Reporting Quality Assessment of Observational Studies of Human Papillomavirus (HPV) Vaccines in Cervical Cancer Prevention, based on STROBE Statement

by

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Abstract

Background: Observational studies find use in many aspects of medical research. One such aspect is vaccine effectiveness. Human Papillomavirus (HPV) vaccination is being implemented since 2007 in several countries. HPV types 16 and 18 have proven to be responsible for the development of cervical cancer. The vaccination aims to reduce that impact on public health. After numerous clinical trials validating the vaccine's efficacy, it is necessary to assess its effectiveness by conducting observational studies. The STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) checklist has been widely used to evaluate the reporting quality of observational studies over the past few years.

Purpose: The aim of this study was to assess the reporting quality of observational studies of HPV vaccination in cervical cancer prevention, based on STROBE statement.

Methods: A literature search was conducted in PubMed, resulting in seven eligible studies. The entire text of the studies was evaluated and scored, using STROBE statement. All 22 items/sub-items (32 in total) of STROBE were used for the evaluation.

Results: 11 out of 32 items/sub-items, were reported in all seven studies, while 17 out of 32 were reported in more than 70% of the studies. The best-written sections were Introduction and Discussion. The worst-written sections were the Results (3 in 11 items in more than 70% of the studies) and Methods (6 out of 14 items in more than 70% of the studies). The total individual scores of studies varied from 80.6% to 46.7%, with an average of 60.6%

Conclusion: The reporting quality of the eligible observational studies appears to be average to good, with some methodological problems common to all studies. It appears that improvements are necessary, in order to increase the credibility of observational studies.

Keywords: STROBE, Human Papillomavirus, HPV, HPV 16/18, cervical cancer, observational studies, reporting quality.

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1. INTRODUCTION

Observational studies play a major part in medical research. [1] Case-control, cohort, cross-sectional studies and any other variation can find use in investigating the cause of diseases. Moreover, they can be more appropriate when searching for rare or late adverse effects of medical interventions [2] or when ethical issues occur, such as when searching the etiology of cancer. Observational studies are, also, less time and money consuming than randomized control trials [3].

Adequate reporting of studies is essential for readers to comprehend the results and validate the study as credible. There is a number of checklists and guidelines that aim to improve the quality of various study designs [4], as well as observational studies [5]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) is one of these checklists. Its use is recommended by numerous medical journals [2, 6, 7].

It consists of 22 criteria (items) that relate to the title, abstract, introduction, methods, results, and discussion sections of articles. Checklists for all three major observational study designs (cohort, case-control, cross-sectional), as well as a combined checklist (appendix table), are available at http://www.strobe--statement.org/. Out of the 22 items 18 are common to all three study designs, while four are design-specific, with different variations for each study design.

Cervical cancer constitutes a major health issue world widely, being the third most common type of cancer among women [8]. The role of HPV as an etiologic agent of cervical cancer has been proved by several epidemiological and molecular studies [9, 10].

Human papillomavirus (HPV) is a non-enveloped double-stranded DNA virus, which belongs to the Papillomaviridae family [11]. More than 35 types of HPV have been identified in genital tract infections caused by sexual transmission [8], with the most common being 6, 11, 16 and 18. [9, 10] There is no evidence associating the first two types with the etiology of cervical cancer [8], thus they are considered low-risk, unlike serotypes 16 and 18 which are considered high-risk. [9, 10]

Non-infectious, adjuvanted vaccines have been developed to reduce the burden of HPV infection and related diseases. [10] The vaccines contain virus-like particles

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(VLPs) for HPV types 16, 18, 6, and 11 (tetravalent) and for HPV types 18 and 16 (bivalent) [10]. Two vaccines were commercialized in 2007 [12]. To date, HPV vaccination against HPV16 and HPV18 among HPV-naïve women has proved to be nearly 100% efficacious in preventing the incidence of related cervical precancerous lesions, for approximately 5–6 years after vaccination [13]. With undeniable evidence of efficacy, it is now the question of effectiveness that matters most [14]. Contrary to vaccine efficacy trials, population-based studies more likely to reflect the true vaccination impact on the population [14, 15]. It can be more accurately approximated in observational studies.

The aim of this study is to critically evaluate the quality of observational studies investigating the effect of Human Papillomavirus (HPV) vaccines in cervical cancer prevention, with the use of STROBE statement. Seven eligible studies were identified and were evaluated using the entirety of the statement.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Checklist of Items That Should Be Addressed in Reports of Observational Studies

Title and abstract
1 (a) Indicate the study's design with a commonly used term in the title or the abstract.
(b) Provide in the abstract an informative and balanced summary of what was done and what was found.

Introduction
Background/ rationale 2
Explain the scientific background and rationale for the investigation being reported.
Objectives 3
State specific objectives, including any prespecified hypotheses.

Methods
Study design 4
Present key elements of study design early in the paper.
Setting 5
Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Participants 6
(a) *Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.
Case–control study: Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.
Cross-sectional study: Give the eligibility criteria, and the sources and methods of selection of participants.
(b) *Cohort study:* For matched studies, give matching criteria and number of exposed and unexposed.
Case–control study: For matched studies, give matching criteria and the number of controls per case.
Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
Data sources/ measurement 8
For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.
Bias 9
Describe any efforts to address potential sources of bias.
Study size 10
Explain how the study size was arrived at.
Quantitative variables 11
Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.
Statistical methods 12
(a) Describe all statistical methods, including those used to control for confounding.
(b) Describe any methods used to examine subgroups and interactions.
(c) Explain how missing data were addressed.
(d) *Cohort study:* If applicable, explain how loss to follow-up was addressed.
Case–control study: If applicable, explain how matching of cases and controls was addressed.
Cross-sectional study: If applicable, describe analytical methods taking account of sampling strategy.
(e) Describe any sensitivity analyses.

Results
Participants 13
(a) Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed.
(b) Give reasons for nonparticipation at each stage.
(c) Consider use of a flow diagram.
Descriptive data 14
(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders.
(b) Indicate the number of participants with missing data for each variable of interest.
(c) *Cohort study:* Summarize follow-up time—e.g., average and total amount.
Outcome data 15
Cohort study: Report numbers of outcome events or summary measures over time.
Case–control study: Report numbers in each exposure category or summary measures of exposure.
Cross-sectional study: Report numbers of outcome events or summary measures.
Main results 16
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence intervals). Make clear which confounders were adjusted for and why they were included.
(b) Report category boundaries when continuous variables were categorized.
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
Other analyses 17
Report other analyses done—e.g., analyses of subgroups and interactions and sensitivity analyses.

Discussion
Key results 18
Summarize key results with reference to study objectives.
Limitations 19
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.
Interpretation 20
Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
Generalizability 21
Discuss the generalizability (external validity) of the study results.

Other information
Funding 22
Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

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2. METHODS

An online literature search was conducted in PubMed, from July 15th 2015 until July 31st 2015. The search included the terms: ("HPV" or "human papillomavirus") and ("vaccine" or "vaccination") and ("cervical cancer" or "cervical lesions" or "cervical abnormalities" or "HPV 16/18") as free text and "epidemiologic studies" as a MeSH Term. Eligibility Criteria included observational studies measuring HPV vaccine effectiveness (either 16/18 HPV type prevalence or cervical abnormalities diagnosed cytologically/histologically). Titles of all studies identified, were examined to determine possible eligibility for our study. Whenever a title appeared to be in line with our criteria, and evaluation of the studies' abstracts followed. In two cases there was the need to evaluate the entire text before exclusion from the assessment [16, 17] (Figure 1).

Special consideration was taken for studies that used prediction models to estimate the impact of vaccination in the population. In the end, it was decided to completely exclude such studies, since their primary design's goal was calculation of HPV type prevalence. The application of computer-based models was conducted as an analysis, by implementing additional HPV vaccine trial data. Therefore, the addition of such publications in the study would cause diversity amongst the evaluated papers.

One study's primary objective was to analyze the dynamics of HPV infection and relevant genital diseases, through time [24]. Nevertheless, it provided analysis on the relation of HPV 16 infection and vaccination, thus it was included in the analysis.

All 22 items of the checklist were considered for the evaluation. Including the sub-items that is a total of 33 items/sub-items. Whenever an item did not apply for a study it was dismissed. In order to clarify whether an item is adequately reported in the articles, we took into account the guidance provided by the STROBE Explanation and Elaboration document [6]. Positive responses are marked as 'yes', whereas negative as 'no'. To gain a positive response the item had to be reported in enough detail for the reader to avoid any misconceptions [3].

It needs to be stated that the STROBE statement provides recommendations and not a mandatory methodology [6]. Hence, there is not one standard scale for dictating the quality of a study.
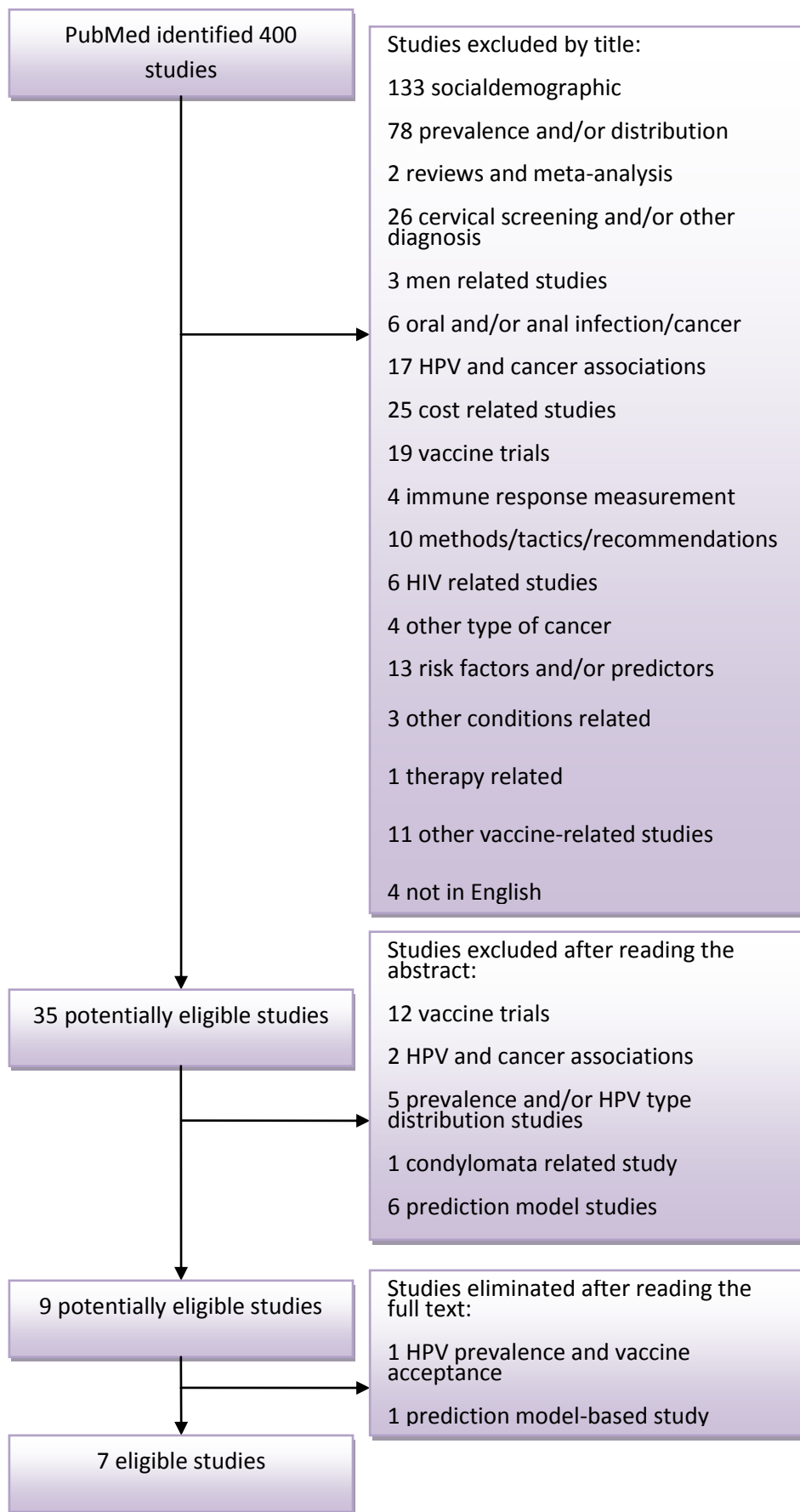
8

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┌─────────────────────┐        ┌──────────────────────────────────┐
│ PubMed identified 400│        │ Studies excluded by title:       │
│      studies         │        │                                  │
└─────────────────────┘        │ 133 socialdemographic            │
           │                    │                                  │
           │                    │ 78 prevalence and/or distribution│
           │                    │                                  │
           │                    │ 2 reviews and meta-analysis      │
           │                    │                                  │
           │                    │ 26 cervical screening and/or other│
           │                    │ diagnosis                        │
           │                    │                                  │
           │                    │ 3 men related studies            │
           │──────────────────► │                                  │
           │                    │ 6 oral and/or anal infection/cancer│
           │                    │                                  │
           │                    │ 17 HPV and cancer associations   │
           │                    │                                  │
           │                    │ 25 cost related studies          │
           │                    │                                  │
           │                    │ 19 vaccine trials                │
           │                    │                                  │
           │                    │ 4 immune response measurement    │
           │                    │                                  │
           │                    │ 10 methods/tactics/recommendations│
           │                    │                                  │
           │                    │ 6 HIV related studies            │
           │                    │                                  │
           │                    │ 4 other type of cancer           │
           │                    │                                  │
           │                    │ 13 risk factors and/or predictors│
           │                    │                                  │
           │                    │ 3 other conditions related       │
           │                    │                                  │
           │                    │ 1 therapy related                │
           │                    │                                  │
           │                    │ 11 other vaccine-related studies │
           │                    │                                  │
           │                    │ 4 not in English                 │
           │                    └──────────────────────────────────┘
           │                    ┌──────────────────────────────────┐
           │                    │ Studies excluded after reading the│
           │                    │ abstract:                        │
           ▼                    │                                  │
┌─────────────────────┐        │ 12 vaccine trials                │
│ 35 potentially       │        │                                  │
│ eligible studies     │        │ 2 HPV and cancer associations    │
└─────────────────────┘        │                                  │
           │                    │ 5 prevalence and/or HPV type     │
           │──────────────────► │ distribution studies             │
           │                    │                                  │
           │                    │ 1 condylomata related study      │
           │                    │                                  │
           │                    │ 6 prediction model studies       │
           │                    └──────────────────────────────────┘
           │                    ┌──────────────────────────────────┐
           ▼                    │ Studies eliminated after reading the│
┌─────────────────────┐        │ full text:                       │
│ 9 potentially        │        │                                  │
│ eligible studies     │        │ 1 HPV prevalence and vaccine     │
└─────────────────────┘        │ acceptance                       │
           │──────────────────► │                                  │
           │                    │ 1 prediction model-based study   │
           ▼                    └──────────────────────────────────┘
┌─────────────────────┐
│ 7 eligible studies   │
└─────────────────────┘
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Figure 1- Flow diagram of the search process

3. RESULTS

Out of the 400 publications resulted, 7 studies were considered eligible to proceed for the quality evaluation [18-24] (Table1). Main reasons for eliminating studies include irrelevant subject (such as socialdemographic-focused studies that investigate the knowledge, attitudes and acceptance of the vaccine), vaccine trials, strictly cost-related studies, pre-vaccination prevalence and HPV type distribution studies, studies that only dealt with the impact of cervical screening, studies that investigated risk factors, HIV or other condition related studies, diagnosis related studies, studies that dealt with other types of cancer etc (Figure 1).

3.1 Study Characteristics

All the studies selected were population-based. Five of them used data linkage from national registries to gather sufficient information. Out of the total, three are described as cohort, three as cross-sectional and one as case-control. Two of them took place in Scotland, two in Germany, two in Australia and one in Denmark. Two were measuring the prevalence of carcinogenic HPV types 16/18 and six considered the outcome to be the diagnosis of cervical abnormalities. Five were published in 2014 and two in 2013. The reason for the existence of solely recent publications is the fact that the vaccine was commercialized in 2007 [12]. It should take a few years to collect viable information for an observational study to deduct a safe conclusion. Study characteristics for each paper are analytically described in Table 2.

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Title	First Author	Reference-Index number
Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types	K. Kavanagh	[18]
Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia—Nationwide Follow-up of Young Danish Women	Birgitte Baldur-Felskov	[19]
Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study	Dorota M. Gertig	[20]
Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland	K. G. J. Pollock	[21]
Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia	Elizabeth Crowe	[22]
Human Papillomavirus prevalence and probable first effects of vaccination in 20 to 25 year-old women in Germany: a population-based cross-sectional study via home-based self-sampling	Yvonne Deleré	[23]
Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84 – results of WOLVES	Karl Ulrich Petry	[24]

Table 1 - Eligible Studies

Title	Publication Date	Magazine	Country	Study Design	Primary Outcome (of interest)	Additional information
[18]	2014	British Journal of Cancer	Scotland	Cross-sectional	HPV16/18 prevalence	Data linkage
[19]	2014	JNCI J Natl Cancer Inst	Denmark	Cohort	Atypia or worse/CIN	Data linkage
[20]	2013	BMC Medicine	Australia	Retrospective cohort	Cervical abnormalities/cytology	Data linkage
[21]	2014	British Journal of Cancer	Scotland	Cohort	CIN diagnosis	Data linkage
[23]	2014	BMJ	Australia	Case-control	Cervical abnormalities/cytology	Nested within population based screening program
[24]	2014	BMC Infectious Diseases	Germany	Cross-sectional	HPV 16/18 prevalence	Population-based
[25]	2013	BMC Infectious Diseases	Germany	Cross-sectional	HPV16 infection/ CIN	Population-based

Table 2 - Study Characteristics

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Table 3 shows the overall results, concerning the frequency by which the 33 total items/sub-items of STROBE statement are being reported. One items (16c) did not apply in any of the studies, therefore it was dismissed. 11 out of the 32 sub-items were reported in all of the studies, whereas 13 out of 32 were reported in more than 85% of the studies and 17 out of 32 in more than 70% of the studies.

It should be noted that the best-written section of the studies appears to be the Introduction, with all of the studies reporting both items of the statement. Next is the Discussion with 3 out of 4 items scoring 7/7.

The worst-written section appears to be the Results with only 3 out of its 11 items being reported in more than 70% of the studies and one being reported in all of the studies. Only 6 out of 14 items in Methods are answered in more than 70% of the studies.

Less reported items in particular, include items 5 (as far as the reporting of dates in concerned) 12c and 14b that deal with missing data and item 16c, which is about the reporting of Attributable Risk Fraction.

Individual scores of studies were 63.3% [18], 61.3% [19], 54.8% [20], 53.1% [21], 80.6% [22], 64.5% [23] and 46.7% [24], with an average of 60.6%

A more precise elaboration of the results (by item) follows.

STROBE statement	[18]	[19]	[20]	[21]	[22]	[23]	[24]	Total
Title and abstract								
1a	No	Yes	No	No	Yes	Yes	No	3/7
1b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
Introduction								
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
Methods								
4	Yes	Yes	Yes	No	Yes	Yes	Yes	6/7
5	No	No	No	No	No	No	No	0/7
6a	Yes	Yes	Yes	Yes	Yes	No	Yes	6/7
6b	-	-	-	-	-	-	-	
7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
8	Yes	No	Yes	No	Yes	Yes	Yes	5/7
9	Yes	No	No	No	Yes	No	No	2/7
10	Yes	No	No	No	No	Yes	No	2/7
11	-	-	-	Yes	Yes	Yes	-	**3/3**
12a	Yes	Yes	Yes	Yes	Yes	No	No	5/7
12b	Yes	Yes	No	Yes	Yes	No	No	4/7
12c	No	No	No	No	No	No	No	0/7
12d	No	Yes	No	No	No	No	No	1/7
12e	Yes	Yes	No	Yes	Yes	No	No	4/7
Results								
13a	No	No	No	No	Yes	Yes	No	2/7
13b	No	No	No	No	Yes	Yes	No	2/7
13c	No	No	No	No	Yes	Yes	No	2/7
14a	No	Yes	Yes	No	Yes	Yes	Yes	5/7
14b	No	No	No	No	No	No	No	0/7
14c	-	No	Yes	No	-	-	-	1/3
15	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
16a	No	Yes	Yes	Yes	Yes	Yes	No	5/7
16b	-	-	-	-	-	-	-	
16c	No	No	No	No	No	No	No	0/7
17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
Discussion								
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
21	Yes	No	No	Yes	Yes	No	No	3/7
Other information								
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**7/7**
Total (Percentage %)	19/30 (63.3 %)	19/31 (61.3%)	17/31 (54.8%)	17/32 (53.1%)	25/31 (80.6%)	20/31 (64.5%)	14/30 (46.7%)	

Table 3 - Scoring

3.2.1 Title and abstract

1(a) Indicate the study's design with a commonly used term in the title or the abstract.

The study design was only clearly indicated in only three out of the seven studies (two in the title and abstract [23, 24] and one only in the abstract [17]). The remaining four studies (three data linkage studies as indicated in table 1) used the term cohort to describe a group of women with similar characteristics and not as a study design term. In fact, two of them are cross-sectional studies [19, 25]. This can potentially cause misunderstandings amongst readers who are not familiar with the alternative use of the term. Furthermore, it can potentially cause incorrect indexing in electronic databases [6].

(b) Provide in the abstract an informative and balanced summary of what was done and what was found.

The abstract was well-structured in all the studies, providing clear sections including background/purpose, methods, results and conclusions [18-22, 24] (or in one case objectives, design, setting, participants, main outcome measures, results, conclusions [23]). Two studies included keywords [23,24]. The cause of this trend may be the recent publication dates (2013-2014) and the fact that several were published in similar magazines (as indicated in table 2).

3.2.2 Introduction

Background/rationale 2 Explain the scientific background and rationale for the investigation being reported.

The scientific background in a paper provides the necessary knowledge on the subject for the reader to comprehend its purpose [6]. All the studies fulfill the criteria for this item. It should be noted, that all papers cited other studies to emphasize their goals.

Objectives 3 State specific objectives, including any prespecified hypotheses.

All papers, at the end of the Introduction, mentioned the goals of the studies. One study [20] gave additional information for the advantages of the study design in regards with their goals.

3.2.3 Methods

Study design 4 Present key elements of study design early in the paper.

They key elements of the study design are important for the reader to further evaluate the investigators course of action and the study's results [6]. In one study the key elements are provided at the end of the introduction [20] (and then again at the middle of the Methods section), but since it is within STROBE's recommendations [6] it scored positive in this item. Another paper [24] described itself as 'prospective population-based surveillance study' and in 'statistical analysis' it mentions that the paper is a representation of a one-time cross-sectional analysis. A third study [21] did not mention the study design used, even though it explained elements such as the surveillance program from which data derived and the data linkage process.

Setting 5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.

All studies adequately described settings and locations. The reports of the exact dates however, was not so accurate. One paper [24] did not provide any dates at all at the Methods section (they were mentioned in results). Another [21] provided very little information on dates as well. Two studies [19] and [18] mentioned follow-up periods (2 out of three cohort studies). Only one [23] provided recruitment dates, though this might be the case since it was the only study that did not derive its data from national registries. One paper [18] provided data collection dates, while another [20] merely stated study period without further explanation. Since, none of the studies covered all the necessary points for this item, they all scored negative.

Participants 6

(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.

Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.

Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participant.

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Most studies described eligibility criteria, along with other information that fulfill the criteria of the item (on regards with their study design). All data linkage cohorts described in detail the linkage process.

Only one study [23] did not explain eligibility, but it may be described elsewhere along with the sampling process, as it is part of a greater project. Nonetheless, in order to score positive in the statement the items have to be clearly stated in the text [3].

In the case-control study [22] it is explicitly explained the criteria upon which the cases and the controls were chosen.

All cohort studies are data linkage studies as well, so the follow-up data were derived from national registries.

(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed.

Case-control study—For matched studies, give matching criteria and the number of controls per case.

None of the studies used matching.

Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

All studies provided information on certain variables of interest, whether they were outcomes, exposures or potential confounders. It should be noted that some were better structured than the rest [20, 22] or provided more detailed information [19, 22]. After consideration, one study [21] scored negative in this item, mainly due to lack of information on diagnostic criteria. Also, none of the studies clearly defined any variables as effect modifiers.

Data sources/Measurement 8 For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

The methods of measurement are described in detail in most studies. They stated the methods and criteria they based their diagnosis on, hence it can be concluded that all there are not any differences in the diagnoses of different groups

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of patients. In two studies, however, the assessment methods were not described [19, 21]. Both were linkage studies that received data from national registries and investigated histological and cytological diagnosis. Therefore, one cannot deny the possibility that multiple laboratories, possibly using different scales of grading, might have caused a differentiation in diagnosis.

Bias 9 Describe any efforts to address potential sources of bias.

Only two studies appear to mention at this point any efforts made for avoiding bias. [18, 22] The first [18], in particular, mentioned it when describing the sensitivity analysis in 'statistical analysis'.

Study size 10 Explain how the study size was arrived at.

Just two studies mentioned the calculations for the study size. One [18] calculated it on accounts of powers and the other [23] based of precision. In the rest of the studies it was implied that, since they are population-based, they used the entirety of the available population data for the age cohorts that they chose.

Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.

Only three studies mentioned qualitative variables [21, 22, 23]. All the numerical variables were distinct. These include age [22, 23], acceptability of practices (1 to 6 scale) [23], and deprivation score (1 to 5 scale) [21].

Statistical methods 12

(a) Describe all statistical methods, including those used to control for confounding.

All studies described the statistical methods of choice. These include z-test [18], logistic regression [18, 22], Poisson regression [19], Mann-Whitney U test [20], chi-square test [18, 23], Fisher's exact test [23] and Cox proportional hazards regression [19, 20]. In some cases, statistical methods were simply described as univariate or multivariate [23, 24]. Adjusting for confounders was clearly stated in four studies [18, 19, 21, 22]. Since the terms univariate and multivariate analysis are considered vague, the studies that addressed them [23, 24] received a negative score.

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(b) Describe any methods used to examine subgroups and interactions.

Four of the studies fulfill the criteria for this sub-item. Two [18, 21] mentioned the possible interactions taken into account. The third [19] described subset analysis and stratification. Stratification was described in the case-control study [22].

(c) Explain how missing data were addressed.

None of the studies mentioned the absence of data. The readers are led to assume that due to the nature of most studies (population-based data linkage studies) there were no missing data. Nevertheless, since it is only an assumption and it is not clearly defined in the studies, all scored negative in the sub-item.

(d) Cohort study—If applicable, explain how loss to follow-up was addressed.

Case-control study—If applicable, explain how matching of cases and controls was addressed.

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy.

All studies, but one [19], failed to score positive in this item. In this cohort study it was described how loss of cytology follow-up was addressed, when analyzing the data. It was implied, though, that the patients did have a follow up examination by the gynecologist, but did not have a Pap test. However, it was decided to emphasize the difference in the data analysis compared with the other studies. Hence, the study scored positive in this sub-item.

(e) Describe any sensitivity analyses.

Sensitivity analysis is used to determine the consistency of the main results with those obtained with alternative analysis strategies or assumptions [25]. Four of the studies [18, 19, 21, 22] conducted sensitivity analyses. The procedure was described in more detail in the case-control study [22].

3.2.4 Results

13 (a) Report numbers of individuals at each stage of study—eg. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.

(b) Give reasons for non-participation at each stage.

(c) Consider use of a flow diagram.

Only two of the studies [22, 23] mentioned the numbers of participants in each stage of the study. While the others stated the number of eligible women they did not provide additional information for the reader to follow the course of the study.

Both studies provide detailed flow diagrams, in which they give explicit reasons for ineligibility at each stage of the study.

Descriptive data 14

(a) Give characteristics of study participants (eg. demographic, clinical, social) and information on exposures and potential confounders.

Five studies [19, 20, 22-24] provided detailed characteristics of the study participants, in the form of a table. Out of the remaining two, only one [21] differentiated the age of the participants, hence it was not considered to provide adequate information.

(b) Indicate number of participants with missing data for each variable of interest.

Same as in the Methods section, there was no indication of missing data and since it was not clearly stated whether all the data were available for analysis, it was considered inadequate reporting.

(c) Cohort study—Summarise follow-up time (eg, average and total amount)

Out of the 3 cohort studies, one [20] mentioned details about follow-up time. In detail, there was mention about average and maximum follow-up years [20]. Another [19] mentioned the follow-up time period, in the methods, but without any additional details.

20

Outcome data 15

Cohort study—Report numbers of outcome events or summary measures over time.

Case-control study—Report numbers in each exposure category, or summary measures of exposure.

Cross-sectional study—Report numbers of outcome events or summary measures.

All three cohorts discussed calculation of person-years. They also provided figures with rates [20, 21] and/or Hazard Ratios [19, 20].

In the case-control study the summary measures of exposure were included in the table with the main results.

The cross-sectional [18, 22, 24] studies provided tables with summary measures (prevalence).

Main results 16

(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

All studies, but three [18, 19, 24], provided adjusted as well as unadjusted estimates. One of them [19] mentioned that there was adjusting for socioeconomic variables, but since it was not statistically significant it was not included in the paper. Thus, since there was adequate information on how adjusting was managed, the study scored positive in the item. Another study [18] provided only the adjusted measures. Even though there was mention of unadjusted measures, only some of them were presented and all of them were excluded from the table given. Therefore, it was not considered well-defined and the paper scored negative.

(b) Report category boundaries when continuous variables were categorized.

No continuous variables were used in any of the studies. All qualitative variables described in the studies were considered distinct (see item 11).

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.

In one study [21], even though they presented relative risks and incidence rates, they did not provide absolute risk measures over a period of time. Two studies [19, 20] calculated Hazard Ratios. The remaining studies provided Odds Ratios. None of the studies calculated attributable risk fractions (or preventable fractions since the exposure of interest is the effectiveness of the vaccination).

Other analyses 17 Report other analyses done—eg. analyses of subgroups and interactions, and sensitivity analyses.

In one paper [24], vaccination can be considered the additional analysis, since the study is described as descriptive. In another paper [19] there was additional analysis using other cut-points, but the results are not shown in the paper. A third study [20], provided additional information on cervical abnormality rates by age is provided. In two papers [21] and [22] there was explicit information on sensitivity analysis. Another [18] provided sensitivity analysis along with a subgroup analysis, indicating the most common pairings of HPV types. In the last paper [23] there were several additional analyses, but none about the main outcome of interest (HPV prevalence on vaccinated and unvaccinated population).

3.2.4 Discussion

Key results 18 Summarise key results with reference to study objectives.

All the studies summarized their results in the beginning of the Discussion section. As advised in the STROBE Explanation and Elaboration document, the studies presented in the first paragraph a small summary of their major findings.

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

All the studies provided extensive text emphasizing potential limitations to their methodology. They pointed out possible bias and how it could have affected their results. Additional information to diminish the magnitude of the bias was also provided. In one paper [24], limitations were being discussed, but in regards with the study's ability to calculate measures of association over time, and not bias.

22

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.

Most of the Discussion section in all studies was dedicated to the interpretation of the results. Objectives, limitations, multiplicity of analyses and similar studies were all taken into consideration in order to come to a safe and accurate conclusion about the studies' results.

Generalisability 21 Discuss the generalisability (external validity) of the study results.

Generalisability of the results was specifically addressed in three of the studies. The first [19] mentioned that their data, and therefore the results of their analysis were generalisable to other countries with high HPV vaccine uptake. The same case applied in the second [18], in which generelisability was addressed but not specifically named as such. The third [22] stated in limitations, that generalisability of their findings may be limited to other studies. Though this, as far as the validity of the study is concerned, may be negative it is positive for the readers' better understanding of the findings and how they can be applied in other situations. Hence, the item is scored positive.

3.2.5 Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

All the studies provided information about their funding, as it is required by journals to declare an absence of conflict of interests. [26, 27]

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4. DISCUSSION

The goal of this study was to evaluate the quality of observational studies investigating the effect of Human Papillomavirus vaccination to cervical cancer prevention. In total, 7 studies were selected. All the articles used were published in the time period 2013-2014, years after the STROBE statement became available online. Nevertheless, the overall quality of the studies is average to good, with 17 out of 32 items/sub-items being reported in more than 70%. This scoring might be harsh considering that several items have many different points and all of them had to be reported in enough detail in order to score positive. Still, there are several methodological gaps that may prevent the readers from assessing the validity of the studies, especially in the Methods and the Results sections.

While the settings and locations of the studies were confirmed, the relevant dates were not explicitly described. In a paper about cancer studies [28], it was estimated that about 24% of 132 studies, using survival analysis, never mentioned the date on which follow-up ended. Moreover, all studies lacked mention of effect modifiers. Missing data was another issue, as none of the studies explained how they were handled in the analysis. There was not even as much as a mention of patients with missing data. In a similar study, assessing the quality of observational studies in cancer [3], it was found that only 23% of the studies explained how missing data was handled in the analysis, while only 31% mentioned the number of subjects with missing data. Furthermore, as it is the case in a great amount of other epidemiologic studies [30, 31], only two of the papers include sample size calculations. The same applies with addressing potential bias [31].

There is a number of limitations to our study. The search was conducted in only one database (PubMed) and used the 'epidemiologic studies' Mesh term, which might have restricted the results. Nevertheless, this methodology was followed in similar studies [3, 29] with adequate and diverse results. Therefore, it is more probable that the limited number of eligible studies is due to the vaccine being commercialized in 2007. It takes years for cancerous lesions, which would demonstrate the effect of vaccination, to develop. Another limitation derives from the fact that there was only one evaluator assessing the studies. Since the term 'adequate' or 'clearly reported' are up to a point subjective, the scores may differ between different evaluators. Adding to the fact that the STROBE statement is a list

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of recommendations and not a scoring scale, one cannot compare the scores to that of other studies. The scoring criteria, however, remain the same for all the papers included in this study.

In conclusion, this study emphasizes the continuous need for improvement on certain aspects of the reporting quality of observational studies, by assessing those addressing the effectiveness of HPV vaccination in cervical cancer prevention.

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