Background: Guillain–Barré syndrome (GBS) is a rare autoimmune disease that can follow viral infections and has in a few cases been linked to vaccinations. Pre-licensure clinical trials did not observe an association between human papillomavirus (HPV) vaccination and GBS, a post-marketing study from 2017 reported an increased relative risk. Aim: We assessed the risk of GBS after HPV vaccination through a systematic literature review and meta-analysis. Methods: We searched Embase, MEDLINE and Cochrane for studies reporting on the risk of GBS after HPV vaccination in individuals aged ≥ 9 years, published between 1 January 2000 and 4 April 2020, excluding studies without a comparator group. Seven studies reporting relative effect sizes were pooled using random-effects meta-analysis. We assessed quality of evidence using the GRADE approach. Study protocol was registered (PROSPERO No. #CRD42019123533). Results: Of 602 identified records, we included 25 studies. Based on over 10 million reports, cases of GBS were rare. In 22 studies no increased risk was observed, while in three studies a signal of increased risk of GBS after HPV vaccination was identified. Meta-analysis yielded a pooled random-effects ratio of 1.21 (95% CI: 0.60–2.43); I² = 72% (95% CI: 36–88). This translates to a number needed to harm of one million to be vaccinated to generate one GBS case. Quality of evidence was very low. Conclusions: The absolute and relative risk of GBS after HPV vaccination is very low and lacks statistical significance. This is reassuring for the already implemented vaccination programmes and should be used in respective communication activities.

Background

More than 10 years after the licensure of the first human papillomavirus (HPV) vaccines, a growing body of evidence supports the large-scale implementation of HPV immunisation programmes. Clinical trials and post-marketing observational studies have shown consistent efficacy, effectiveness and safety of the available HPV vaccines: (i) the bivalent Cervarix, (targeting HPV types 16 and 18, GlaxoSmithKline Biologicals, Rixensart, Belgium); (ii) the 4-valent recombinant Gardasil (targeting HPV types 6, 11, 16, and 18, MSD VACCINS, Lyon, France) and; (iii) the 9-valent Gardasil 9 (targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, MSD VACCINS) [1,2]. Vaccination against HPV reduces the prevalence and incidence of cervical intraepithelial neoplasia grade 2 or 3 or worse (CIN2/3 or worse) among girls and women and anogenital warts diagnoses among girls, women, boys and men [3]. Since 2007, HPV vaccination programmes have been implemented in most European countries, usually targeting females. In recent years, several countries have extended their recommendation to a gender-neutral programme [4]. Notably, herd effects have been measured in countries with high HPV vaccination coverage [3,5].

The future public health impact of HPV vaccination on HPV-associated disease will rely on the vaccination coverage achieved. While the expansion of vaccination programmes is encouraging and uptake is increasing, overall HPV vaccination rates remain low and below national targets in a number of countries [6,7]. Suboptimal vaccination coverage is often driven by vaccine hesitancy, which in turn is often related to public debates and fear of vaccine-induced side effects [8,9].
Among the possible risks associated with vaccination, Guillain–Barré syndrome (GBS) is one of the most serious. Guillain–Barré syndrome is a rare autoimmune disease where the body’s immune system damages nerve cells, causing muscle weakness and, in some cases, paralysis. Most people recover, however, some have lasting long-term weakness and GBS can be fatal. It occurs with a frequency of less than one case per 100,000 person-years in the age group relevant for HPV vaccination, i.e. those aged 10–19 years [10,11].

The causes of GBS are not yet fully understood, however, it often occurs after viral or bacterial infections and, in rare cases, after vaccination [12].

While pre-licensure clinical trials showed no association between HPV vaccination and subsequent occurrence of GBS, a French study from 2017 reported a more than threefold increased relative risk [13]. No evidence of an association between HPV vaccination and any autoimmune disorder has been found so far [9].

Figure 1
PRISMA flow diagram of studies that were screened to identify the risk of Guillain–Barré syndrome after vaccination against human papillomavirus, 1 January 2000–4 April 2020 (n = 602)*

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline.

* The full search strategy and list of the excluded full-text papers can be found in the Supplement.

b Two studies published findings with a large overlap in data based on the VAERS dataset [34,35] with similar findings. The effect estimate by Geier et al. 2017 [35] was used in the primary analyses and Geier et al. 2015 [34] estimate in the sensitivity analysis. Therefore, the results of the meta-analysis show findings of six studies.
best of our knowledge, there is no systematic literature review investigating the potential association between the HPV vaccination and GBS specifically. We assessed the available evidence on the risk of GBS after HPV vaccination by including both randomised controlled trials (RCT) and post-marketing non-randomised studies.

Methods
We registered our systematic literature review protocol at the International Prospective Register for Systematic Reviews (PROSPERO) under the registration number CRD42019123533 [14]. We report our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [15].

We included all studies reporting on individuals aged 9 years and older (i.e. the licenced age) who have been vaccinated against HPV with one of these vaccines: the bivalent Cervarix; (ii) the 4-valent recombinant Gardasil and; (iii) the 9-valent Gardasil 9. We included all possible vaccination schedules, including stopped schedules.

We did not restrict any study design, however, we excluded studies lacking a comparator group and any type of control group would suffice, given the fact that there is one (e.g. placebo, no/other vaccination). We did not restrict our search based on language or geography.

The outcome of interest was GBS after HPV vaccination, as sub-defined by Brighton criteria [16] and all other non-Brighton criteria. According to the Brighton criteria, GBS includes acute inflammatory demyelinating polyradiculoneuropathy and acute motor axonal neuropathy. Other, non-Brighton criteria include Miller Fisher syndrome, which is a subtype of GBS characteristically consisting of the triad of ataxia, areflexia, ophthalmoplegia, acute motor and sensory axonal neuropathy and overlap syndromes between GBS and Miller Fisher syndrome.

We reviewed all literature reporting on the risk of occurrence of GBS after HPV vaccination, published between 1 January 2000 and 21 January 2019 and indexed in Embase, MEDLINE and the Cochrane Central Register of Controlled Trials. On 2 April 2020, we updated our search and included an additional search for publications in PubMed. We provide the full search strategy in the Supplement. The second reviewer (TH) revised the citation lists of included studies. Additionally, we used the snowballing approach to include additional studies by hand-searching the citation lists of included studies.

Study selection and data collection
We uploaded all records to Covidence, a screening and data extraction tool for systematic reviews. Two reviewers (TSB and TH) independently included and excluded studies, using a stepwise approach based on title and abstract screening and a subsequent full-text screening. Subsequently, one reviewer (TSB) extracted data from the included studies using a pre-defined data extraction sheet (the data extraction sheet is included in the Supplement). The second reviewer (TH) revised the data extractions against the original papers to identify potential errors. In case of disagreement, a final decision was made by consensus between the reviewers.

From the included studies, we extracted: (i) information on the study set-up (design, location, study period and follow-up time in person-years, inclusion and exclusion criteria); (ii) study population, (sex; age; number of people included in total, and by vaccinated/control group); (iii) intervention (type of vaccine used); (iv) control group; (v) potential co-interventions and; (vi) outcome (GBS definition; source of outcome reporting; incidence in the HPV-vaccinated and control groups).

When available, we also extracted the incidence rate (IR) and all reported measures of association, including the incidence rate ratio (IRR), relative risk (RR), odds ratio (OR), hazard ratio (HR) and potentially corrected confounding factors. Furthermore, we collected funding source and reported conflict of interest as risk of bias indicators.

Assessment of risk of bias and quality of the body of evidence
Two reviewers (TSB and TH) independently assessed included studies for risk of bias. For RCT we used the revised Cochrane Collaboration’s tool (RoB 2.0) [17] and for non-randomised studies the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool was used [18]. The overall assessment of the quality of the body of evidence followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [19] in its most recent version adapted for use of ROBINS-I [20].

Meta-analysis
All relative effect measures were pooled into one relative effect measure (ratio). Between-study heterogeneity in random-effects meta-analysis is reported through I². Meta-analyses were conducted using the meta-package in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Pre-specified subgroup analyses were planned to explore the potential effect of study design, vaccine type (i.e. bivalent vaccine, 4-valent recombinant vaccine and 9-valent vaccine) and GBS case definition (Brighton vs non-Brighton) on the pooled effect estimate. When multiple studies were reporting on the same data source but with different subgroups of reporting timeframes, the most recent and/or most complete study was used for the primary analysis. Sensitivity analysis was performed by vaccine type and by outcome measurement to assess the robustness of the results of primary meta-analyses.
### Table 1A
Characteristics of the included studies reporting on the risk of Guillain–Barré syndrome after human papillomavirus vaccination, 1 January 2000–4 April 2020 (n = 25)

| Study publication | Country | Study period | Study design | Selection criteria | Sex | Age at enrolment (years) | Number cases/controls, reports, or doses | Participants | Follow up/time-window after vaccination | Person-years | Conflict of Interest / study sponsorship | Statement |
|-------------------|---------|--------------|--------------|--------------------|-----|-------------------------|-------------------------------------------|-------------|----------------------------------------|-------------|----------------------------------------|-----------|
| Deceuninck et al. 2018 [36] | Canada | 1999–2014 | Retrospective ecological population-based | GBS as a main diagnosis, hospitalised | Only the first hospitalisation in a patient was retained | 52 | 48 | 7–17 | 100 cases/background rate | NA | Quebec Ministry of Health and Social Services | Author received grants from GSK and Pfizer and travel reimbursement to attend an ad hoc advisory board meeting of GSK |
| Chao et al. 2012 [37] | US | 2006–2008 | Cohort | All ages who received one dose or more of the 4-valent recombinant vaccine, with ≥ 12 month health plan membership before vaccination | ≥ 12 month health plan membership before vaccination | 100 | NA | 99% was 9–26 | 561,457; 149,306 vaccinated/412,151 controls | 180 days | Merck and Co | Funded and employed by pharmaceutical companies which had significant input into the study |
| Gee et al. 2011 [38] | US | 2006–2009 | Cohort (VSD) | Identified at the seven VSD sites | | 100 | NA | 9–26 | 50,055 vaccine doses / background rate | NA | 42 days | Supported through “Vaccine Safety Surveillance and Assessment Projects contract” with America’s Health Insurance Plans, funded by US CDC |
| Gee et al. 2017 [39] | US | 2006–2015 | Cohort (VSD) | One dose or more of the 4-valent recombinant vaccine | | | 68.5 (calculated) | 31.5 (calculated) | 9–26 | 2,772,138 vaccine doses / background rate | NA | 42 days | “The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.” |
| Donahue et al. 2019 [40] | US | 2015–2017 | Cohort (VSD) | One dose or more of the 4-valent recombinant vaccine | Doses ≥ 42 days of a previous dose in the same person | 47.6 | 52.4 | 9–29 | 128,645 vaccinated; 472,407 historical controls | 560,046 | Up to 180 days | Author(s) report research support from Merck (including a HPV4 vaccine phase 4 post-marketing safety study), Sanofi Pasteur, GSK, Protein Science (now Sanofi Pasteur), and Pfizer |
| Slade et al. 2009 [41] | US | 2006–2008 | Cohort (VAERS) | Reported between June 2006 and December 2008 | | | 97 | 3 | 6–29 | 12,244 reports / background rate | NA | 0–145 days; 6 weeks (4–42 days) considered biologically plausible | US CDC and FDA study |
| Souayah et al. 2011 [42] | US | 2006–2009 | Case–control (VAERS) | Reported between June 2006 and September 2009 | NA (case–control study) | | Mean: 16.2 (SD: 6.3) | 31,189 reports; 15,115 HPV-16 vaccinated/13,881 other vaccination | NA | 66 weeks | US CDC and FDA study | The authors declare no financial conflicts of interest; CDC was directly involved in all aspects of the study |

CPRD GOLD: Clinical Practice Research Datalink General Practice Online Database; FDA: the United States Food and Drug Administration; GBS: Guillain–Barré syndrome; GSK: GlaxoSmithKline; incl: including; NA: not applicable; NR: not reported; RCT: randomised controlled trial; VAERS: Vaccine Adverse Event Reporting System; VSD: Vaccine Safety Datalink; SD: standard deviation; UK: United Kingdom; US: United States; US CDC: United States Centers for Disease Control and Prevention.
### Table 1b
Characteristics of the included studies reporting on the risk of Guillain–Barré syndrome after human papillomavirus vaccination, 1 January 2000–4 April 2020 (n = 25)

| Study and publication | Country | Study period | Study design | Selection criteria | Sex | Age at enrolment (years) | Number cases /controls, reports, or doses | Participants | Follow up/time-window after vaccination | Person-years | Conflict of interest / Study sponsorship |
|-----------------------|---------|--------------|--------------|--------------------|-----|-------------------------|------------------------------------------|-------------|----------------------------------------|--------------|----------------------------------------|
| Geier et al. 2015 [34] | US      | 2006–2012    | Case–-control (VAERS) | Inclusion: Listed US residence | Female % | 100 | Male % | 0 | 18–39 | 22,013 reports | NA | NR | Non-profit 501(c)(3) Institute of Chronic Illnesses Inc, by a grant from the Dworkin Family Foundation. The authors declare they have no conflicts of interest |
| Ojha et al. 2014 [43] | US      | 2010–2012    | Cohort (VAERS) | All reports on the 4-valent recombinant HPV vaccine or other vaccinations among females and males aged 9–26 years | NR | 63% | 37% | 9–26 | 14,812 reports; 4,670 HPV vaccination reports / 10,152 other vaccine reports | NA | 5–47 days | NR | Authors were supported by the American Lebanese Syrian Associated Charities, National Cancer Institute awards to the University of Alabama at Birmingham Comprehensive Cancer Center. The authors declare no financial or non-financial competing interests |
| Geier et al. 2017 [35] | US      | 2006–2014    | Case–control (VAERS) | Inclusion: Listed US residence | Female % | 100 | Male % | NA | 6–39 | 48,832 reports | NA | NR | Non-profit 501(c)(3) Institute of Chronic Illnesses. The authors declare that they have no conflicts of interest |
| Arana et al. 2018 [44] | US      | 2009–2015    | Cohort (VAERS) | All reports on the 4-valent recombinant vaccine between 2009 and 2015 | NA | 60.2 | 22.6% sex unknown | 17.2 | 11–17 (40.7%); unknown (42.7%) | 19,260 4-valent recombinant vaccination reports/ 60,461,220 doses distributed | NA | Partially according to Brighton criteria | NA | US CDC study None |
| Neha et al. 2020 [45] | US      | 2009–2015    | Cohort (VAERS) | All reports on HPV vaccination between 2006 and 2017 | NA | NR | NA | NR | 49,444 reports | NA | NR | NA None None |
| Lehtinen et al. 2016 [24] | Finland | 2007–2010    | Community-based RCT | 33 major, non-adjacent Finnish communities; Finnish or Swedish-speaking; 1992–1995 birth cohorts | NR | 63.8 (calculated) | 36.2 (calculated) | 12–16 Mean: 14.1 (SD: 0.76) | NA | 32,176 | 12 months | NR | GSK funded GSK involved in all stages of the study and analysis |
| Bi et al. 2018 [25] | Finland | 2007–2010    | Community-based RCT | 33 major, non-adjacent Finnish communities; Finnish or Swedish-speaking; 1992–1995 birth cohorts | NR | 63.8 (calculated) | 36.2 (calculated) | 12–16 Mean: 14.1 (SD: 0.76) | NA | 32,175 | Up to 6.5 year | NR | GSK funded GSK involved in all stages of the study and analysis |
| Skufca et al. 2018 [26] | Finland | 2013–2016    | Nationwide population-based retrospective register cohort | Females | Persons who have been vaccinated in clinical trials before the NVP were included in this study (birth cohorts 1992–1995) | 100 | NA | 11–15 | NA | 24,066/ 134,615 vaccinated/ 105,990 controls | 0–18/0.65–365/ 75–365 days | 431,075 | National Institute for Health and Welfare, GSK and Pfizer | Authors received grants from several pharmaceutical companies |
| Grönlund et al. 2016 [27] | Sweden   | 2006–2012    | Open cohort | All girls and women living in Sweden, diagnosed with one or more autoimmune diseases | Vaccinated before the start of individual follow-up, those who had died or emigrated before the start of follow-up | 100 | NA | 10–30 | NA | 70,265 | 180 days after each dose | 253,695 | Swedish Foundation for Strategic Research and the Strategic Research Area in Epidemiology | Authors received pharmaceutical companies |

CPRD GOLD: Clinical Practice Research Datalink General Practice Online Database; FDA: the United States Food and Drug Administration; GBS: Guillain–Barré syndrome; GSK: GlaxoSmithKline; incl: including; NA: not applicable; NR: not reported; RCT: randomised controlled trial; VAERS: Vaccine Adverse Event Reporting System; VDS: Vaccine Safety Datalink; SD: standard deviation; UK: United Kingdom; US: United States; US CDC: United States Centers for Disease Control and Prevention.
| Study and publication year | Country                  | Study period | Study design     | Selection criteria                                                                                           | Study design                                                                 |
|----------------------------|--------------------------|--------------|------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Hviid et al. 2018 [28]     | Sweden and Denmark       | 2006–2013    | Register-based   | All women living in Sweden and Denmark                                                                       | Bivalent vaccination                                                          |
| Frisch et al. 2018 [29]    | Denmark                  | 2006–2016    | National cohort  | All boys born in Denmark in 1988–2006                                                                        | GBS diagnosis before study entry                                              |
| Grimaldi-Bensouda et al. 2014 [30] | France                  | 2007–2011    | Case–control     | Specialised centres recruited incidence cases of six types of autoimmune disorders (incl. GBS)            | NR                                                                            |
| Miranda et al. 2017 [31]   | France                   | 2008–2013    | Longitudinal    | All girls aged 13–16 years old covered by the general insurance scheme                                        | Living in France; able to undergo a telephone interview in French (participants or parents) |
| Andrews et al. 2017 [32]   | UK (England)             | 2007–2016    | Self-controlled  | Admissions with any mention of ICD-10 code for GBS (G61) in any of the 20 diagnosis fields              | History of HPV vaccination; any of the autoimmune diseases of interest before enrolment to the cohort. |
| Cameron et al. 2016 [33]   | UK (Scotland)            | 2004–2014    | Ecological       | Hospital admissions in Scotland, a selection of 60 conditions                                                | Hospital admissions in Scotland, a selection of 60 conditions                |
| Willeme et al. 2016 [34]   | UK                       | 2005–2010    | Pooled analysis | One exposed female cohort and three unexposed cohorts: historical female, concurrent male, and historical male | One exposed female cohort and three unexposed cohorts: historical female, concurrent male, and historical male |
| Vesteraaten et al. 2008 [46] | NR                      | Up to mid-2007| Pooled analysis  | All completed or ongoing RCT of AIPOJ, adjuvanted HPV2, HSV1 and HBV vaccines conducted by GSK Biologicals or collaborators | Four cohorts: two female cohorts, two male cohorts                             |

**Table 1c** Characteristics of the included studies reporting on the risk of Guillain–Barré syndrome after human papillomavirus vaccination, 1 January 2000–4 April 2020 (n=25)
Public health perspective
To assess the public health implications of our findings, we calculated the number needed to harm (NNH) to generate one additional case of GBS using GRADEprofiler version 3.6 (Informer Technologies, Los Angeles, United States (US)), based on the pooled findings of this study and the baseline risk for the age group of 10–19-year-olds (males: 0.97/100,000; females: 0.55/100,000; overall 0.75/100,000) [21]. For comparison, the number needed to vaccinate (NNV) was calculated in respect to the prevention of one case of cervical cancer [22].

Results
In total, we identified and screened 602 citations and included 25 studies (Figure 1).

Study characteristics
Population
The 25 included studies (Table 1) were conducted between 1999 and 2017. Twelve studies were conducted in Europe [13,23-33] and 12 studies were conducted in North America [34-45]. One study reported pooled RCT outcomes [46] without reporting the study location(s).

While most study populations comprised of adolescents, older and younger participants were also included. Age ranged from 6–72 years. We planned for inclusion of people aged 9 years and older [14] because the HPV vaccines are approved for people aged 9 years and older. However, for completeness, we decided not to exclude studies reporting on a broader age group. The majority of studies reported exclusively on the vaccination of girls and women. Twelve studies reported exclusively on females (100% females in 11 studies and 97% females in one study), nine studies reported on both sexes (some of which had males only as comparator), one study reported exclusively on males and three studies did not report the sex of the participants (Table 1).

The included studies comprised data of more than 10 million reports in total. Of 25 studies, 14 reported the number of cases/controls, reports or vaccine doses (range: 4,133,370–4,415,894), 10 studies reported the number of participants (range: 6,622,607–6,843,326) and one study [23] did not report any number of participants, reports or case/control numbers.

Three studies had a randomised design: two studies reported on the same community-based randomised controlled trial [24,25] and one was a pooled analysis of RCT [46]. The remaining 22 studies had a non-randomised design [13,23,26-45]: 14 cohort studies, five case–control studies, two ecological studies and one self-controlled case series. The cohort studies were based on either registry data, adverse event notification data and/or clinical or hospital databases.

Intervention
Fourteen of 25 studies reported exclusively on vaccination with the 4-valent recombinant vaccine [27-30,34-39,41-44] and five reported exclusively on the bivalent vaccine [24,26,33,46] (Table 2). Three studies reported on both the 4-valent recombinant vaccine and the bivalent vaccine [13,31,32], while one reported only on the 9-valent vaccine [40]. Two studies did not specify the type of HPV vaccine used [23,45].

Comparator
Studies compared the risk of occurrence of GBS after HPV vaccination to either the risk of GBS after no vaccine (e.g. non-targeted populations such as boys), to another vaccine e.g. hepatitis B (HBV vaccine), meningococcus or influenza vaccine), or against historical background rates (Table 2). Case–control studies compared frequency of HPV vaccination in GBS cases to the frequency of HPV vaccination in controls; the controls being the general population or other adverse events reported to the vaccine safety registry.

Outcome
The duration of follow-up time varied, ranging from 42 to 180 days post-vaccination to the total accumulated number of person-years available in the registry or medical records. Eight studies reported the total follow-up time [13,26-29,33,36,37], which adds up to 42,055,425 reported person-years in total.

While five studies referred to the Brighton criteria for GBS case definitions [30,38,39,41,44], in the majority of studies GBS diagnosis was based on original and expanded International Classification of Diseases codes (ICD-9 and ICD-10) as well as other coding systems such as Medcode, MedDRA and VAERS and free-text notes in medical files (Table 2).

Risk of bias
We summarised the findings of our risk of bias assessment in Figure 2 and Supplementary Table S3. The risk of bias in the community-based RCT by Lehtinen et al. and Bi et al. [24,25] was considered to be low for most indicators, but high regarding the selection of the reported results, which was limited for GBS. We were not able to assess the risk of bias in the pooled analysis of 42 studies by Verstraeten et al. [46], of which 16 reported HPV vaccination, because of the complexity of the pooled design and lack of reporting of the key indicators for the risk of bias assessment. The risk of bias in 14 of 22 non-randomised studies was assessed as being critical and eight studies were assessed as being at serious risk of bias. The risk of bias was mostly introduced by the critical risk of confounding (i.e. lack of confounding correction), or because of the outcome measurement i.e. GBS diagnosis not based on Brighton criteria [15]. Risk of bias because of the classification of the intervention (vaccination status) was moderate when based on a registry and critical when self-reported. Less than 10 studies per outcome and per study design were available for pooling, which
| Study and publication year | Study design | Vaccine | Comparator | GBS diagnosis | Brighton criteria | Outcome | After HPV vaccination | Comparator | Ratio/comparison |
|----------------------------|--------------|---------|------------|---------------|------------------|---------|----------------------|------------|-------------------|
| Decouvinck et al. 2018 [36] | Retrospective ecological population-based | 4-valent recombinant | No vaccine; non-targeted boys and girls | ICD-9 (357.0) or ICD-10 (G61.0) as main diagnosis | No | Age 7–8: NA | NA | Girls: 1,190,272 Boys: 1,242,827 | Girls: 6 Boys: 3 | Adjusted RR: 0.81 (95% CI: 0.29–2.26) |
|                            |              |         |            |               |                  |         | Age 9–14: 211,291 | 1 | Girls: 402,139 Boys: 662,494 | Girls: 2 Boys: 1 | |
|                            |              |         |            |               |                  |         | Age 10–13: NA | NA | Girls: 2,659,304 Boys: 2,648,862 | Girls: 15 Boys: 19 | |
|                            |              |         |            |               |                  |         | Age 14–17: 222,751 | 1 | Girls: 433,951 Boys: 685,975 | Girls: 2 Boys: 1 | |
|                            |              |         |            |               |                  |         | Age 15–17: 174,953 | 2 | Girls: 1,094,104 Boys: 1,785,852 | Girls: 2 Boys: 1 | |
| Chao et al. 2012 [37]      | Cohort       | 4-valent recombinant | No vaccine | ICD-9 (original and expanded) | No | NR | 0 | NA | NR | 0 | 0 | Historical background IR (per 100,000 py), per age group (years): 9–10: 0.945; 11–14: 1.257; 15–17: 2.130; 18–26: 2.512 |
| Gee et al. 2011 [38]       | Cohort (VSD) | 4-valent recombinant | Historical background rate using HCUP data | ICD-9 (357.0) | Yes | NR | 0 | NA | NR | 0 | 0 | Not reported; attributable risk: 0 |
| Gee et al. 2017 [39]       | Cohort (VSD) | 4-valent recombinant | Published background rate | ICD-9 (357.0) | Yes | NR | 0 | NA | NR | 0 | 0 | Not possible |
| Donahue et al. 2019 [40]   | Cohort (VSD) | 9-valent | Historical comparison (2007–2014), concurrent comparison | ICD-10 (G61.0) | No | NR | 0 | 0 | NR | 3 | NA |
| Slade et al. 2009 [41]     | Cohort (VAERS) | 4-valent recombinant | Background rate for females aged 9–26 years (based on Healthcare Cost and Utilisation Project data for 2000–2004) | MedDRA term GBS or text containing GBS or Guillain-Barré | Yes | NR | 12 cases by Brighton criteria | Reporting rate 0.3/10,000 py | NR | Reporting rate 1.27/10,000 py |

CI: confidence interval; CPRD GOLD: Clinical Practice Research Datalink General Practice Online Database; GBS: Guillain–Barré syndrome; GSK: GlaxoSmithKline; HR: hazard ratio; ICD: International Classification of Diseases; IR: incidence rate; MedDRA: Medical Dictionary for Regulatory Activities; NA: not applicable; ND: not done; NP: not possible; NR: not reported; OR: odds ratio; py: person-year; RC: randomised controlled trial; RI: relative incidence; RR: relative risk; VAERS: Vaccine Adverse Event Reporting System; VSD: Vaccine Safety Datalink.
| Study and publication year | Study design | Vaccine | Comparator | Outcome | Brighton criteria | After HPV vaccination | Comparator | Ratio/comparison |
|----------------------------|-------------|---------|------------|---------|------------------|----------------------|------------|-----------------|
| Souayah et al. 2011 [42]   | Case-control (VAERS) | 4-valent meningococcal vaccine/4-valent influenza vaccine | general population (literature) | GBS diagnosis | No | NR | 45 cases within the first 6 weeks | Weekly reporting rate in the first 6 weeks: 6.6/10,000,000 | ND |
| Geier et al. 2015 [34]     | Cohort (VAERS) | 4-valent recombinant | Controls: other (non-GBS) reported adverse events associated with the 4-valent recombinant vaccine | VAERS code: 10018767 | No | NR | 18 cases/5,106 controls | NR |
| Gjha et al. 2014 [43]      | Cohort study: VAERS | 4-valent recombinant | All other vaccinations | MedDRA term: Guillain–Barré syndrome | No | NR | 9 cases/4,620 reports (0.19%) | NR |
| Geier et al. 2017 [35]     | Cohort (VAERS) | 4-valent recombinant | Controls: other (non-GBS) reported adverse events associated with the 4-valent recombinant vaccine | VAERS code: 10018767 | No | NR | 56 cases/15,330 controls | NR |
| Arana et al. 2018 [44]     | Cohort (VAERS) | 4-valent recombinant | Other reports | MedDRA term: Guillain–Barré syndrome and clinical review | Yes | NR | 14 by Brighton criteria | NA |
| Neha et al. 2020 [45]      | Cohort (VAERS) | NR | Other reports | MedDRA term: Guillain–Barré syndrome and clinical review | No | NA | 26 | NR |
| Lehtinen et al. 2016 [24]  | Community-based RCT | Bivalent | HBV vaccination | ICD-10 | No | NR | 0 | No case during 12 months follow up | NR |
| Bi et al. 2019 [45]        | Community-based RCT | Bivalent | HBV vaccination | ICD-10 | No | NR | 63,927 years | Not possible | 75,460.8 years | 1 | Not possible | ND |

CI: confidence interval; CPRD GOLD: Clinical Practice Research Datalink General Practice Online Database; GBS: Guillain–Barré syndrome; GSK: GlaxoSmithKline; HR: hazard ratio; ICD: International Classification of Diseases; IR: incidence rate; MedDRA: Medical Dictionary for Regulatory Activities; NA: not applicable; ND: not done; NP: not possible; NR: not reported; OR: odds ratio; py: person-year; RCT: randomised controlled trial; RI: relative incidence; RR: relative risk; VAERS: Vaccine Adverse Event Reporting System; VDS: Vaccine Safety Datalink.
| Study publication year | Study design | Vaccine | Comparator | Outcome | Brighton criteria | After HPV vaccination | Comparator | Ratio/comparison |
|------------------------|-------------|---------|------------|---------|-----------------|----------------------|------------|-----------------|
|                        |             |         |            | GBS diagnosis | Person-years | Number of cases of GBS | Incidence rate | Person-years | Number of cases of GBS | Incidence rate |
|                        |             |         |            | Overall: 186,934 | Overall: 6 | 0–180 days: 55,270 | 0–180 days: 2 | NR | 244,141 | 1 | NR |
|                        |             |         |            | 181–365 days: 48,332 | 181–365 days: 2 | 1365 days: 82,832 | 1365 days: 2 | 0–180 days: | 2.64 (95% CI: 0.23–30.18); adjusted HR: 2.76 (95% CI: 0.62–11.73) |
|                        |             |         |            | > 365 days: 82,832 | > 365 days: 2 | > 365 days: 2 | > 365 days: 2 | > 365 days: | 27.56 (95% CI: 1.41–53.8); adjusted HR: 32.17 (95% CI: 1.59–62.4) |
|                        |             |         |            | Overall: 186,934 | Overall: 6 | 0–180 days: 55,270 | 0–180 days: 2 | NR | 244,141 | 1 | NR |
|                        |             |         |            | 181–365 days: 48,332 | 181–365 days: 2 | 1365 days: 82,832 | 1365 days: 2 | 0–180 days: | 2.64 (95% CI: 0.23–30.18); adjusted HR: 2.76 (95% CI: 0.62–11.73) |
|                        |             |         |            | > 365 days: 82,832 | > 365 days: 2 | > 365 days: 2 | > 365 days: 2 | > 365 days: | 27.56 (95% CI: 1.41–53.8); adjusted HR: 32.17 (95% CI: 1.59–62.4) |
|                        |             |         |            | Overall: 186,934 | Overall: 6 | 0–180 days: 55,270 | 0–180 days: 2 | NR | 244,141 | 1 | NR |
|                        |             |         |            | 181–365 days: 48,332 | 181–365 days: 2 | 1365 days: 82,832 | 1365 days: 2 | 0–180 days: | 2.64 (95% CI: 0.23–30.18); adjusted HR: 2.76 (95% CI: 0.62–11.73) |
|                        |             |         |            | > 365 days: 82,832 | > 365 days: 2 | > 365 days: 2 | > 365 days: 2 | > 365 days: | 27.56 (95% CI: 1.41–53.8); adjusted HR: 32.17 (95% CI: 1.59–62.4) |

**Table 2c** Occurrence of Guillain–Barré syndrome and association between Guillain–Barré syndrome and vaccination status, 1 January 2000–4 April 2020 (n = 25)

- **GBS**: Guillain–Barré syndrome
- **GSK**: GlaxoSmithKline
- **HR**: hazard ratio
- **ICD**: International Classification of Diseases
- **IR**: incidence rate
- **MedDRA**: Medical Dictionary for Regulatory Activities
- **NA**: not applicable
- **ND**: not done
- **NP**: not possible
- **OR**: odds ratio
- **pY**: person-year
- **RI**: relative incidence
- **RR**: relative risk
- **VAERS**: Vaccine Adverse Event Reporting System
- **VDS**: Vaccine Safety Datalink
## Table 2d

Occurrence of Guillain–Barré syndrome and association between Guillain–Barré syndrome and vaccination status, 1 January 2000–4 April 2020 (n = 25)

| Study and publication year | Study design | Vaccine | Comparator | Outcome | Brighton criteria | After HPV vaccination | Co-comparator | Ratio/comparison | Estimator | Confounders corrected for |
|---------------------------|--------------|---------|------------|---------|-------------------|----------------------|--------------|-------------------|----------|--------------------------|
| Miranda et al. 2017 [13]  | Longitudinal observational cohort | Bivalent, 4-valent recombinant | Unvaccinated | GBS diagnosis | Person-years | Number of cases of GBS | Incidence rate | Person-years | Number of cases of GBS | Incidence rate | Age-standardised IR: 0.37 |
|                           |              |         |            | ICD-10 (G61.0) | No | 1,393 | 20 | 1.36 | 100,000 py | 4,246,753 py | 23 | Unadjusted HR: 3.62 (95% CI: 1.73–7.59); adjusted HR: 3.78 (95% CI: 1.79–7.98) |
|                           |              |         |            | Age (time scale), year of inclusion, geographical zone, CMU, history of use of healthcare and other vaccinations, use of healthcare and other vaccinations after inclusion |
| Andrews et al. 2017 [32]  | Self-controlled case series | Bivalent and 4-valent recombinant | Self-controlled: same person, incidence in different risk timeframe | ICD-10 (G61.0) | No | NR | 0–91 days | Nine cases | RI: 1.04 (95% CI: 0.47–2.28) | NR | RI risk period 0–91 days: 1.04 (95% CI: 0.47–2.28) |
|                           |              |         |            | 0–183 days: 14 cases | RI: 0.83 (95% CI: 0.41–1.69) | NR | Age, period and season |
| Cameron et al. 2016 [23]  | Ecological study | NR | Population based: boys (not eligible for HPV vaccination in Scotland) | ICD-10 (G61.0, G61x, G618, G65x) | No | NR | Observed/expected | NA |
| Willame et al. 2016 [33]  | Pooled analysis of observational cohorts: CPRD GOLD | Bivalent | Unexposed cohorts | MedDRA | No | 64,705 | 0 | IR: 0.00/100,000 py | Unexposed historical female cohort: 64,861 py | 0 | IR: 0.00/100,000 py |
|                           |              |         |            |             |       |       |       | Unexposed historical male cohort: 64,868 py | 1 | IR: 1.54/100,000 py |
| Verstraeten et al. 2008 [46] | Pooled analysis of RCT | Bivalent | Non-adjuvanted control vaccine, aluminium adjuvanted vaccines, or aluminium hydroxide alone | MedDRA | No | NR | ND; RR not calculated unless an event occurred in one group | NA |

CI: confidence interval; CPRD GOLD: Clinical Practice Research Datalink General Practice Online Database; GBS: Guillain–Barré syndrome; GS/ GlaxoSmithKline; HR: hazard ratio; ICD: International Classification of Diseases; IR: incidence rate; MedDRA: Medical Dictionary for Regulatory Activities; NA: not applicable; ND: not done; NP: not possible; NR: not reported; OR: odds ratio; py: person-year; RCT: randomised controlled trial; RI: relative incidence; RR: relative risk; VAERS: Vaccine Adverse Event Reporting System; VDS: Vaccine Safety Datalink.
among those who received the 4-valent recombinant vaccine developed new-onset GBS (7,845 person-years); 194 cases were observed among the unvaccinated (23 cases), with an adjusted hazard ratio (aHR) of 1.36 cases per 100,000 person-years among vaccinated individuals (20 cases), compared with 0.37 cases per 100,000 person-years among unvaccinated individuals (23 cases), with an adjusted hazard ratio (aHR) of 3.78 (95% CI: 1.79–7.98). The association was particularly marked in the first 2 months after vaccination and decreased over time, and did not differ with the type of HPV vaccine or whether or not GBS was preceded by a recent history of gastrointestinal or respiratory tract infection. Seasonality and calendar year did not affect the findings. In the two included case–control studies, no exposure to HPV vaccine was observed in cases with GBS [30,31].

A cohort study with 3,126,790 Swedish and Danish women [28] did not observe a single case of GBS among those who received the 4-valent recombinant vaccine (319,298 person-years); 194 cases were observed among the unvaccinated (16,067,162 person-years). Grünlund et al. [27] studied a cohort of 70,265 adolescents, no GBS cases were diagnosed after the bivalent vaccine (or HBV vaccination). Verstraeten et al. [46] described the findings of a pooled analysis of all RCT of AS04-adjuvanted bivalent vaccines, HSV and HBV vaccines. One GBS case was observed among 68,512 participants in the control group.

Non-randomised studies
One cohort study [13] and two case–control studies [30,31] investigated the potential association between the HPV vaccine and autoimmune disease in France. In the cohort study of more than two million girls and women with pre-existing autoimmune disease in France. Seasonality and calendar year did not affect the findings. In the two included case–control studies, no exposure to HPV vaccine was observed in cases with GBS [30,31].

A cohort study with 3,126,790 Swedish and Danish women [28] did not observe a single case of GBS among those who received the 4-valent recombinant vaccine (319,298 person-years); 194 cases were observed among the unvaccinated (16,067,162 person-years). Grünlund et al. [27] studied a cohort of 70,265 adolescents, no GBS cases were diagnosed after the bivalent vaccine (or HBV vaccination). Verstraeten et al. [46] described the findings of a pooled analysis of all RCT of AS04-adjuvanted bivalent vaccines, HSV and HBV vaccines. One GBS case was observed among 68,512 participants in the control group.

Results of individual studies
The reported occurrence of GBS following HPV vaccination is summarised in Table 2 and described by study design and by geographic region.

Randomised studies
Two randomised studies did not observe a single GBS case among people who received the HPV vaccine and found no increased risk of GBS after HPV vaccination. Lehtinen et al. [24] and Bi et al. [25] reported on a large community-based RCT in Finland. Among 32,176 adolescents, no GBS cases were diagnosed after the bivalent vaccine (or HBV vaccination). Verstraeten et al. [46] described the findings of a pooled analysis of all RCT of AS04-adjuvanted bivalent vaccines, HSV and HBV vaccines. One GBS case was observed among 68,512 participants in the control group.
and influenza vaccine (1.3 cases per week/10,000,000), based on VAERS reports between 2006 and 2009. Furthermore, these rates were compared with the expected weekly incidence in the general population (0.65–2.57 cases per week/10,000,000) based on a literature review. The authors summarise these findings as “There was nearly a 2.5-to 10-times greater risk of acquiring GBS within 6 weeks after Gardasil vaccination when compared with the general population.” [42].

For the period of 2010–2012, Ojha et al. [43] compared the reporting of GBS cases to VAERS following vaccination with the 4-valent recombinant vaccine (nine cases/4,670 reports; 0.19%) to those of other vaccines (36 cases/10,152 reports; 0.35%) with a proportional reporting ratio of 0.54 (95% CI: 0.26–1.1).

Two case–control studies were based on data from 22,011 VAERS reports in the period of 2006–2012 targeting 18–39-year-old women [34] and on 48,852 reports in 2006–2014 targeting 6–39-year-old girls and women [35]. Both studies found no association between GBS and the 4-valent recombinant vaccine, with an unadjusted OR of 0.75 (95% CI: 0.42–1.3) and 0.84 (95% CI: 0.60–1.15), respectively.

Three studies reported on 2006–2017 VSD safety monitoring data of the bivalent vaccine and the 4-valent recombinant vaccine [38-40]. Two studies on the 4-valent recombinant vaccine based on the 2006–2015 VSD safety monitoring data found lower GBS incidences following vaccination, compared with the background rates. Gee 2011 et al. [38] observed one case of GBS among 2,773,185 4-valent recombinant vaccine doses administered between 2006 and 2015 (IR: 0.36/1,000,000 doses; one-sided 95% CI: 1.71). Donahue et al. [40] reported on safety data of the 9-valent vaccine based on 128,645 doses given between 2015 and 2017, and did not observe GBS among the vaccinated; three cases of GBS were reported in the historical comparison group.

Additionally, Chao et al. [37] conducted a cohort study in California among 189,629 women who received one dose or more of the 4-valent recombinant vaccine in the period of 2006–2008 and did not observe a single GBS case among both vaccinated and unvaccinated women.

**Meta-analysis**

Seven studies reported an effect-estimate suitable for meta-analysis [13,26,32,34-36,43]. The remaining 18 studies were not suitable because only descriptive outcomes were available, or because one or both groups did not observe a single case. Two studies by Geier et al. published findings with overlap in data based on the VAERS dataset [34,35], with similar findings. The effect estimate by Geier et al. 2017 [35] was used in the primary analyses and the Geier et al. 2015 [34] estimate in the sensitivity analysis. Therefore, the results of the meta-analysis show findings of six studies.

Meta-analysis yielded a pooled random-effects model ratio of HPV vaccination on GBS of 1.21 (95% CI: 0.60–2.43); I²=72% (95% CI: 36–88) (Figure 3). Sensitivity analysis including Geier et al. 2015 [34] instead of Geier et al. 2017 [35], yielded similar results: 1.19 (95% CI: 0.58–2.43); I²=73% (95% CI: 37–88). The pooled estimate was 0.88 (95% CI: 0.60–1.31) for self-/case-controlled studies and 1.49 (95% CI: 0.50–4.38) for
cohort studies. Findings of the subgroup analysis by vaccine type (bivalent vaccine, 4-valent recombinant vaccine or both) and outcome measure are provided in the Supplement.

Additional subgroup analysis by Brighton vs non-Brighton GBS case definition was not possible because all seven studies used non-Brighton criteria. The included studies were heterogeneous in terms of study design, analysis and reporting, which was also reflected in the high I², which indicates the percentage of variability in the effect sizes which is not caused by sampling error.

Quality of the body of evidence
According to the GRADE approach, the quality of the body of evidence is very low. We had to downgrade the quality of evidence three times: (i) for risk of bias (residual confounding at least); (ii) for imprecision (wide 95% CI around the pooled estimate including substantial benefit as well as substantial harm) and; (iii) heterogeneity (inconsistency; I² = 72%).

Number needed to harm and number needed to vaccinate
Translating the pooled random-effect ratio of 1.21 (95% CI: 0.60–2.43) to the number needed to harm (NNH), we estimated that one million people need to take the HPV vaccine to generate one case of GBS (95% CI: –3 to 8 cases). In contrast, 324 (80% credibility interval: 195–757) people need to be vaccinated to prevent one case of cervical cancer [48].

Discussion
The results of our systematic review and meta-analysis indicate that absolute risk of GBS after HPV vaccination is low. Reported historical background rates of GBS incidence were between 0.55 and 2.25 cases per 100,000 person-years [38,39]. A slightly increased RR of GBS after HPV vaccination is low, far away from statistical significance based on findings from our meta-analysis. From a public health point of view, up to one million people would need to be vaccinated to generate one additional case of GBS, while the NNV to prevent one case of cervical cancer is ca 300.

We performed a comprehensive and systematic search on this topic that includes all licenced HPV vaccines. It was specifically targeted at investigating the association with GBS, in the context of other reviews that focussed on the potential association between HPV vaccination and autoimmune and/or neurological diseases [49-51].

---

**Figure 3**
Meta-analysis of studies reporting an effect estimate of the risk of Guillain–Barré syndrome after HPV vaccination, by study design, 1 January 2000–4 April 2020 (n = 7)

| Study              | Design                          | Vaccine                  | Outcome          | Effect ratio | Estimate | 95% CI      |
|--------------------|---------------------------------|--------------------------|------------------|--------------|----------|-------------|
| Andrews et al. 2017 [32] | Self−controlled case series     | Bivalent and 4-valent recombinant | ICD-10 VAERS     | 1.04         | (0.47; 2.29) |
| Geier et al. 2017 [35]   | Case–control                    | 4-valent recombinant     |                  | 0.84         | (0.54; 1.30) |
|                     |                                 | 4-valent recombinant     |                  | 0.88         | (0.60; 1.31) |
| Deceuninck et al. 2018 [36] | Ecological study                | 4-valent recombinant     | ICD-9 or ICD-10  | 0.81         | (0.29; 2.26) |
| Miranda et al. 2017 [13] | Cohort                          | Bivalent, 4-valent      | ICD-10           | 3.76         | (1.79; 7.98) |
|                     |                                 | recombinant              |                  | 0.54         | (0.26; 1.11) |
| Ojha et al. [43]      | Cohort                          | 4-valent recombinant     | MedDRA           | 5.31         | (0.62; 45.43) |
| Skufca et al. [26]    | Cohort                          | Bivalent                 | ICD-10           | 1.49         | (0.50; 4.38) |

CI: confidence interval; ICD: International Statistical Classification of Diseases and Related Health Problems (International Classification of Diseases); VAERS: vaccine adverse event reporting system.

* Meta-analysis yielded a pooled random-effects model ratio of HPV vaccination on GBS of 1.21 (95% CI: 0.60–2.43); I² = 72% (95% CI: 36–88).

* Two studies published findings with a large overlap in data based on the VAERS dataset [34,35] with similar findings. The effect estimate by Geier et al. 2017 [35] was used in the primary analyses and Geier et al. 2015 [34] estimate in the sensitivity analysis. Therefore, the results of the meta-analysis show findings of six studies. When substituting the effect estimate of Geier et al. 2017 for Geier et al. 2015 (OR: 0.75; 95% CI: 0.42–1.3), the pooled estimate for case–control studies is 1.19 (95% CI: 0.58–2.43), I² = 72% (95% CI: 37–88).

All effect (adjusted) effect estimates (odds ratios, hazard ratios, relative risks, proportional reporting ratio, relative incidence, incidence rate ratio) are combined in one overall ratio.
The quality of our findings depended on the quality of the studies, which were largely registry studies and based on non-Brighton GBS outcomes. There was risk of bias because of large heterogeneity in the design and reporting of the studies, as well as the control groups. Confounding was the biggest limiting factor of the quality of the evidence, because many studies were not designed to correct for confounding and cohorts were highly confounded. Often, the control group was not matched based on sex or age group. Outcome ascertainment was challenging, given the heterogeneity of case definitions for GBS; only one of five studies used the Brighton criteria.

The follow-up period for the detection of GBS varied between studies and many of the cohorts or registry-based studies were partially underpowered by design because of the rarity of GBS. In the three studies that signalled increased risk of GBS after HPV vaccination, conflicting temporal trends were reported. In the study by Miranda et al. [13] the association between vaccination and GBS was particularly marked in the first 2 months after vaccination and decreased over time, while Skufca et al. [26] reported a substantial increase in the association (with very wide CI). Souayah et al. [29] also noted increased reporting of GBS during the first 6 weeks after vaccination, although interpreting this trend was challenging in this VAERS reporting study since all five other studies reporting VAERS data found no association between HPV vaccination and GBS. Interpretation of these results in terms of causality should be made with caution.

In future studies, consensus on the case definition for GBS and the risk timeframe is needed to generate uniform and comparable findings. Studies in settings with gender-neutral vaccination policies are required to further assess the risk of GBS after HPV vaccination among boys and men. Furthermore, studies should be expanded to geographical areas outside of western Europe and North America, where HPV vaccination is being implemented on large scale. To generate the highest quality of evidence on this topic, we recommend further research with a self-controlled case series design using Brighton-outcomes. The self-controlled case series design has been proved most suitable for rare events and limits confounding to time-dependent confounding [21], as also used to assess the risk of intussusception after rotavirus vaccination [52].

This study aims to provide up to date vaccination safety information for healthcare providers and policymakers as well as the general public [53]. Transparent communication of potential safety issues is essential to build trust and strengthen confidence in HPV vaccination. Concern about vaccine safety is one of the key determinants of vaccine hesitancy and poses a threat to public health. Healthcare providers play an important role in communicating information on HPV safety [54]. The low potential risk of GBS after HPV vaccination should have minimal impact on the risk consideration for HPV vaccination programmes, reassure vaccine confidence and ultimately increase vaccination rates.

Conflict of interest

TBS is a fellow of the Centre for Disease Prevention and Control (ECDC) Fellowship Programme, supported financially by ECDC. The views and opinions expressed herein do not state or reflect those of ECDC. ECDC is not responsible for the data, information collation and analysis and cannot be held liable for conclusions or opinions drawn.

Authors’ contributions

TBS conducted the database searches, screened and assessed studies as primary reviewer, extracted the data, conducted the meta-analysis and wrote the first version of the manuscript. TH conceived the study, screened and assessed studies as second reviewer and held general oversight of the conducted work. TBS, TH, BB, LC and OW contributed to the interpretation of the data, provided important intellectual content, revised and approved to the manuscript.

References

1. Harder T, Wichmann O, Klug SJ, van der Sande MAB, Wiese-Posselt M. Efficacy, effectiveness and safety of vaccination against human papillomavirus in males: a systematic review. BMC Med. 2018;16(1):110. https://doi.org/10.1186/s12916-018-3098-3 PMID: 30016957
2. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012;30(Suppl 5):F123-38. https://doi.org/10.1016/j.vaccine.2012.04.108 PMID: 23199956
3. Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boyle M-C, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394(10197):497-509. https://doi.org/10.1016/S0140-6736(19)30298-3 PMID: 3195301
4. Sha BE. Adult immunization update. JAMA. 2019;322(11):1096-7. https://doi.org/10.1001/jama.2019.12739 PMID: 31424523
5. Palmer T, Wallace L, Pollock KG, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019;365:l1161. https://doi.org/10.1136/bmj.l1161 PMID: 30944092
6. Patel EU, Grabowski MK, Eisenberg AL, Packman ZR, Gravitt PE, Tobian AAR. Increases in Human Papillomavirus vaccination among adolescent and young adult males in the United States, 2011-2016. J Infect Dis. 2016;218(3):307-13. https://doi.org/10.1093/infdis/jiw165 PMID: 29584878
7. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 2016;4(7):e453-63. https://doi.org/10.1016/S2214-109X(16)30099-7 PMID: 27340003
8. DeStefano F, Bodenstab HM, Offit PA. Principal controversies in vaccine safety in the United States. Clin Infect Dis. 2019;69(4):726-31. https://doi.org/10.1093/cid/ciz135 PMID: 30753348
9. Jiang HY, Shi YD, Zhang X, Pan LY, Xie YR, Jiang CM, et al. Human papillomavirus vaccination and the risk of autoimmune disorders: A systematic review and meta-analysis. Vaccine. 2019;37(23):3031-9. https://doi.org/10.1016/j.vaccine.2019.04.049 PMID: 31063452
10. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide: A systematic literature review. Neuroepidemiology. 2009;32(2):150-63. https://doi.org/10.1159/000187487 PMID: 19088488
11. Seijvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33. https://doi.org/10.1159/000314270 PMID: 21422765
12. Haber P, Seijvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Saf. 2009;32(4):309-23.
46. Verstraeten T, Descamps D, David MP, Zahaf T, Hardt K, Izurieta P, et al. Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine. 2008;26(51):6630-8. https://doi.org/10.1016/j.vaccine.2008.09.049 PMID: 18845199

47. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the vaccine adverse event reporting system (VAERS). Vaccine. 2015;33(36):4398-405. https://doi.org/10.1016/j.vaccine.2015.07.035 PMID: 26209838

48. Baggs J, Gee J, Lewis E, Fowler G, Benson P, Lieu T, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. Pediatrics. 2011;127(Suppl 2):S45-53. https://doi.org/10.1542/peds.2010-1722H PMID: 21502260

49. Mouchet J, Salvo F, Raschi E, Poluzzi E, Antonazzo IC, De Ponti F, et al. Human papillomavirus vaccine and demyelinating diseases-A systematic review and meta-analysis. Pharmaco Resist. 2018;132:108-18. https://doi.org/10.1016/j.phrs.2018.04.007 PMID: 29665426

50. Meggiolaro A, Migliara G, La Torre G. Association between Human Papilloma Virus (HPV) vaccination and risk of Multiple Sclerosis: A systematic review. Hum Vaccin Immunother. 2018;14(5):1266-74. https://doi.org/10.1080/21645515.2017.1423155 PMID: 29333935

51. Genovese C, LA Fauci V, Squeri A, Trimarchi G, Squeri R. HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. J Prev Med Hyg. 2018;59(3):E194-9. PMID: 30397675

52. Koch JHT, von Kries R, Wichmann O. The risk of intussusception after rotavirus vaccination—a systematic literature review and meta-analysis. Dtsch Arztebl. 2017;114(15):255-62.

53. Ammon A, Prats Monné X. Vaccines, trust and European public health. Euro Surveill. 2018;23(17). https://doi.org/10.2807/1560-7917.ES.2018.23.17.18-00210 PMID: 29717694

54. European Centre for Disease Prevention and Control (ECDC). Let’s talk about hesitancy. Stockholm: ECDC; 2016. Available from: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/lets-talk-about-hesitancy-vaccination-guide.pdf

**License, supplementary material and copyright**

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence and indicate if changes were made.

Any supplementary material referenced in the article can be found in the online version.

This article is copyright of the authors or their affiliated institutions, 2022.
