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REVIEW

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# HPV vaccination in a context of public mistrust and uncertainty: a systematic literature review of determinants of HPV vaccine hesitancy in Europe

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**ABSTRACT**

Europe is increasingly described as the region in the world with the least confidence in vaccination, and particularly in the safety of vaccines. The aim of this systematic literature review was to gather and summarise all peer-reviewed and grey literature published about determinants of Human Papillomavirus (HPV) vaccine hesitancy in Europe. Ten thematic categories were identified across the 103 articles which were included in the review. Participants from European studies most commonly reported issues with the quantity and quality of information available about HPV vaccination; followed by concerns about potential side effects of the vaccine; and mistrust of health authorities, healthcare workers, and new vaccines. Comparative analyses indicated that confidence determinants differed by country and population groups. This evidence supports the need to develop context-specific interventions to improve confidence in HPV vaccination and design community engagement strategies aiming to build public trust.

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HPV; HPV vaccination; cervical cancer; vaccine hesitancy; vaccine confidence vaccination

## Introduction

Human Papillomavirus (HPV) vaccination was introduced into national immunisation programmes in all European Union (EU) countries, apart from Poland, between 2006 and 2018.[1]

The HPV vaccine is mainly given to adolescent girls (9–18 years old) to prevent cervical cancer and/or genital warts, but sometimes also given to boys (e.g. Austria) or men who have sex with men (e.g. the United Kingdom (UK)) to prevent other HPV-induced cancers.[1] Coverage rates have been suboptimal in some EU countries, particularly in Eastern Europe but also in Ireland, France, and Denmark.[2] Romania had initiated a programme in 2008, but discontinued their HPV vaccination in 2014, due to very low acceptance.[1] These variations could partly be explained by contextual and implementation factors because the vaccine is currently delivered through schools or public or private health systems, depending on the country and immunisation programme. However, HPV vaccination coverage rates are also affected by healthcare worker (HCW) recommendations and public demand which are both known to be influenced by confidence in the vaccine.[3]

In recent years, HPV vaccination has suffered from growing public distrust and criticism in Europe.[4] Vaccine hesitancy has been defined by the World Health Organization (WHO) SAGE working group as a behaviour influenced by issues of confidence, complacency, and convenience. Vaccine hesitancy does not always imply vaccine refusal, as hesitant individuals can accept certain vaccines but still have doubts about them.[5] European vaccine hesitancy can partly be attributed to a lack of confidence in vaccine safety, perceptions that vaccines do not work, distrust of information, perceived low risks of vaccine-preventable diseases, as well as a lack of trust in HCWs, authorities, and pharmaceutical companies.[4,6]

Many studies have been conducted in Europe and around the world to explore public confidence in HPV vaccination. Some reviews have tried to summarise these studies,[7-10] but they have generally focused on a particular population group or outcome. The aim of this study was to systematically review all available literature on determinants[1] of HPV vaccine hesitancy for any population group in Europe. The specific objectives of the review were to understand determinants of HPV vaccine hesitancy in

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[1]In this paper, the expression "determinant" refers to "*influences of vaccine acceptance*", as understood by the WHO Sage working group on vaccine hesitancy, and does not always imply causation.

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the EU, compare determinants of HPV vaccine hesitancy in different European Member States, and examine the importance of safety concerns around HPV vaccination.

## Methods

### Search strategy and inclusion/exclusion criteria

A search strategy was developed in OVID Medline and adapted for use across Embase, PsycINFO, Social Policy and Practice, and Global Health in November 2016. Keywords were drawn from the SAGE review on vaccine hesitancy[5] and reviewed by a panel of European experts, selected by the European Centre for Disease Prevention and Control (ECDC) as reviewers for this project. A grey literature search was simultaneously conducted across Open Grey, Web of Science, PsycEXTRA, and organisation websites (ECDC, WHO, the UK Department for International Development, and the Communication Initiative Network).

The selection criteria, developed from the research question by two researchers (EK, HL) and reviewed by the European experts, were broad enough to ensure access to as many studies as possible on determinants of HPV vaccine hesitancy in Europe. The search also focused on reasons for refusal or concern, public trust and confidence, perceptions, attitudes, and beliefs about HPV vaccination as the expression "vaccine hesitancy" was not commonly used before the WHO SAGE Working Group on Vaccine Hesitancy brought more attention to and usage of the term, as well as characterising and defining it.[11] Articles were excluded when they did not include results about hesitancy, confidence, or trust in HPV vaccination, for instance, articles focusing solely on reasons for accepting HPV vaccination, knowledge or awareness, or uptake or intentions to vaccinate (without reasons). While certain socio-economic determinants (i.e. age, income, education level) may be associated with HPV vaccination uptake or intentions, they were excluded from this study in order to retain focus on the less-studied, non-socio-economic determinants such as mistrust and uncertainty. Articles about all types of HPV vaccine were included.

No restrictions were made on study participants, settings, or publication year. Articles from any EU or European Economic Area (EEA) countries and language were included, although only English language search terms were used. Articles comparing different vaccines or countries from inside and outside Europe were included only if data for HPV vaccination and/or EU countries were included. Quantitative (observational cross-sectional studies) and qualitative studies were included, but articles without original data (i.e. commentaries or editorials) or those which had the following foci were excluded: safety or efficacy research, serologic or immunogenicity studies, pre-clinical trials, cost-benefit or cost-effectiveness analysis. Intervention studies without data about determinants of vaccine hesitancy were also excluded as this review focused only on determinants of vaccine hesitancy.

### Selection, management, and analysis of articles

Articles were stored in Endnote X7 (Thomson Reuters) and after duplicates were removed, were screened independently by two (EK, CS) reviewers (title and abstract followed by full text appraisal). Reviewers met to discuss differences in selection by reviewing reasons for exclusion or inclusion until consensus was met. The number of articles included at various stages were summarised using the PRISMA chart. Data from articles in English, Spanish, French, or Italian was directly collected by EK and CS on a Microsoft Excel spreadsheet while articles in other European languages were first translated by experts at ECDC.

Methodologies for mixed-methods systematic literature reviews – which combine the synthesis and analysis of qualitative and quantitative research – are relatively new and developing rapidly.[12] There is currently insufficient methodological evidence on how to conduct mixed-methods reviews to identify and develop an understanding of health-related beliefs and/or behaviours. The methods for this study were therefore developed by combining and adapting methodologies from different types of mixed-methods reviews and are described in more details in the paragraph below.[12-19]

Data extraction and analysis were performed by one researcher (EK) and reviewed by two researchers (CJ, HL). Two separate descriptive summaries and analyses of the studies were undertaken: one qualitative and one quantitative. No integration of qualitative and quantitative studies was performed. Data from mixed methods studies were included in both analyses. Qualitative studies were analysed thematically: a set of relevant themes was developed inductively, into which each concern was categorised and analysed. No meta-analysis could be performed for the quantitative studies, due to the heterogeneity of the studies. Instead, a descriptive analysis was performed by reporting average proportions of participants with specific concerns about HPV vaccination. Due to some studies not presenting the raw data, each proportion was calculated by averaging proportions extracted from the studies. The quantitative studies identified through the systematic review were found to assess determinants of vaccine hesitancy by looking at i) concerns among participants who had refused (or would refuse) the HPV vaccine; ii) concerns among participants who had accepted (or would accept) the HPV vaccine; or iii) concerns among participants in general (those do not correspond to the sum of the two first groups but to studies that did not specify whether participants had refused or accepted the HPV vaccine). These three categories, summarised respectively as i) "*hesitant*" participants, ii) vaccine "*favourable*" participants and iii) "*general*" participants were created by the reviewer (EK) to sort data extracted from all studies, and to limit bias when reporting proportions based on different denominators. It is important to note that concerns or doubts were reported in all three groups, and hesitant individuals can be found in hesitant, favourable and general participants (see definition of hesitancy in the introduction).

Critical appraisal of studies was performed by one researcher (CJ) and checked by another (EK). The "Effective public health practice project quality assessment tool"[20] was used to appraise quantitative studies and the "Critical appraisal skills programme qualitative checklist"[21] was used for qualitative studies. Mixed methods studies were appraised using both of these tools. Studies were included regardless of the outcome of their appraisal.

## Results

The systematic literature review yielded 3,143 unique peer-reviewed and grey literature articles, of which 2,934 were excluded after title and abstract review based on the inclusion and exclusion criteria. From the 209 full text articles screened, 103 were included in the final analysis (see Figure 1).

Twenty out of the 31 qualitative studies were found to be of "good" quality (vs. 6/31 "reasonable" and 5/31 "insufficient"); and 1/65 studies with quantitative data were assessed as "strong" (vs. 25/65 "moderate" and 39/65 "weak") (see supplementary material 1). From the mixed methods studies, 0/7 were assessed as "strong" for their quantitative sections (vs. 2/7 "moderate" and 5/7 "weak"), while 2/7 were as assessed as "good" for their qualitative sections (vs. 3/7 "reasonable" and 2/7 "insufficient").

Most studies were conducted with parents (34/103, 10 of which were with mothers only) and HCWs (22/103); and reported results from the UK (28/103), Italy (12/103), France (10/103), and Sweden (10/103). Readers should exert caution when looking at the data, as studies included in the review were conducted both before or after the introduction of the vaccine (from 2005–2016), which could have influenced some public opinions and therefore might not be representative of current public perceptions in countries. The years in which study data were collected are added in the results section wherever country-specific data is presented (if data collection year was not available, the publication year is instead presented). More information about study characteristics, including whether the study was conducted before or after the vaccine was introduced, are available in supplementary material 2.

### *Determinants of HPV vaccine hesitancy in Europe*

Ten thematic categories of determinants of HPV vaccine hesitancy in Europe were identified across the literature: i) information issues, ii) concerns about vaccine safety, iii) issues of trust, iv) effectiveness of the vaccine, v) influencers, vi) issues related to sexual behaviour, vii) against all or too many vaccines, viii) access barriers, ix) perceived need for the vaccine and risk of disease, and x) fear of injections. These are discussed in more detail in the following subsections. The themes most frequently identified in qualitative studies (Figure 2) were: concerns about potential side effects of HPV vaccination (37 studies with qualitative data), beliefs that information about the vaccine is insufficient and inadequate (31), and issues related to the sexual health aspects of the vaccine (22). The categories of concerns raised by the highest average proportions of hesitant

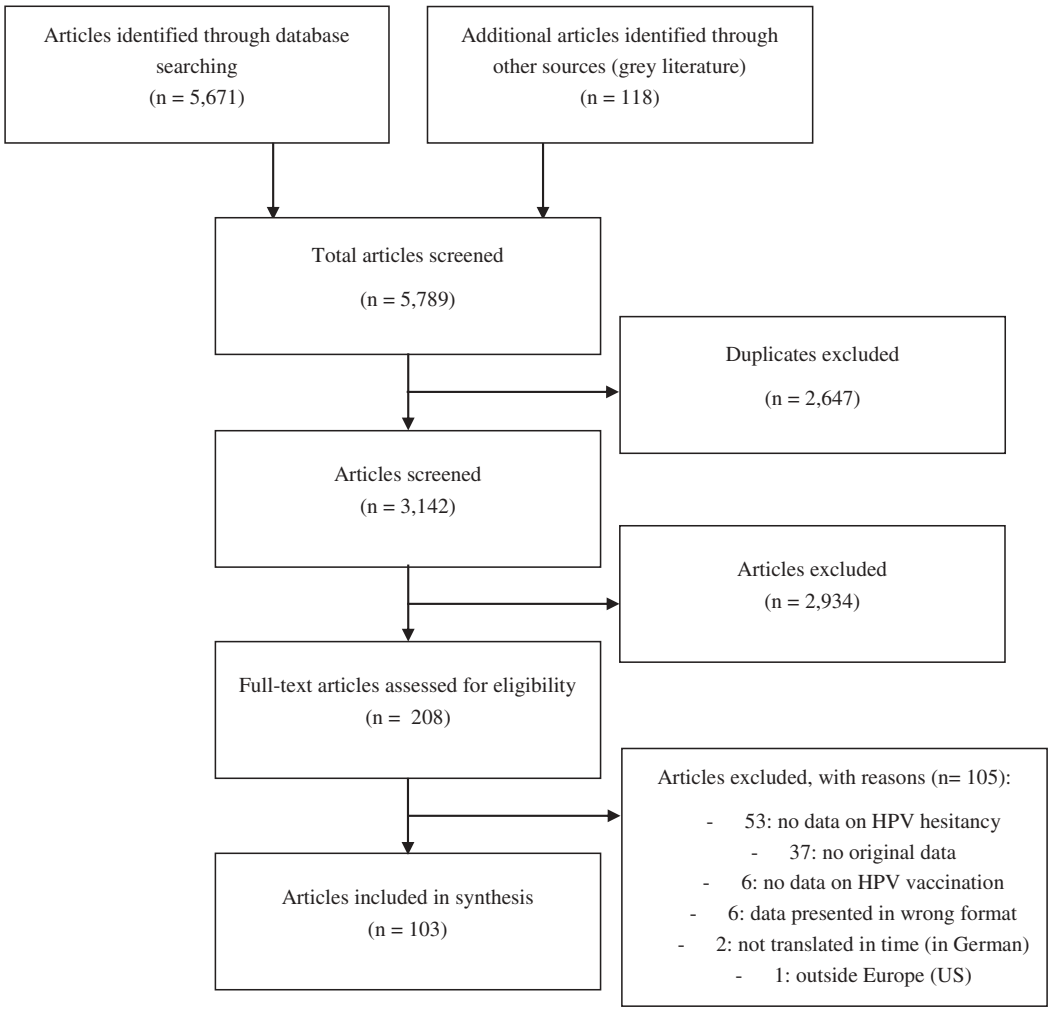



**Figure 1.** PRISMA flow diagram.

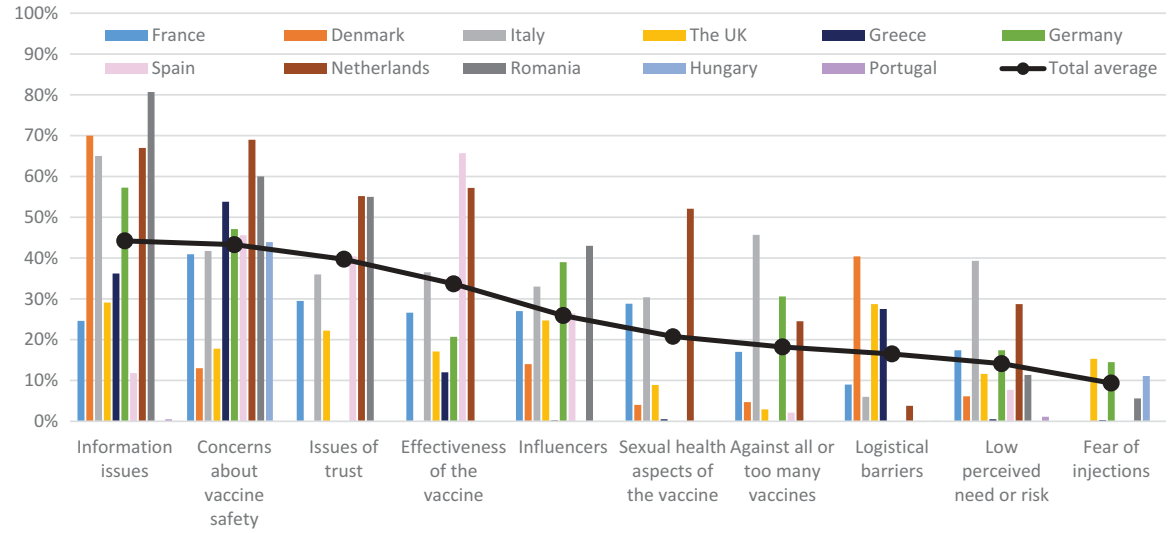



**Figure 2.** Average proportions of hesitant participants who reported certain categories of determinants of HPV vaccine hesitancy, by country.

participants across all quantitative studies in the review (Figure 2) were: perceived insufficient and/or inadequate information and knowledge about the vaccine (average of 44.2% of participants across all studies), fear of perceived side effects (43.3%), mistrust of health authorities, any type of doctor and new vaccines (39.7%), and doubts about the effectiveness of the vaccine (33.7%). Fear of needles and injections (9.4%) and low perceived need for the vaccine or low risk of HPV/cervical cancer (14.1%) were the categories least often reported by hesitant participants across all studies.

Differences between countries (Figure 2) and population groups (Figure 3) were identified, although care should be taken when looking at these differences throughout the paper as they could be due to differences in study design, variable definitions, and participant selection. For instance, overall results for a specific theme such as perceived lack of information could reflect the views of a particular population if more studies were conducted with this group. While perceived insufficient and inadequate information about HPV vaccination was found to be the most important theme in studies with hesitant participants in Romania, Denmark, Italy, Germany, and the UK, fear about potential vaccine side effects predominated the studies in the Netherlands, Greece, Hungary, and France. In Spanish studies, the most commonly reported theme was doubt about the effectiveness of the vaccine.

Concerns about potential side effects of HPV vaccination were commonly reported by hesitant parents and HCWs in studies but came second for studies with hesitant adolescents. Adolescents included in studies mostly reported dissatisfaction with the quality and quantity of information available about HPV vaccination. This was the second most important issue for hesitant parents included in studies. For studies with hesitant HCWs, the second most commonly reported theme was a low perceived need for the vaccine or a low perceived risk of HPV and/or cervical cancer.

## *Information issues*

### *Quantitative results*

Insufficient knowledge or information, and beliefs that the information available is unclear, biased and/or inadequate were identified in almost all articles reviewed. An average of 44% of hesitant participants from quantitative studies reported that there was insufficient information available about HPV vaccination, and/or that their own knowledge was insufficient,[22-41] particularly in studies in Romania (2015, 81%),[30] the Netherlands (2009–2011, 67%),[26,28] and Denmark (2010, 70%).[35] This was also reported by 53% of general study participants[42-51] and 11% of favourable study participants.[25] Additionally, 92% of hesitant parents in a study from 2009 from the Netherlands believed information about the vaccine

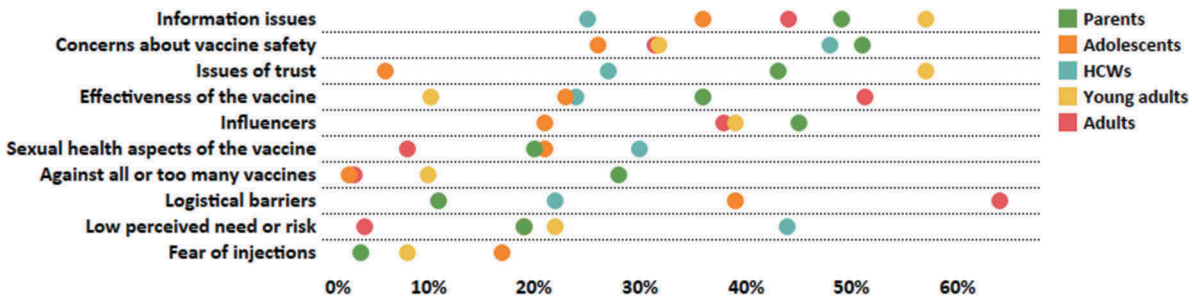



**Figure 3.** Average proportions of hesitant participants who reported certain categories of determinants of HPV vaccine hesitancy, by population groups.

was biased and unclear,[26] while 32% of general parents in a study from 2012 in Italy[45] and 18% of general parents in a study from 2009 in the Netherlands[44] believed information was unreliable. General parents in studies in the UK (2005) and Italy (2007) most frequently reported a need for more information about HPV vaccination efficacy (74%),[50,51] followed by vaccine safety (48%),[50] and duration of protection (10%).[50]

#### *Qualitative results*

In qualitative studies, a need for clearer, more transparent, and unbiased information about HPV vaccination[52-69] was identified by some participants, together with the need for more verbal, interactive communication.[52,55,57,65,69] Additionally, some participants recommended providing information in schools, for instance by organising peer discussion groups with vaccinated girls[53,55-57,61,62,67,69]; while others preferred social media or communication methods that allow more discretion.[52-54,62,69]

### *Concerns about vaccine safety*

#### *Quantitative results*

Concerns about the safety of HPV vaccination and potential long- or short-term side effects were reported by an average of 43% of hesitant study participants.[23-29,31,32,34-38,40,42,46,49,70-81] Fear of side effects was reported by an average of 52% of general study participants[51,82-97] and 17% of favourable study participants.[25,37,71] Concerns about side effects were particularly prevalent among hesitant participants from studies in the Netherlands (2009–2011, 69%),[26,28] Romania (2010, 60%),[79] and Greece (2005–2014, 54%).[31,34,40,42,78]

#### *Qualitative results*

Almost all qualitative articles described concerns about potential side effects of HPV vaccination,[52-57,59,60,62,64,66,69,98-107] often described as fears of long-term side effects not yet identified through trials.[54,55,59,60,62,64,66,69,81,98-104,106] In qualitative studies, the most commonly reported perceived side effect by parents was infertility.[52,57,59,60,65,100,102,106] Other perceived side effects included: autoimmune complications,[56,57,64,99,104,108] resistance of the virus to vaccines and/or treatment,[99,102,105] cancer,[52] menstrual complications,[65] HPV infection,[59] and death.[65]

In France, mothers and HCWs in studies conducted between 2007–2010 discussed rumours about Hepatitis B vaccination allegedly causing multiple sclerosis and some expressed worries HPV vaccination could have similar side effects.[22,81,107,109] In Sweden, study participants in 2012 worried about the safety of HPV vaccination due to reports of narcolepsy following H1N1 vaccination.[56]

### *Issues of trust*

#### *Quantitative results*

Mistrust of health authorities was reported by an average of 47% of general participants from studies in Sweden (2007),[110] Hungary (2009),[72] and the UK (2006)[91] as well as 55% of hesitant participants from studies in France (2015)[74] and the Netherlands (2009).[26] Additionally, 12% of general practitioners (GPs) in general in a study conducted between 2007–2010 in France reported mistrust because of "excessive marketing" around HPV vaccination.[22]

Mistrust of doctors was raised by 41% of hesitant parents in a 2009 study from the Netherlands,[26] and 45% of general parents and young adults in studies from Hungary (2009)[72] and the UK (2006).[91]

Mistrust of new vaccines and concerns about the relative newness of the HPV vaccine was reported by an average of 36% of hesitant study participants.[22,27,45,74,75,107,111,112] In French studies, concerns about the newness of the vaccine, reported by general GPs, decreased with time but remained important: from 42% in 2007[22,107] to 37% in 2010[22] and 30% in 2015.[74] Mistrust of new vaccines was reported only by 9% of general study participants in 2010 in Germany[95] and 1% of favourable study participants in Italy in 2013.[111]

#### *Qualitative results*

Beliefs that governments were not transparent,[57,59] influenced by vaccine manufacturers[52,98] or were withholding information about side effects[65,98] were reported in some qualitative studies. Some participants shared concerns about transparency,[52,59] commercial influences from pharmaceutical companies,[52,98,104,113] and perceptions that doctors were dismissive and deliberately withheld information about side effects.[52,65,98,104] Mistrust of pharmaceutical companies due to their underlying profit-making motives and doubts about the trustworthiness of vaccine trials and safety claims were also reported in studies in Bulgaria (2009–2014),[98,104] Romania (2010–2012),[52] Sweden (2010, 2012),[55,56] Ireland (2012),[63] the Netherlands (2008),[60] Spain (2014),[98] and the UK (2014).[98]

Finally, conspiracy theories about the vaccine allegedly contributing to reducing world population or being an experiment on young girls were reported in studies in Bulgaria (2010–2013),[104] Romania (2010–2012),[52] Sweden (2014),[57] the Netherlands (2015),[65] and the UK (2007–2016).[59,100,105]

### *Effectiveness of the vaccine*

#### *Quantitative results*

Across all studies, an average of 34% of hesitant participants were found to doubt the effectiveness of the vaccine,[23,24,26,32,34,37,73-75,77,114] as well as 39% of general participants[43,46,82,84-86,96] and 3% of favourable participants.[26,37] Perceived low vaccine effectiveness was particularly prevalent among hesitant participants in studies in Spain (2013, 66%),[112] the Netherlands (2009, 57%),[26] and Italy (2006–2014, 37%).[73,75,114] Additionally, 41% of hesitant study participants[74,112] and 31% of general study participants[84,86,97] doubted the length of protection of the vaccine.

#### *Qualitative results*

In addition to worries about the duration of effectiveness of the vaccine,[22,52,55–57,60,64,67,99,104,105,108,109,115] participants in qualitative studies also reported concerns that the vaccine did not protect against all types of HPV.[22,58,101,105,109,115,116]

### Influencers

#### Quantitative results

While an average of 30% of hesitant parents reported not having received any recommendation to vaccinate from HCWs in studies in Spain (2010–2011),[36] Italy (2012–2015),[29,45,75] Denmark (2010)[35] and France (2015),[29] an average of 26% of hesitant parents in studies from Spain (2010–2011)[36] and Italy (2012–2014)[27,75] were advised not to vaccinate by their HCW. Additionally, 19% of general adolescents in a study from Germany in 2010 reported having been advised not to get the HPV vaccine by their physician.[95]

Furthermore, an average of 47% of hesitant parents from studies in Romania (2010)[79] and Italy (2012)[27,45] mentioned they had received contradictory advice and opinions from different healthcare professionals or specialists. A study published in 2015 in Italy, where both boys and girls have been vaccinated since 2017, showed 38% of general men who attended sexual health clinics reported receiving contradictory advice.[87]

Some adolescents also reported being influenced by their parents, with 25% of hesitant adolescent girls from studies in the UK (2008–2013),[23,68] 39% of general adolescent girls from a study in Germany (2010)[95] and 1% of general adolescent girls from a study in Sweden (2008)[47] mentioning they could not get vaccinated because their parents had refused the vaccine.[25,70] Additionally, 11% of hesitant adolescent girls from a 2015 study from Romania reported that their parents thought the vaccine was unsafe.[30]

An average of 75% of hesitant parents from a 2010 study from Romania[79] and 39% of hesitant young women from a 2013 study from Germany[37] reported being influenced by others who had refused HPV vaccination or who had recommended against it. Additionally, 49% of general adolescent girls from a 2007 study from the UK reported being influenced by rumours.[23]

#### Qualitative results

Healthcare professionals, including school nurses and GPs, were commonly referred to in qualitative studies as having the most influence on HPV vaccination decisions.[52,57,68,80,99,104,117] Additionally, the influence of family members, friends, and parents of other children who did not vaccinate or who recommended against the vaccine were reported across some studies.[52,57,67,100]

### Issues related to sexual behaviour

#### Quantitative results

The belief that HPV vaccination might encourage promiscuity or earlier sexual debut in young girls was observed in an average of 11% of hesitant study participants.[22,23,26,32,50,71] This belief was also reported among 30% of general study participants[51,75,85,89,90,110,118] and 6% of favourable study participants.[22,71]

An average of 20% of hesitant study participants,[22,26,27,50,74,75,107] 20% of general study participants,[43,90,93,97,110] and 23% of favourable study participants[22] also believed that the vaccine would lead to unsafe sexual behaviour and a decrease in the use of condoms and cervical cancer screening. This fear was reported by 19% of hesitant HCWs in studies in France (2007–2015)[22,74,107] and 23% of hesitant parents in studies in Italy (2007–2014).[27,50,75]

Concerns about girls being too young were reported by an average of 13% of hesitant study participants[23,26,27,29,30,32,35,45,75] and 30% of general study participants.[48,110] It was most commonly reported by hesitant parents in a study in the Netherlands (2009, 52%)[26] and hesitant school nurses in a study in Sweden (2013, 48%).[110] The concern that it is too difficult to discuss HPV vaccination with adolescent girls was also discussed in studies by an average of 21% of hesitant parents and paediatricians,[35,73] and 11% of general parents and HCWs.[22,51,82,107,109] An average of 27% of general GPs in a 2014 study in France[82] and 32% of general adolescents in a 2008 study in Sweden[47] also believed it was difficult to talk about the vaccine with parents, while 21% of general adolescents in a study in the UK (2007–2008) reported embarrassment around getting a vaccine against a sexually transmitted infection.[85]

Cultural and religious barriers to vaccination were indicated by an average of 16% of hesitant participants,[26,29,31,32] particularly in a study in the Netherlands (2009, 70%).[26]

#### Qualitative results

Qualitative studies reported beliefs that HPV vaccination might encourage promiscuity or earlier sexual debut in young girls[61,65-67,100,101,106,108,119] and that the vaccine could lead to unsafe sexual behaviour and a decrease in the use of condoms and cervical cancer screening.[55,57,63,64,66,67,80,106,108,109,119]

Additionally, some participants mentioned that the vaccine is being given to girls when they are too young because they have not started to menstruate, are not yet sexually active or married,[54,57,58,61,100,108] or because they are too "naïve and immature" to give their consent.[98,103] Some also reported that it is not easy to talk about HPV vaccination with girls that are so young.[20,53,54,59,61,63,79,98,99,105,108,114]

Finally, cultural and religious influences on vaccine acceptance reported in studies included perceived low risk of infection because of certain lifestyles (being virgins when marrying, having only one partner),[54,57,60,61,65,99,100,105,108,109] and having a strong sense of fatality and/or belief that God will protect girls.[113]

### Against all or too many vaccines

#### Quantitative results

An average of 18% of hesitant study participants[25,26,32,36,37,77,80] were against all vaccines in general. Additionally, 33% of general study participants[90,91] and 28% of hesitant study participants[26,29,35,50,75,80] believed children already receive too many vaccines, with 47% of hesitant parents in a 2015 study in Germany[29] and 46% of hesitant parents in studies in Italy (2007–2015)[29,50,75] raising this concern.

#### Qualitative results

A few qualitative studies reported that some participants were against all vaccines.[54,57,59,69,99,104]

### Access barriers

#### Quantitative results

In quantitative studies, cost was raised as an issue by an average of 32% of hesitant participants,[31,38,74,75,80] particularly in studies in Denmark (2009, 62%)[80] and Greece (2008–2014, 54%),[31] and was also raised as a concern for an average of 47% of general study participants in Germany, Greece, Hungary, Ireland, and Sweden.[46,47,94,97,120] The inconvenience of receiving multiple doses was reported by 56% of general participants in studies in Sweden (2007–2013),[96,110] 25% of hesitant participants in studies in France (2015)[74] and the UK (2007–2008),[71] and 10% of favourable participants in a study in the UK (2007–2008).[71]

Increased workload created by administering the vaccine was raised as a barrier by general school nurses in a study in Sweden (2013, 40%),[110] while general adolescents in studies in Germany (2010, 12%)[95] and Greece (2008–2014, 1%)[31] reported being too busy to get vaccinated.

Other accessibility issues such as not having a consent form, being absent from school when vaccination was being administered, recent migration or not being in the target age group were also reported by an average 10% of hesitant participants in studies in the Netherlands (2009),[26] the UK (2011–2013),25,39 Italy (2008–2009),[121] Denmark (2009),[80] and Portugal (2007–2008).[33]

#### Qualitative results

The high cost of the HPV vaccine was mentioned in five qualitative studies, from 2009–2010 in Sweden,[64,102] 2010–2014 in Bulgaria,[98,104] 2014 in the UK,[98] 2014 in Spain,[98] and 2012 in Ireland.[63] Another access barrier was the inconvenience of going to get multiple injections.[67,115]

The challenge of vaccinating in schools was discussed in studies in Sweden (2010–2014)[55-57] and in the UK (2006–2015),[59,61,101,116] with reasons including a lack of privacy, children needing a calmer environment, missing classes, and parental informed consent. The question of which healthcare professional should administer the vaccine was raised in studies in Sweden (2010)[55,64] and the UK (2007–2008),[59] with feelings of competition and distrust between gynaecologists and paediatricians identified in a study in Greece (2016).[99]

### Perceived need for the vaccine and risk of disease

#### Quantitative results

A perceived lack of need for the HPV vaccine was reported by an average of 14% of hesitant study participants,[25,31,32,36,38,70,75,121] 5% of general study participants,[88,95] and 2% of favourable study participants.[25]

A perceived low risk of contracting HPV infection or developing cervical cancer was reported by an average of 22% of hesitant study participants[23,24,26,33,35,49,76,77,79,80,114] and 26% of favourable study participants.[26] Among hesitant participants, the perceived low risk of HPV was particularly prevalent in studies in Italy (2007–2015, 44%)[49,76,114] and the Netherlands (2009, 38%).[26]

#### Qualitative results

Some participants in qualitative studies expressed a perceived lack of need for the HPV vaccine due to a perceived low risk of contracting HPV and/or cervical cancer,[55,59,66,80,100,109,115] a perceived low severity of the disease,[63,66,81] and/or the availability of alternative prevention methods or abstinence.[54,60,66,69,101,105,108,115]

### Fear of injections

#### Quantitative results

Fear of needles and injection pain was reported by 29% of general study participants,[47,85,89,92] 9% of hesitant study participants,[24,25,30,31,37,39,46,72] and 5% of favourable study participants.[25]

#### Qualitative results

Qualitative studies reported rumours among adolescents about vaccination pain,[102,116] the size of the needles and the pain at injection increasing with each dose,[62,116] the mistaken belief of the vaccine being administered in the cervix,[106,116] concerns about needle cleanliness,[116] and the fear that the injection could lead to a loss of virginity.[68]

## Discussion

This systematic literature review identified 103 unique articles on determinants of HPV vaccine hesitancy in Europe. Across European studies, the most prevalent concerns were about: insufficient and inadequate information about HPV vaccination; potential side effects of the vaccine; issues around trust of health authorities, doctors, and new vaccines; and perceived low vaccine effectiveness. While issues about the sexual health aspects of the vaccine were reported in many qualitative studies, they were less prevalent in quantitative studies, which could be explained by the nature of qualitative studies that ask open-ended questions.

Some differences were observed between studies from different European countries, with studies from Italy reporting the highest average proportion of participants with concerns about vaccination in general, issues related to the sexual health aspects of the vaccine, and perceived low risk of HPV/cervical cancer and consequent doubts about the need for the HPV vaccine. Differences might be explained by different contexts and national immunisation programmes as well previous experiences with vaccination confidence crises but could also be due to differences in study designs and the methodology used for the systematic review.

Many concerns identified in this review were more frequently observed among study participants in general rather than in vaccine-hesitant participants, while some concerns were also reported by large proportions of favourable participants. This could be an effect of the methodology used to summarise proportions from different studies in this review: the differences could be explained by the fact that proportions from different years, countries, and population groups were

averaged and compared. However, it could also point to other issues. More research should therefore be conducted to further explain these differences and explore perceptions about HPV vaccination across the continuum of vaccine hesitancy.

The most frequent concerns reported across studies and among most study participants were a perceived lack of information together with a fear of potential HPV vaccine side effects. This confirms results from previous studies about perceptions of vaccine safety being the most important determinant of vaccine hesitancy for vaccines in general in Europe.[4,6] While some study participants raised specific concerns about infertility, most reported having general safety fears that they could not explain or specify. This could be a consequence of the vaccine still being perceived as too new and general uncertainty about the vaccine. A number of studies have shown that uncertainty can influence as much as empirical evidence in vaccination decision-making.[122,123]

Uncertainty is still often framed as something that can be overcome by filling information gaps with more facts; however, mistrust of health authorities and some doctors was commonly reported in this review, indicating that communication strategies need to include efforts to build and maintain public trust.[124] Communication strategies should engage communities, for instance by building alliances with civil society or disease associations, organising school information and discussion sessions with parents and peers, and online discussion groups overseen and managed by local health professionals. More research is needed to understand information-seeking behaviours as well as how individuals appraise and use information about HPV vaccination, and finally to evaluate which communication and engagement strategies are most effective with different population groups (e.g. parents, teenagers, ethnic/religious minorities, or HCWs).[4,125,126] Evaluations should focus on communication and engagement strategies developed by health authorities, but also on information that the public is exposed to every day, such as social media, online news, or television documentaries.

While influences from family members, friends, other parents or HCWs were commonly reported by parents in certain studies, adolescents in those studies also reported rumours circulating about HPV vaccination. The viral spread of negative rumours, particularly among adolescents through social media, could prove to be an important challenge should a confidence crisis arise. An example is the recent spread of unverified and subsequently disproved concerns in Denmark through YouTube videos and other social media that HPV vaccine might cause Postural Tachycardia Syndrome (PoTS) and Complex Regional Pain Syndrome (CRPS), as well as the occurrence of mass-psychogenic illnesses that have been observed and linked to HPV vaccination in Colombia and Australia.[127-129] These examples illustrate the rapidity by which rumours can spread through social media and the importance of influencers and group dynamics in HPV vaccination confidence among adolescents as well as parents. Faster research is therefore needed, such as through media monitoring, to identify possible anxiety reactions, and to inform time-sensitive strategies – including crisis communication plans – on how to respond to them. The confidence crisis that occurred in Denmark provides a good example of how comprehensive strategies using a combination of social and online media interventions, engagement with mothers and adolescents, and risk communication strategies can successfully reinstate public trust in vaccination. Denmark's success in reversing the decreasing vaccination coverage trend is in the process of being evaluated and will constitute a good case study for other countries facing similar issues.

HCWs, including GPs, paediatricians, and school nurses were identified in many studies as strong influencers for parents and adolescents but they were also found to have concerns about the safety and effectiveness of HPV vaccination, which could prevent them from recommending the vaccine.[109,129] As HCWs are often considered the most trustworthy source of medical information,[130] it is important to address their own hesitancy, for instance by improving their training on the introduction of new vaccines. Additionally, as HCWs also reported facing difficulties talking about HPV vaccination in some studies, it is important to provide more support to HCWs and develop skills to manage difficult conversations. Some methods, such as motivational interviewing[131,132] have been employed outside of Europe and could be adapted and evaluated in European countries.

### Limitations

The results from this systematic literature review should be interpreted with some caution. While the screening of articles was conducted by two independent reviewers, data extraction and critical analysis of studies could only be conducted by a single reviewer. The results from the critical appraisal showed that many quantitative studies were methodologically weak, which can mainly be explained by the fact that the tool used to assess quantitative studies was designed for intervention studies while most studies in the field of vaccine hesitancy are observational, and often cross-sectional. This resulted in low scores for studies that did not use methods such as blinding, which are not applicable to observational studies. This limitation means that the results in this paper could not be discussed together with the critical appraisal results. While readers can refer to the results from the critical appraisal in the supplementary materials, they should therefore interpret these with caution. Information about each article's reported conflicts of interests and funding sources was also extracted and is available at readers' request. Additionally, two articles from Germany had to be omitted due to translations not being finalised in time for this report, which could have affected the findings for the country. The database searches were also only performed in English, which means some articles in other languages might have been omitted.

The heterogeneity of the data and the analysis conducted in the different studies, which did not allow for a meta-analysis, might have introduced some bias in the quantitative analysis. For instance, proportions of participants with specific concerns were compared across countries and population groups, although the denominators (i.e. entire population,

vaccine refusers, or vaccine acceptors) were sometimes very different. This was partly managed by separating the analysis for different groups. Averages were used to quantify different concerns, although data from individual studies might have been misrepresented especially as very high ranges of proportions were observed. Finally, articles looking at socio-economic determinants of vaccine hesitancy were excluded as they were outside the scope of this review. Future reviews should be conducted looking specifically at the impact of those determinants on hesitancy.

### *Conclusion*

Trust in HPV vaccination is currently being shaken in many European countries, the impact of which is indicated by low and/or decreasing coverage rates. Strategies developed with the goal of addressing HPV vaccine hesitancy should not only focus on providing more information about the safety and effectiveness of the vaccine, but also aim to rebuild and maintain trust in public health institutions, including HCWs and health authorities, in order to prevent or manage future potential confidence crises.

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