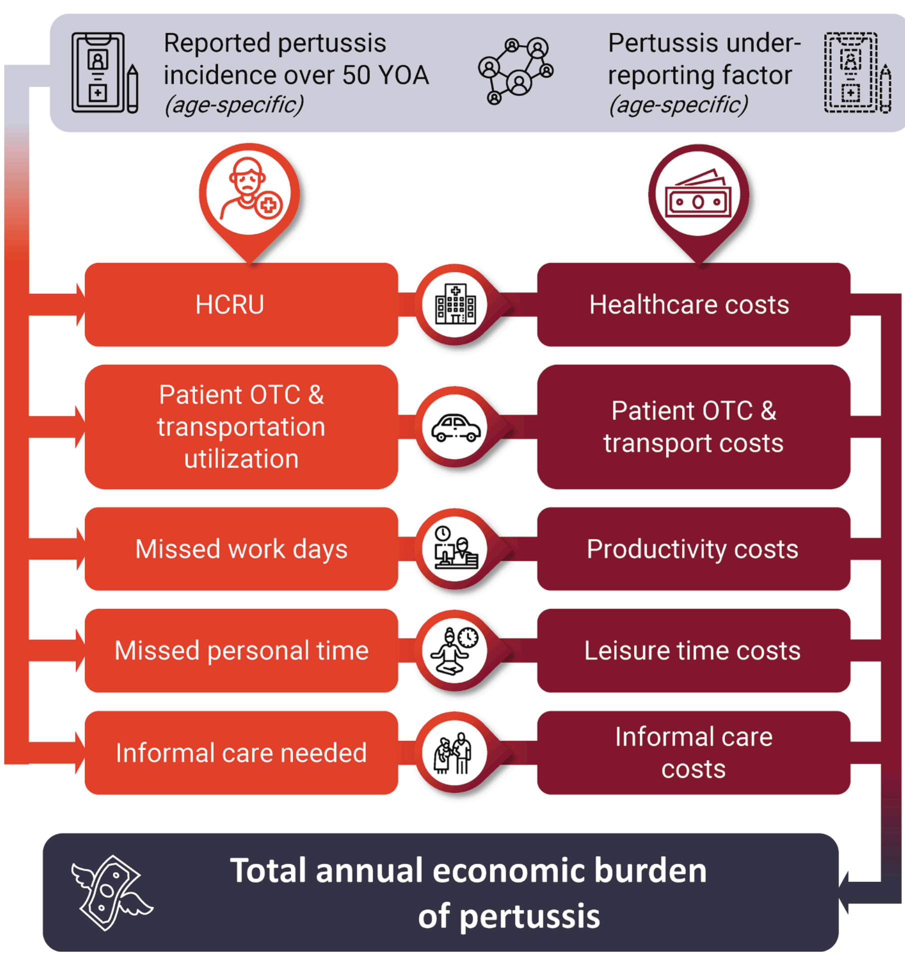



**Fig. 1.** Study design. HCRU, healthcare resource utilization; OTC, over the counter; YOA, years of age.

**Annex I, Table S3**) [23–25] for confirmed pertussis cases only. Diagnostic costs for the selected methods were obtained from the UK National Health Service (NHS) [26]. Costs for polymerase chain reaction (PCR) assay were based on published literature [27] and costs for pertussis oral fluid tests were calculated based on the cost of other oral fluid tests.

Healthcare resource utilization (HCRU) data included general practitioner (GP) visits, clinical values (laboratory tests and clinical assessments [e.g. blood pressure, weight etc.]), accident and emergency (A&E) department visits, outpatient specialist visits, and inpatient care (see **Annex I, Table S3**) [12]. Frequencies of healthcare resource utilization are presented in **Annex I, Table S4**. These data were assessed based on confirmed pertussis cases by comparing the baseline (a period of 18 months to 6 months before diagnosis date) with the period around pertussis diagnosis (from 6 months before to 6 months after diagnosis date). The period around pertussis diagnosis (duration up to one year) was defined as a period of one year, including 6 months prior to diagnosis date up to 6 months after diagnosis date, because medical care use may be sought before the actual diagnosis date and diagnosis can often be delayed.

Medical care costs were presented according to the following types of resource use: (1) clinical values and prescription costs, calculated as the average cost of the five most frequently used clinical values and prescriptions during the pertussis infection period [12,28]; (2) the costs of A&E department visits and inpatient care, obtained from the 2019 NHS guidelines as weighted average costs for the codes used during infection [26]; (3) outpatient costs and costs of GP visits, obtained from the 2019 Unit Costs of Health and Social Care as weighted average costs (GP visits included visits to the GP practice and consultations at home or via telephone) [29].

### 2.3. Patient costs

Patient costs were defined as all direct non-medical costs and included transport costs, over the counter (OTC) medication, and prescription fees (**Annex I, Table S5**).

Transportation costs were extracted from a non-pertussis UK study in which patients completed a travel questionnaire [30]. This included the mean transport cost per GP, outpatient, and inpatient visit. Total transport costs were calculated as the mean cost per visit multiplied by the number of visits. Published transportation costs for A&E visits were not available and were assumed to be the same as outpatient transport costs.

Since estimates of OTC medication costs for pertussis were also unavailable, this was estimated from the results of a study that measured the burden of acute cough [31].

Prescription fee costs were estimated based on NHS costs [32].

### 2.4. Indirect costs

Indirect costs were calculated as the sum of productivity loss, lost leisure time, and informal care needs (**Annex I, Table S6**).

Productivity loss was calculated using the friction cost approach (FCA) and the human capital approach (HCA). Notably for FCA, we utilized a productivity reduction of 80 % for a maximum duration of 2.7 months [33,34]. The probability and duration of lost leisure time were obtained from a previously published study conducted in the US [35]. Employment rates, average hourly wage, and work-week duration were obtained from the UK Government [36,37]. Productivity losses due to healthcare visits were calculated using the opportunity costs per GP, outpatient, and inpatient visit. Opportunity costs were added based on travel time (see transport costs **Annex I, Table S5**) [30].

Leisure time loss was included in the current analysis because the population consisted of older adults, most of whom were retired [38]. It was calculated using the probability and duration of lost leisure time based on the study reported by Lee et al. [35]. The valuation of leisure time was based on the Verbooy et al. study [38].

Informal care costs were calculated using the estimated travel time for each medical visit and the probability of being accompanied [30]. The valuation of informal care was based on a previously published systematic review [39].

### 2.5. Sensitivity and scenario analysis

Sensitivity (deterministic and probabilistic) and scenario analyses were performed to assess the uncertainty of the analysis.

The deterministic sensitivity analysis (DSA) assessed which parameters had the highest impact on analysis uncertainty. Ranges were utilized with a 95 % confidence interval (CI) if available, or an assigned range of −20 % to + 20 % was used to form a conservative lower and upper bound. The probabilistic sensitivity analysis (PSA) assessed the overall uncertainty of the analysis. To calculate the alpha and beta of the chosen parameter distribution, a standard error of 10 % was used when standard deviation was unavailable. A standard error of 20 % was assumed for underreporting as higher deviations were expected for this category. A beta distribution was selected to estimate the uncertainty associated with probability and percentages given its constraints between 0 and 1. A Gamma distribution was selected to estimate the uncertainty associated with costs, healthcare resource use, and underreporting factors, and pertussis incidence, given its skewness to the right. The Dirichlet distribution was utilized for interdependent variables. Sensitivity parameters can be found in **Annex I, Tables S1, S3, S5 and S6**.

Scenario analyses were based on the DSA results and were utilized to further analyse high-impact parameters (see **Annex I, Table S7**).

Analysis assumptions summarized the key assumptions of the sensitivity analysis and assessed their uncertainty (**Annex I, Table S8**).

### 2.6. Framework validation

The framework was validated using black-box testing and white-box testing tools.

Black-box testing checks whether calculations in the economic analysis have been applied correctly. During this test, parameters are changed to see if the outcome would also change. White-box testing is another tool recommended for key calculations or when black-box testing yields unexpected results. During this test, calculations are checked cell by cell (i.e., more thoroughly) [40].

## 3. Results

### 3.1. Base-case results

At base-case, the total annual cost of pertussis in the UK was approximately £238 million (M) for 2020. The majority of these costs was comprised of indirect costs (∼£159 M), followed by medical costs (∼£66 M) and patient costs (∼£13 M) (Fig. 2).

Analysis of the age distribution for total costs (Table 1, Fig. 3) showed costs were highest for patients aged 55–59 years, followed by the 60–64 years and 50–54 years age groups. Total costs were substantially lower for the 70–74 years and older age groups.

GP/nurse visits were the greatest contributor to medical costs, representing over 50 % of these costs (Table 1). Conversely, diagnostics (∼£13,000) had the lowest impact on total medical costs because it was only applied to diagnosed patients. The majority of medical costs for patients were transport costs (∼£10 M). Regarding indirect costs, leisure time costs (∼£72 M) were the largest contributor, closely followed by productivity loss (∼£71 M).

### 3.2. Sensitivity analysis results

The DSA showed the impact of parameters on the estimated

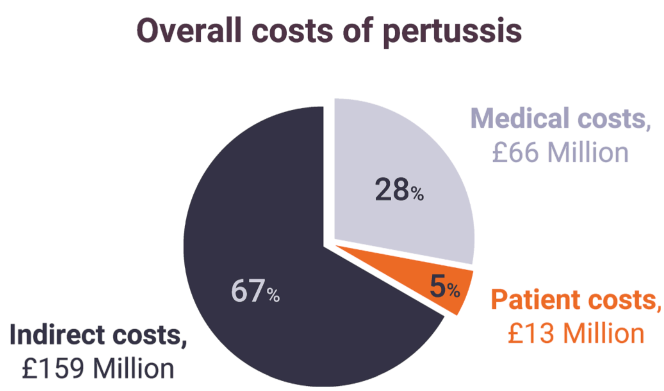



**Fig. 2.** Base-case annual total costs of pertussis*, 2020. *Percentages (%) represent the proportion of overall costs related to each cost category.

economic burden. These included workweek duration, inpatient visits, underreporting factors, leisure time loss, and productivity loss (Fig. 4).

When assessing parameter uncertainty, the PSA showed that 95 % of total economic burden simulations were within 2 standard deviations of the lower and upper range. Furthermore, the simulation with the lowest outcome estimated a minimum total cost of approximately £106 M while the simulation with the highest outcome estimated a maximum total cost of approximately £407 M (see Fig. 5).

### *3.3. Scenario analyses*

Only scenario 3, which used incidence values from the 2012 outbreak, yielded higher total costs (£518 M) than the base-case scenario (£238 M) (Table 2). Underreporting factors (scenarios 1 and 2) had the second largest impact on total costs; no underreporting (0 % underreporting) drastically reduced the estimated economic burden from the base-case scenario to £2M, while 50 % underreporting reduced the total costs to £119 M. Analysing a scenario with no leisure time (scenario 7) reduced the total costs to roughly £166 M. Further removing indirect costs, as seen in scenarios 8 (no indirect costs) and 9 (no indirect costs and underreporting), also greatly reduced the total costs to approximately £79 M and £0.75 M, respectively. Furthermore, we observed that medical care use timeframe, hospital costs or the use of FCA analyses did not cause large deviations from the base-case estimate.

### *3.4. Framework validation results*

Validation analyses through black-box and white-box testing revealed that the framework performed as expected and thus is proven to be technically valid (see **Annex I, Table S9**).

## 4. Discussion

This cost-of-illness study describes the overall economic burden of pertussis in adults aged 50 years or older in the UK. The greatest contribution to the total cost was indirect costs, representing 67 % of the total, followed by medical costs (28 %) and patient costs (5 %). Leisure time costs represented 45 % of the total indirect costs and, overall, the highest costs were registered among patients aged 55–59 years. Following this peak, the age-specific distribution of costs was observed

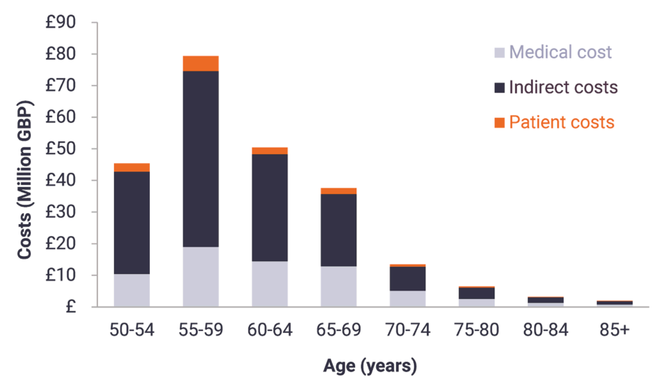



**Fig. 3.** Base-case annual total costs by age group, 2020. GBP, Great Britain Pound (£).

**Table 1**
Total annual costs (medical, patient and indirect costs) by age group.

| | Age groups (years) | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 50–54 | 55–59 | 60–64 | 65–69 | 70–74 | 75–79 | 80–84 | ≥85 | |
| **Medical costs** | | | | | | | | | |
| GP/nurse visit | £5,856,696 | £10,718,729 | £8,132,542 | £7,230,798 | £2,867,405 | £1,427,439 | £705,247 | £443,188 | £37,382,043 |
| GP prescription | £20,464 | £37,453 | £28,416 | £25,265 | £10,019 | £4,988 | £2,464 | £1,549 | £130,618 |
| Clinical values | £46,621 | £85,324 | £64,737 | £57,559 | £22,825 | £11,363 | £5,614 | £3,528 | £297,571 |
| Outpatient visit | £613,300 | £1,122,441 | £851,621 | £757,193 | £300,268 | £149,478 | £73,852 | £46,410 | £3,914,563 |
| A&E visit | £554,925 | £1,015,606 | £770,563 | £685,122 | £271,688 | £135,251 | £66,823 | £41,992 | £3,541,970 |
| Inpatient visit | £3,310,947 | £6,059,584 | £4,597,543 | £4,087,763 | £1,621,020 | £806,969 | £398,695 | £250,546 | £21,133,067 |
| Diagnostics | £3,715 | £2,994 | £2,029 | £1,620 | £1,358 | £676 | £334 | £210 | £12,937 |
| **Total** | £10,406,668 | £19,042,131 | £14,447,451 | £12,845,321 | £5,094,584 | £2,536,164 | £1,253,029 | £787,422 | **£66,412,769** |
| **Patient costs** | | | | | | | | | |
| OTC | £18,796 | £34,400 | £26,100 | £23,206 | £ 9,202 | £4,581 | £2,263 | £1,422 | £119,971 |
| Transport | £1,506,371 | £2,756,910 | £2,091,729 | £1,859,796 | £737,510 | £367,144 | £181,393 | £ 113,990 | £9,614,844 |
| Prescriptions | £1,089,728 | £1,994,384 | – | – | – | – | – | – | £3,084,112 |
| **Total** | £2,614,895 | £4,785,694 | £2,117,829 | £1,883,003 | £746,713 | £371,725 | £183,656 | £115,412 | **£12,818,928** |
| **Indirect costs** | | | | | | | | | |
| Productivity loss* | £18,570,880 | £30,265,331 | £14,664,720 | £5,807,928 | £887,965 | £211,812 | £104,649 | – | £70,513,286 |
| Leisure time loss | £11,220,651 | £20,535,661 | £15,580,869 | £13,853,247 | £5,493,566 | £2,734,783 | £1,351,159 | £849,089 | £71,619,026 |
| Informal care costs | £1,178,446 | £2,156,752 | £1,636,376 | £1,454,933 | £576,960 | £287,220 | £141,905 | £89,175 | £7,521,768 |
| Opportunity costs** | £1,406,400 | £2,573,947 | £1,952,911 | £1,736,371 | £688,565 | £342,779 | £169,355 | £106,425 | £8,976,753 |
| **Total** | £32,376,377 | £55,531,690 | £33,834,877 | £22,852,479 | £7,647,057 | £3,576,594 | £1,767,068 | £1,044,689 | **£158,630,832** |

A&E, Accident and Emergency; GP, general practitioner; OTC, over the counter.
Notes: * Productivity loss using the HCA (human capital approach).
**Opportunity costs per visit.

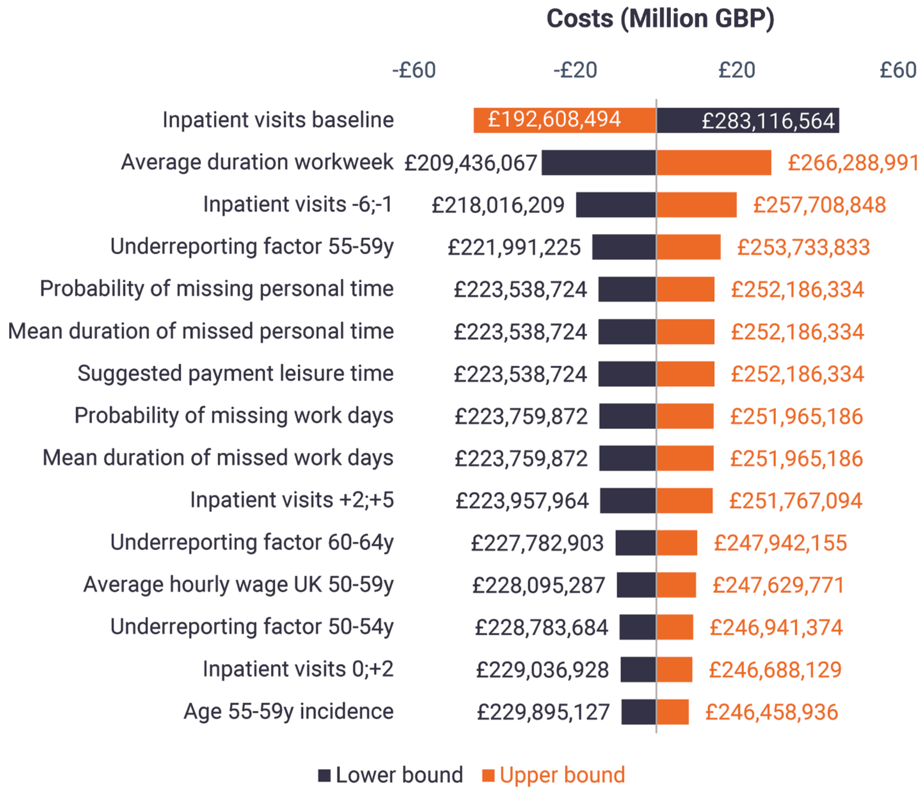



**Fig. 4.** Deterministic sensitivity analysis - top 15 parameters. GBP, Great Britain Pound (£); UK, United Kingdom; y, years of age; −6;-1, period from 6 months to 1 month prior to diagnosis date; +2;+5, period from 2 months to 5 months after diagnosis date; 0;+2, period from diagnosis date to 2 month after diagnosis.

to decline with progressively older age groups.

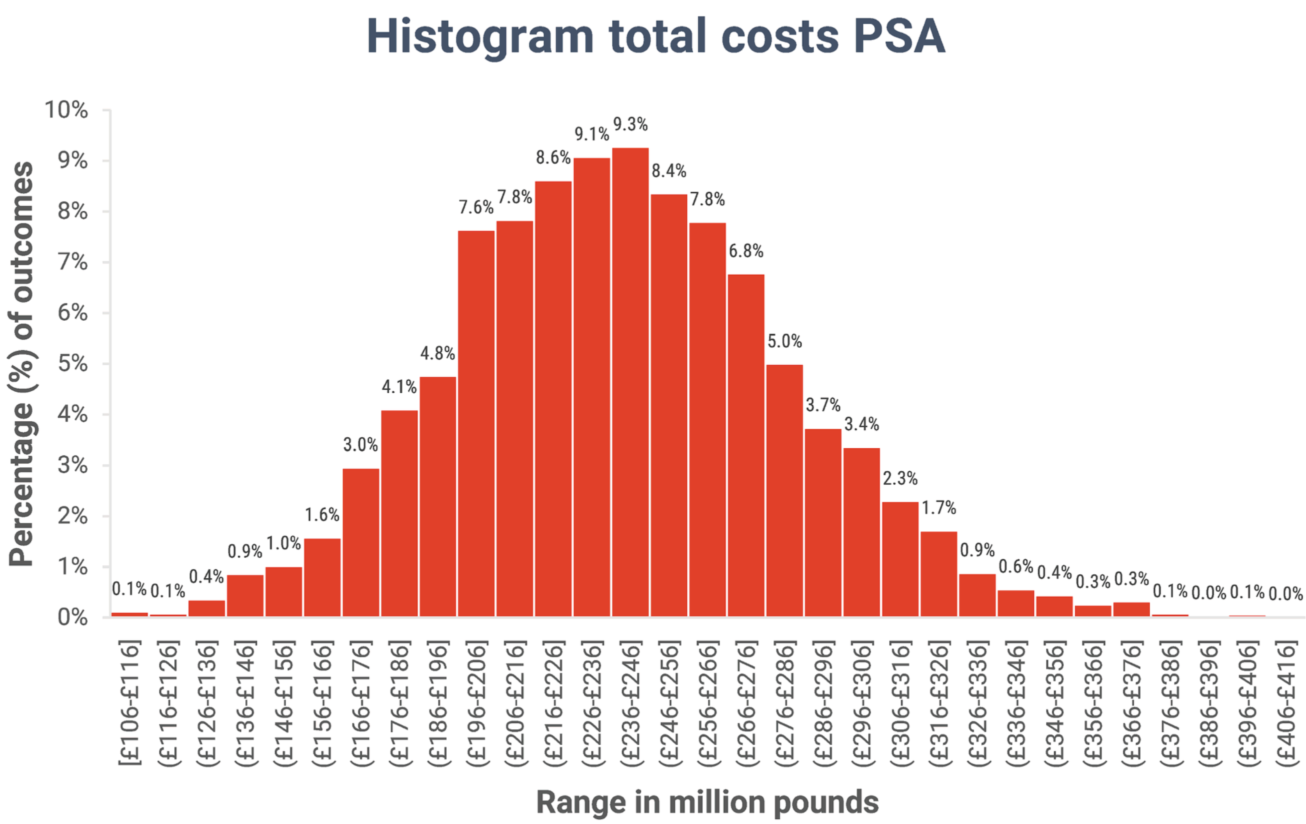
A reason for higher costs for the 55–59 years age group could be the higher reported incidence in this age group than in older individuals [12]. The impact of incidence is amplified in the analysis because age-specific underreporting factors are high for patients aged 55–59 years (underreporting factor of 134). Although two other age groups have higher underreporting factors than the 55–59 years age group, the population size, incidence rate and employment rate for these two age groups is comparably lower than the 55–59 years age group (**Annex I, Table S1**) [9]. Another driver for high costs could be that the 55–59 years age group has higher employment rates than the older age groups. As pertussis negatively impacts the ability to work and has a low fatality rate, this age group experiences the highest loss of productivity which increases indirect costs. While the 50–54 years age group has a higher employment rate, population size and incidence rate compared to the 55–59 years age group, it has a much lower underreporting factor which may influence the overall impact of incidence [9].

The DSA results suggest that parameters introducing the highest variation are incidence, hospitalization, and indirect costs. The scenario analyses suggest that factors related to the number of patients (i.e. incidence and underreporting factor) have the largest influence on the outcome of the current analysis. Total cost-of-illness increased with higher incidence and decreased with lesser underreporting. While indirect costs were attributed to the cost-of-illness, the total economic burden remains substantial (£79 M) because of the sizable burden from medical costs and patient costs which remain unchanged in such a scenario (Scenario 8). The PSA showed that 95 % of total economic burden simulations were within 2 standard deviations of the lower and upper range.

The four previous studies assessing the economic burden of pertussis cannot be compared to our findings, given important differences in methodologies and because they were conducted in countries with size, pertussis epidemiology, and healthcare systems considerably different from the UK [15–18]. McLaughlin et al. [17] calculated the total economic burden of pertussis in the US by multiplying the age-specific incidence with the cost per case and reported a total economic burden of $398 M for patients older than 50 years of age, which is around £280 M (using the conversion rate of 1 US dollar [$]= £0.72 from June 2021). In-line with this result, the total economic burden in the UK calculated using our framework (£238 M) is lower but within range of the outcome reported by McLaughlin et al. [17] However, the average cost per case was reported to be $1,025 (~£725) by McLaughlin et al. [17] which is much lower than the cost estimated in the current analysis (£1,526). This may be because McLaughlin et al. [17] did not include leisure time and informal care in their calculations. Despite the higher cost per case in our study, the total costs are lower than those reported by McLaughlin et al. [17] which may be due to differences in country size, as well as in the methods and assumptions used in the two studies.

Two other studies conducted in the US, reported by McGarry et al. [15,16], studied the cost-effectiveness of tetanus, diphtheria and acellular pertussis (Tdap) vaccination in adults ≥ 65 years of age. In the study from 2014, McGarry et al. [15] reported that the costs per case were $99.22 (~£70), $203.13 (~£144) and $7,221.97 (~£5,122) for a mild, moderate and severe infection, respectively. Therefore, the average cost per case in the current study (£1,526) falls within the range of the costs per case reported by McGarry et al. [15,16]. The mild and moderate infection costs per case were lower in these US studies than the mean cost per case in our study, possibly because mild and moderate cases are associated with less healthcare resource use. Furthermore, McGarry et al. [15,16] did not consider the indirect costs that were included in the present study. Notably, the very high cost for severe cases reported by McGarry et al. [15,16] potentially reflects that hospitalization costs in the US are significantly higher than hospitalization costs in the UK, as documented previously [41].

Lastly, a microsimulation study by McGirr et al. [18] reported the total burden of pertussis in Canada. Total medical costs were estimated at Canadian dollar [CAD] $26 M (~£15 M calculated using the conversion rate of 1 CAD $ = 0.58 £ from June 2021) in a non-outbreak year




| | Total costs | Medical costs | Patient costs | Indirect costs |
|---|---|---|---|---|
| Average | £238 205 773 | £66 170 079 | £12 848 147 | £159 187 546 |
| Min | £105 709 378 | -£56 055 084 | £7 266 179 | £78 660 330 |
| Max | £407 450 656 | £167 721 932 | £20 510 275 | £282 512 940 |
| 95% low | £236 993 753 | £65 443 984 | £12 792 838 | £158 402 570 |
| 95% high | £239 417 792 | £66 896 174 | £12 903 457 | £159 972 523 |

**Fig. 5.** Uncertainty of the results as shown by the PSA. Disaggregated results of the PSA (seen in the table) from 5000 simulations are summarized in a histogram. 95% low, 95% confidence interval lower bound value; 95% high, 95% confidence interval upper bound value; Min, minimum range value; Max, maximum range value; PSA, probabilistic sensitivity analysis.

**Table 2**
Results of the different scenario analyses.

| | Scenario analyses | Medical costs | Patient costs | Indirect costs | Total |
|---|---|---|---|---|---|
| Scenario | **Base case** | £66,412,769 | £12,818,928 | £158,630,832 | £237,862,529 |
| 1 | **0 % underreporting** | £626,940 | £123,372 | £1,503,238 | £2,253,551 |
| 2 | **50 % underreporting** | £33,212,853 | £6,409,464 | £79,315,416 | £118,937,733 |
| 3 | **Incidence as in 2012** | £142,519,109 | £28,172,425 | £347,661,462 | £518,352,996 |
| 4 | **Medical care use as T-1; T + 11*** | £65,860,473 | £11,917,737 | £157,790,895 | £235,569,105 |
| 5 | **Hospital costs reduced by 50 %** | £55,846,236 | £12,818,928 | £158,630,832 | £227,295,995 |
| 6 | **Friction cost approach (FCA) instead of the human capital approach (HCA)** | £66,412,769 | £12,818,928 | £144,528,175 | £223,759,872 |
| 7 | **No leisure time** | £66,412,769 | £12,818,928 | £87,011,806 | £166,243,503 |
| 8 | **No indirect costs** | £66,412,769 | £12,818,928 | – | £79,231,697 |
| 9 | **No indirect costs and underreporting** | £626,940 | £123,372 | – | £750,312 |
| 10 | **No opportunity costs per visit** | £66,412,769 | £12,818,928 | £149,654,079 | £228,885,776 |

T, the date of diagnosis.
*T-1 and T + 11 refer to time period between one month before and 11 months after date of diagnosis.

and CAD $72 M (~£42 M) in an outbreak year for the total population. For both scenarios, medical costs were lower than the findings in the current analysis (~£66 M). This difference could be explained by the different country size and epidemiology, and by the underreporting factor used in McGirr et al. [18] which was lower (5.6) than the one used in our study (from 59 to 167 based on age group).

A major strength of this study is the use of the Clinical Practice Research Datalink database that allowed extensive evaluation of different types and frequencies of healthcare resource use. Although the data were generated for England only, a comparison of publicly available source about the incidence of pertussis among adults 50 years and over in Scotland and Wales, show that using England data is deemed acceptable given the comparable incidence level. A second strength is that the cost-of-illness analysis integrated a societal perspective which is not extensively published in the literature for this setting. In this study, we not only consider medical costs and productivity loss, but also patient costs, leisure time costs, and informal care costs. Both sensitivity and scenario analyses further strengthen the results of this study as these analyses allow for a direct comparison of HCRU related to pertussis versus baseline.

Limitations of this study include the underreporting factors which were obtained from a large perspective serological study by Stefanoff et al. conducted in Poland [9]. It is assumed that the UK situation is similar to that of Poland as neither country has adult vaccination recommendations in place, both have a similar pertussis notification system and comparable incidence rates among notified cases [42]. The two scenario analyses suggest that the influence of the underreporting factor is significant and therefore further understanding on underreporting will be needed to characterize the economic burden more accurately. A further limitation of this study is that the geographical location of patients within the UK was not known, which is important to estimate the costs of prescriptions since patients in certain UK regions do not pay any costs. As such we might have overestimated the prescription fee costs, however this would not have substantial impact on the outcome of the study because the estimate was applied only to the two younger age groups.

The use of OTC medication and costs could be underestimated as they are based on acute cough-related costs while pertussis is a longer-lasting disease [31]. A limitation of the indirect cost estimate concerns the uncertainty of whether healthcare visits are included in 'time missed from work' in the study reported by Lee et al. [35], which is used in our analyses to estimate the probability and duration of lost leisure time. Due to this uncertainty, additional productivity loss is assumed in the analysis for each healthcare visit. The influence of this assumption is tested in a scenario analysis in which these costs are not included. The scenario analysis shows that the assumption has a moderate influence on the results of the analysis with the total economic burden being around £9M lower than the base-case result.

## 5. Policy implications & future research

From a societal perspective, preventing disease occurrence leads to substantial benefits. A decreased disease incidence is likely to reduce medical and patient costs, while also reducing losses in working and leisure time. As such, policy makers could enhance the pertussis notification system to better inform healthcare professionals within the NHS about pertussis diagnosis and the true incidence of pertussis in the adult population. Furthermore, if pertussis cases were detected faster and more often, additional secondary infections could be prevented by early treatment initiation [3].

A further preventive measure could include the implementation of an immunization program among adults $\geq$50 years of age with pertussis booster vaccines (Tdap) which is effective and safe for patients of all ages [43]. In the US, McGarry et al. [15,16] found that supplementing baseline practice with vaccinating 10 % of eligible patients using Tdap could prevent over 97,000 cases annually and save a total of $48 M after deducting the cost of vaccination [15,16]. Notably, McGarry et al. [15,16] did not correct for underreporting, thus implementing these preventive effects could lead to higher savings than reported. Unfortunately, such research was not yet performed in the UK, and findings from other countries should be read carefully. Therefore, to build on our analysis, future research could include a cost-benefit analysis of such programs, to assess the resources needed to implement of such program with the expected gains in terms of health impacts and spending in the UK. Also, cost-effectiveness analysis would help understand what value for money such programs would have.

Finally, additional research is also needed to identify new treatments that could effectively reduce the severity of pertussis infections [43].

## 6. Conclusion

The total economic burden of pertussis in the population older than 50 years in the UK is substantial. As the UK population ages, this burden is expected to increase alongside the aging population due to the frequent underreporting/misdiagnosis in the older population. The economic burden of pertussis is highest among adults aged 55–59 years and indirect costs are the largest contributor to total costs. These results highlight the importance of considering vaccination programs for adults. Even though the current study has several limitations, the results are valuable for creating awareness among healthcare authorities and professionals. This study emphasizes the importance of future research to reduce the overall pertussis disease burden by focusing on reducing pertussis underreporting, assessing and implementing cost-effective preventive measures, and improving curative strategies. These findings could be used to inform policy decisions and interventions aimed at reducing the economic impact of pertussis.

## CRediT authorship contribution statement

**Jan-Willem Versteeg:** Conceptualization; Data Curation; Methodology; Formal Analysis; Writing - review & editing. **Nicolas Jamet:** Conceptualization; Methodology; Supervision; Validation; Writing - review & editing. **Ken Redekop:** Conceptualization; Methodology; Supervision; Writing - review & editing.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicolas Jamet is employed by GSK and declares no other financial and non-financial relationships and activities. Jan-Willem Versteeg and Ken Redekop declare no financial and non-financial relationships and activities and no conflicts of interest.

## Acknowledgements

The authors thank Kinga Meszaros and Emmanuel Aris for their review of this manuscript. The authors also thank Business & Decision Life Sciences platform for editorial assistance, manuscript coordination and writing support, on behalf of GSK. Athanasia Benekou (Business & Decision Life Sciences) and Kavin Kailash (Arete Access, Berlin) provided medical writing support.

### *Funding*

GlaxoSmithKline Biologicals SA funded the study (study identifier: VEO-000220) and was involved in all stages of study conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also took in charge all costs associated with the development and publication of this manuscript.

### *Data sharing*

GSK makes available, the anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.vaccine.2023.10.010.

## References

[1] Kilgore PE, Salim AM, Zervos MJ, Schmitt H-J. Pertussis: microbiology, disease, treatment, and prevention. Clin Microbiol Rev 2016;29:449–86.
[2] Gopal DP, Barber J, Toeg D. Pertussis (whooping cough). BMJ 2019;364:l401.
[3] Guidelines for the public health management of pertussis in England. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762766/Guidelines_for_the_Public_Health_management_of_Pertussis_in_England.pdf [accessed 13 April 2022].
[4] Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. https://www.cdc.gov/vaccines/pubs/pinkbook/pert.html#bordetella-pertussis [accessed February 14].
[5] World Health Organization. Pertussis https://www.who.int/health-topics/pertussis#tab=tab_1 [accessed 14 April 2022].
[6] Zepp F, Heininger U, Mertsola J, Bernatowska E, Guiso N, Roord J, et al. Rationale for pertussis booster vaccination throughout life in Europe. Lancet Infect Dis 2011;11:557–70.
[7] Nitsch-Osuch A, Korzeniewski K, Kuchar E, Zielonka T, Życińska K, Wardyn K. Epidemiological and immunological reasons for pertussis vaccination in adolescents and adults. Respir Physiol Neurobiol 2013;187:99–103.
[8] Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. Expert Rev Vaccines 2019;18:439–55.
[9] Stefanoff P, Paradowska-Stankiewicz IA, Lipke M, Karasek E, Rastawicki W, Zasada A, et al. Incidence of pertussis in patients of general practitioners in Poland. Epidemiol Infect 2014;142:714–23.
[10] Decker MD, Edwards KM. Pertussis (Whooping Cough). J Infect Dis 2021;224:S310–20.
[11] Riffelmann M, Littmann M, Hülße C, Hellenbrand W, Wirsing von König CH. Pertussis: not only a disease of childhood. Dtsch Arztebl Int 2008;105:623–8.
[12] Harrington L, Aris E, Bhavsar A, Jamet N, Akpo EIH, Simeone JC, et al. Burden of pertussis in adults aged 50 years and older: a retrospective database study in England. Infect Dis Ther 2023.
[13] Public Health Wales Health Protection. Notifications of WHOOPING COUGH in Wales 2018-2021 https://public.tableau.com/app/profile/public.health.wales.health.protection/viz/NotificationsofWHOOPINGCOUGHinWales2018-2021/Dashboard2 [accessed 13 September 2023].
[14] Hellenbrand W, Beier D, Jensen E, Littmann M, Meyer C, Oppermann H, et al. The epidemiology of pertussis in Germany: past and present. BMC Infect Dis 2009;9:22.
[15] McGarry LJ, Krishnarajah G, Hill G, Masseria C, Skornicki M, Pruttivarasin N, et al. Cost-Effectiveness of Tdap vaccination of adults aged ≥65 years in the prevention of pertussis in the US: a dynamic model of disease transmission. PLoS One 2014;9:e72723.
[16] McGarry LJ, Krishnarajah G, Hill G, Skornicki M, Pruttivarasin N, Masseria C, et al. Cost-effectiveness analysis of Tdap in the prevention of pertussis in the elderly. PLoS One 2013;8:e67260.
[17] McLaughlin JM, McGinnis JJ, Tan L, Mercatante A, Fortuna J. Estimated human and economic burden of four major adult vaccine-preventable diseases in the United States, 2013. J Prim Prev 2015;36:259–73.
[18] McGirr A, Fisman DN, Tuite AR. The health and economic burden of pertussis in Canada: a microsimulation study. Vaccine 2019;37:7240–7.
[19] Akobundu E, Ju J, Blatt L, Mullins CD. Cost-of-illness studies: a review of current methods. Pharmacoeconomics 2006;24:869–90.
[20] Onukwugha E, McRae J, Kravetz A, Varga S, Khairnar R, Mullins CD. Cost-of-illness studies: an updated review of current methods. Pharmacoeconomics 2016;34:43–58.
[21] Overview of the UK population: January 2021 https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/january2021 [accessed 31 March 2022].
[22] RPI All Items: Percentage change over 12 months: Jan 1987=100 https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/czbh/mm23 [accessed 7 April 2022].
[23] Pertussis: laboratory confirmed cases reported in England 2019 https://www.gov.uk/government/publications/pertussis-laboratory-confirmed-cases-reported-in-england-2019 [accessed 31 March 2022].
[24] Pertussis: laboratory confirmed cases reported in England 2018 https://www.gov.uk/government/publications/pertussis-laboratory-confirmed-cases-reported-in-england-2018 [accessed 31 March 2022].
[25] Pertussis: laboratory confirmed cases reported in England 2017 https://www.gov.uk/government/publications/pertussis-laboratory-confirmed-cases-reported-in-england-2017 [accessed 31 March 2022].
[26] 2018/19 National Cost Collection Data Publication https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/ [accessed 31 March 2022].
[27] Moloney E, Lee KW, Craig D, Allen AJ, Graziadio S, Power M, et al. A PCR-based diagnostic testing strategy to identify carbapenemase-producing Enterobacteriaceae carriers upon admission to UK hospitals: early economic modelling to assess costs and consequences. Diagn Progn Res 2019;3:8.
[28] Jamet N, Aris E, De Melo J, Ramond A, Simeone J, Berlaimont V. The economic burden of pertussis among adults aged above 50 years, in England: post-hoc analyses of a retrospective database study in England. Eur Respir J 2022;60:S66.
[29] Unit Costs of Health and Social Care 2019 https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ [accessed 31 March 2022].
[30] Pickard R, Chadwick T, Oluboyede Y, Brennand C, von Wilamowitz-Moellendorff A, McClurg D, et al. Continuous low-dose antibiotic prophylaxis to prevent urinary tract infection in adults who perform clean intermittent self-catheterisation: the AnTIC RCT. Health Technol Assess 2018;22:1–102.
[31] Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. BMC Fam Pract 2008;9:10.
[32] NHS prescription charges https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/nhs-prescription-charges/ [accessed 31 March 2022].
[33] Pike J, Grosse SD. Friction cost estimates of productivity costs in cost-of-illness studies in comparison with human capital estimates: a review. Appl Health Econ Health Policy 2018;16:765–78.
[34] Kigozi J, Jowett S, Lewis M, Barton P, Coast J. Valuing productivity costs using the friction-cost approach: estimating friction-period estimates by occupational classifications for the UK. Health Econ 2017;26:1862–8.
[35] Lee GM, Lett S, Schauer S, LeBaron C, Murphy TV, Rusinak D, et al. Societal costs and morbidity of pertussis in adolescents and adults. Clin Infect Dis 2004;39:1572–80.
[36] Economic labour market status of individuals aged 50 and over, trends over time: September 2020 https://www.gov.uk/government/statistics/economic-labour-market-status-of-individuals-aged-50-and-over-trends-over-time-september-2020/economic-labour-market-status-of-individuals-aged-50-and-over-trends-over-time-september-2020 [accessed 31 March 2022].
[37] Average actual weekly hours of work for full-time workers (seasonally adjusted) https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/timeseries/ybuy/lms [accessed 31 March 2022].
[38] Verbooy K, Hoefman R, van Exel J, Brouwer W. Time is money: investigating the value of leisure time and unpaid work. Value Health 2018;21:1428–36.
[39] Oliva-Moreno J, Trapero-Bertran M, Peña-Longobardo LM, Del Pozo-Rubio R. The valuation of informal care in cost-of-illness studies: a systematic review. Pharmacoeconomics 2017;35:331–45.
[40] Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics 2019;37:1391–408.
[41] Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. J Am Med Assoc 2018;319:1024–39.
[42] European Centre for Disease Prevention and Control. Pertussis. Annual Epidemiological Report for 2018. Stockholm: ECDC; 2020.
[43] Weston WM, Friedland LR, Wu X, Howe B. Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix(®)): results of two randomized trials. Vaccine 2012;30:1721–8.