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Literature Review

Method

For this literature review we used Pubmed database. The search equation to identify articles was: “(HPV[tiab] OR "Human papillomavirus"[tiab] OR papillomavirus[tiab]) AND (vaccin*[tiab] OR immunization[tiab] OR prevent*[tiab])” .

We have a continuous monitoring process to keep up to date with the latest articles and publications related with HPV vaccination. Each week, a search query is submitted with relevant articles and publications that have been published. We then screened and filtered those results.

A total of 33 articles, published between 2012 and 2022 were included in this literature review.

Main features of the records included (first and second grid)

Lack of knowledge among young girls and mothers

We have observed that in most articles, one of the main elements contributing to vaccine hesitancy is the lack of knowledge regarding the HPV vaccine. It is found that girls and mothers who hesitate or refuse the vaccine are not necessarily against vaccination, but they are not sufficiently informed to accept it.

It is necessary to inform and engage dialogues with young girls so that they are aware of this vaccine and can participate in the decision-making process.

a) Target population and age recommended

The recommended population is not precisely known by adolescents and mothers. In fact, according to a study, 61% of high school students thought that this vaccine was only for girls, compared to 46% for girls and boys. The age for HPV vaccination is also not precisely known and is unknown to some mothers.

b) Cervical Cancer

It is also observed that only few women are aware that HPV infection is the main cause of cervical cancer. This is particularly important for low educated women.

c) HPV and sexual habits

The lack of information is also observed regarding the link between HPV and sexual habits, virginity. A study found that some mothers believe that the HPV vaccine eradicates all sexually transmitted diseases.

d) The lack of information linked to social inequalities

It turns out that adolescent girls living in urban areas had much more knowledge about HPV vaccination than those living in rural areas.

Source of Information on HPV vaccination

a) Media and internet

Media is a major source of information on HPV vaccination. An average of 55% of woman had heard of the vaccine through television. Internet have a negative impact on vaccination uptake. Studies found that mothers who search for vaccine information on internet was associated with a lower HPV vaccination by their daughters. Indeed, results on the internet can be confusing for mothers who found contradicting pieces of information. This leads to an unfavourable attitude, or discouragements towards vaccination.

b) Mothers

For girls, mothers are the main sources of information (80%). It is important to provide information to these girls outside of this source, in order to avoid repeating the mother's hesitations, in case shedoes not pass on a favourable attitude

c) Physicians, teachers and school nurse

A lack of information provided by the physicians constitutes a barrier for high school students.

Crucial role of physicians

Family physicians, play a crucial role in vaccine offer and acceptance. Young girls have better knowledge and information when they consulted their family physicians, which increase HPV vaccine uptake among them.

However, when physicians express doubts about the HPV vaccine, it raises doubts among young girls and mother. Moreover, some mothers didn't want to vaccinate their daughters because their GP was against it. Indeed, a strong trust in doctors can be barrier to vaccine acceptance, depending on the doctor position toward HPV vaccination. A study shows that 14.1% preferred to rely on their physician's decision and waited to know his opinion to make a decision. It seemed that, mothers from a low socio-economic background adhere more to their physician's opinion than mothers in a higher professional category who want to know their opinion but had a more critical point of view.

GP recommendation is very important in vaccine uptake. HPV vaccine initiation in girls aged 14 was a physician's recommendation. Parents justified the non-vaccination of their children by a non-proposal of their GP.

a) Reasons of hesitant physicians

Some doctors express a low confidence in the vaccine due to concerns about the risks and benefits of HPV vaccination. According to a study, some have an unfavourable perception of its risk-benefit balance (OR=0.13), doubts about vaccine utility in general (OR= 0.78). 60% considered that not enough is known about its risks

Moreover, there are statements against HPV vaccination, not based in science (insufficient effectiveness of the vaccine, fear that the vaccine would stop girls' growth...). We also observed, a lack of trust in the Ministry of Health and pharmaceutical industry which leads to doubts on this vaccine that they disclose to their patients. Some explain it by repeated public health scandals in France.

Some GP think also that a cervical cancer screening alone would be more feasible and efficient than HPV vaccination.

b) Organisational and relational barriers

A low vaccine proposal is also due to a low rate of adolescent's consultation, inappropriate reasons for consultation, and an incomplete vaccination schedule due to spaced-out consultations over time. The role of parental vaccine hesitancy is major in the low proposal rate.

c) Insufficient information provided by school medicine

It is necessary for school and university medicine to inform high school and college students about HPV vaccination. Studies have shown that providing information and brochures to students can significantly increase the percentage of girls vaccinated and intentions to vaccinate. In fact, the percentage of vaccinated girls was significantly higher after information (10.9% versus 3.2%) and there was a significant increase in the percentage of intentions to vaccinate after brochure distribution ($p < 0.001$).

Role of parents

The role of parents, especially mothers, was highlighted in studies. We observed a higher intention to vaccinate among mothers. They have an important role in promoting the vaccination to their children, even more when they have a health-related job, as they have a better understanding of benefits of vaccination. Studies found that information about the vaccine and discussions around sexuality were most effective when there was a trusting relationship between mother and daughter. In fact, adolescents who had such a relationship, were more likely to share misbeliefs and obstacles to vaccination, and were more likely to receive the anti-HPV vaccine.

Also, girls who had broken links with their parents were less likely to initiate vaccination.

Fear of side effects

Fear of side effects is a major barrier to vaccination against HPV. Many parents express potential adverse effects associated with the vaccine, particularly because it is a new vaccine and there is not enough experience to look back on (54.9% of parents cited it in a study). Mothers with low educational level, reported their fear that anti HPV vaccine could cause difficulties with pregnancy. Some mothers were concerned about the possible association between hepatitis B vaccination and multiple sclerosis, following a large-scale immunization campaign among adolescents in France in 1994 which sparked controversy.

HPV vaccine safety and effectiveness

The perception of vaccine safety and effectiveness is a major factor in vaccine hesitancy. According to a study, more than 60% of parents and EP considered HBV, HPV and SIV vaccines to be ineffective or unsafe. It is explained by a lack of scientific evidence around its safety and effectiveness. Students also expressed uncertainty regarding the safety of the HPV vaccine.

Perception of risk

Perceptions of risk play a significant role in HPV vaccine acceptance. Studies have reported unfavourable perceptions of the vaccine's risk-benefit balance, by parents and healthcare providers perceiving the vaccine's risks as outweighing its benefits. 60% of respondents in a survey believed that not enough was known about the vaccine's risks.

Sexuality

To increase acceptance of the HPV vaccine, it may be necessary to dissociate the vaccine from sexuality. Some mothers (5.6% in a study) found it challenging to discuss sexuality with their daughters, fearing it may encourage sexual activity. Religious factor is also not negligeable, leading to the belief that vaccination can wait since it is forbidden to have sex before marriage in some religions.

Adolescents themselves expressed concerns about the timing of vaccination in relation to sexual activity: the necessity of injection after the first or between two sexual activities. Also, confessing their sexual life to their parents is a source of concern.

GP also have the fear of parents' reaction due to the association with sexuality.

Unfavourable opinion about vaccination in general

According to a study, those who refused the vaccine have an unfavourable opinion (or no opinion) about vaccination in general. (72.7% vs 28.0% among non-uniform respondents, $p < 0.001$)

Mistrusted and controversial vaccine

The HPV vaccine is often perceived as different from other vaccines and is therefore less trusted and more controversial. Additionally, there have been controversies surrounding the safety and effectiveness of the vaccine, which may contribute to vaccine hesitancy. There is a lack of trust in new vaccines and it is a major barrier to vaccine. Long-term exposure to such controversial information, especially during adolescence, could have lasting effects on the trust adolescents place in vaccines and public health recommendations.

Some parents wish the health authorities to make this vaccine mandatory as other child vaccine.

a) Media controversies

Internet and social media facilitate the spread of controversies, misinformation surrounding vaccines. This discourages acceptance and increase hesitancy. Trust in health authorities

For example, some mothers had in mind the controversy over a possible link between hepatitis B vaccination and multiple sclerosis which affected France after a mass hepatitis B immunization campaign among adolescents in 1994. A study said: "a health system's past performance can influence public trust in institutions, particularly around their competency and ability to deliver similar interventions or programmes".

Vaccine hesitancy associated with socio-demographic characteristics

Vaccine hesitancy in general was associated with higher levels of education, low income in parents of adolescent girls, poor self-perceived health in elderly people, and more frequent among women than men (perhaps because they are often more involved in the medical follow-up of their children).

A study shows that, vaccine hesitancy was highest in parents of adolescents (10-15 years) (48%) than parents of children aged 0-9 years (43%).

Those who were less likely to accept vaccination were also less likely to be in favor of vaccination in general, more likely to speak another language at home, and be unaware of their parents' education level, which may indicate a lower understanding of the study or be a proxy for lower socioeconomic status. While the socioeconomic status of parents, family composition, and tobacco use were found to be associated with HPV vaccine initiation in girls aged 15 and above.

Acceptance of HPV vaccine

a) Educational level

We observe more favourable attitude regarding the acceptance of HPV vaccine among LEL mothers than HEL mothers.

b) School location

HPV vaccine initiation rate was twice than in rural schools.

c) Socio economic status

Higher family incomes were associated with higher initiation rate

d) Religion

It appears that, there is a reduced acceptance among people who regularly practiced a religion.

e) New technologies, vaccination programs

The use of new technologies in interventions appears to be well-suited for younger populations, easily replicable, and has the advantage of reaching numerous individuals at a low cost.

Implement vaccination programs in schools increases vaccine coverage and reduces social inequalities by reaching a larger population.

Favourable reasons

Mothers who were in favour of the HPV vaccine for their daughters often cited the opportunity to prevent their children from developing a severe and potentially fatal disease as their primary reason. This reason was mentioned by 72.7% of low education level (LEL) mothers, 65.7% of medium education level (MEL) mothers, and 47.0% of high education level (HEL) mothers.

Fear of cancer and the desire to prevent their daughters from telling them they have cervical cancer while a vaccine exists were also cited as important reasons for supporting vaccination. Genital warts don't generate higher acceptance.

Incomplete vaccine protocol (once vaccination had been initiated)

It appears that, among those who initiated their vaccination, girls who attended private school, who belonged to family higher outcomes, who live with a single parent and who smoke; don't complete their vaccination protocol.

Country specific considerations.

On the 28th February 2023, the French President announced the implementation of a vaccination campaign against HPV in school throughout the national territory, starting September 2023. This news

led us to re-think the best way to lead the surveys and the deliverables expected within the framework of WP6.

It therefore seems very complicated for us to carry out the surveys in the exact way it was planned, considering the latest news in our country and also the deadline: authorization needed couldn’t match the deadlines (as we had the protocol very recently). Thus, we decided to use surveys carried out very recently by Judith Mueller's team on the subject.

Methods section for the focus groups (or questionaire) for students and teachers.

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Methods section for the focus groups for students

Concerning the survey toward students, it was a cross-sectional study among middle-school pupils in France. Data was collected between 22 November 2021 and February 2022, using anonymous web-based survey published on the REDcap online survey platform. A random selection of middle-schools in nine regions throughout the French mainland territory was offered participation in the trial. Ninety schools were included and randomised in the trial, and 19,885 pupils attending 3rd and 4th grade classes (typically aged 13-15 years) were eligible to participate. . Given constraints during the COVID-19 pandemic, only 61 middle-schools with approximately 13,233 pupils in 3 rd and 4th grades participated in the trial.

Adolescents completed the questionnaires during in-class sessions, under the supervision of their biology teacher or a school nurse.

There is one questionnaire on socio-demographic characteristics of the adolescents' family, awareness, knowledge, attitudes and behaviour around HPV-related disease and vaccination, their self-declared HPV vaccination status and intention to get vaccinated.

1. **HPV awareness and vaccination status**

To assess the participants awareness and vaccination status, 'Have you heard about a vaccine against human papilloma virus?' (Yes/No/Unsure) was asked. Among those aware of HPV vaccine, vaccination status was evaluated as 'Are you vaccinated against HPV?' Participants stating that they were not sure about vaccination were included into the unvaccinated group.

Vaccine intentionality was assed among unvaccinated adolescents who had heard of HPV vaccine: refusal ('HPV vaccination is not relevant for me'), indecision ('I consider HPV vaccination as relevant for me, but I am not sure about getting vaccinated') and intention ('I have the intention to soon get vaccinated')

2. **Participant's socio-educational characteristics**

To assess the participants' socio-educational characteristics, individual and ecological variables were collected. Educational level of mother and father was grouped as ≤baccalaureat (up to high school), >baccalaureat (higher education), and 'do not know'. Multilingualism was assessed by the question 'Do you commonly speak another language than French at home' (only French-monolingual / other languages-multilingual). For specific analyses, was collated parental education (the highest achieved level among parents) and multilingualism. This followed the hypothesis that the significance of a multilingual family environment for the uptake of prevention messages depends on the parental educational level. As ecological variable for schools' municipalities, we collected the 2015 French deprivation index, which is based on the median household income, % high-school graduates among

the ≥15-year-old population, % blue-collar workers in the active population and the unemployment rate, with a mean of 0 for mainland France. Municipalities of participating schools had an index spanning from -2.2 to 2.2, which represents approximately the range of the index in French municipalities. We created four categories of school area deprivation level: low (least deprived: index ≤-1); moderate low (index >-1 to 0); moderate high (index >0 to 1); and high (most deprived: index >1).

Variables representing hypothetical mitigation related to school curriculum and referring physician (RP) visits. Most questions included a 'do not know' modality, which was included into 'no'.). School curriculum was assessed by whether pupils remembered specific topics during class (bacteria and viruses; vaccination in general; human reproduction; sexual education; and sexually transmittable infections). These topics can be addressed in biology classes in middle-schools in France, but neither content nor format is standardised. We assessed recent contact with RP by the question 'Have you visited your referring physician (RP) during the past 12 months?' and 'Has your RP offered HPV vaccination?'. In France, adolescents commonly visit RPs for acute or chronic health issues and for sport certificates. Three RP visits dedicated to health promotion are fully reimbursed for children aged 8-16 years. For specific analyses, we collated these variables into one RP influence variable (no visit/visit with offer/visit without vaccine offer).

Additionally, was collected variables known to impact health behaviour. This included personal aptitudes - evaluated as: self-efficacy (confidence in being able to respond to questions on one's health, rated on a 10-point scale), ease of finding information concerning HPV, and ease of talking to health professionals and close persons about HPV; and social influence variables, relating to the attitudes of family and their social environment towards vaccinations in general and to HPV, respectively, and the HPV vaccination status of friends. Was assessed specific knowledge and attitude items regarding HPV using a 5-point Likert scale, coding responses as disagree/undecided/agree.

Methods section for the focus groups for teachers

Middle school nurses, teachers and support staff from four French regions participated between January 2020 and May 2021. We combined: quantitative data from self-administered online questionnaires (n = 301), analysed using descriptive statistics; and qualitative data from three focus groups (n = 14), thematically analysed.

This study was conducted among school staff (nurses, teachers and support staff) from middle schools (pupils typically aged 11-14 years, corresponding to grades 6-9 in the US educational system). We selected schools located in four regions (out of 13 regions in mainland France), hereafter called "study regions", where the PrevHPV teams were settled and representing a diversity of geographical, demographic and socioeconomic contexts as well as HPV vaccine coverage rates: Ile-de-France (HPV VC among 16-year girls in 2018: 19%), Auvergne-Rhône-Alpes (23%), Grand Est (29%) and Pays de la Loire (30%). The study was planned to be conducted from January to April 2020 but was interrupted due to the Covid-19 pandemic and the schools' closure in March 2020 in France; it lasted until May 2021.

Regarding the quantitative data, it was planned to collect 300 questionnaires, a sample size calculated to obtain estimates on knowledge, beliefs and attitudes with a 5% precision and considered feasible in terms of the recruitment. Regarding the qualitative data, we planned to perform three to six focus groups (five to eight participants to each) depending on data saturation.

1. **Participants' recruitment**

First, using data from the Ministry of National Education, was selected middle schools located in the study regions to ensure a balanced distribution of urban/rural areas, public/private schools, and, public schools belonging to a high-priority educational network (high level of social deprivation)/others. Then, the head of each middle school was contacted by email/phone to ask him/her to participate in the study. As we aimed to recruit 30 to 40 middle schools, we first selected 80 schools (expected acceptation rate: 50%) and planned to select additional schools if needed.

School staff interested in participating in a focus group were invited to contact the research team by email. The participant information sheet attached to the invitation stated that participants to the focus groups would be offered a 20€ shopping voucher.

2. Data collection:

a) Quantitative Data:

The questionnaire was administered online using LimeSurvey software. It was designed by 155 the PrevHPV multidisciplinary study group based on the existing literature on determinants of HPV vaccination and previous studies among school staff.

It included 157 closed-ended questions on:

- knowledge about HPV infections: 10 items (yes, no, unsure) and one item on whether cervical cancer is due to a persistent HPV infection (yes, no, some cervical cancers only, unsure)
- knowledge about HPV prevention and vaccination: 12 items (yes, no, unsure);
- psychological antecedents of vaccination, assessed using the long-version of the 5C (Confidence, Complacency, Constraints, Calculation and Collective responsibility) scale: 15 items 7-point Likert scale (from 1=strongly disagree to 7=strongly agree)
- personal vaccination status and attitudes towards HPV vaccination: being vaccinated against HPV (yes, no, unsure) and, if no or unsure, acceptability to receive HPV vaccine if it was possible and recommended for them (5-point Likert scale from 1=strongly disagree to 168 5=strongly agree);
- appropriate period to propose HPV vaccination among pupils (before 169 middle school, grade 6, grade 7, grade 8, grade 9, never

Data on demographic personal and professional characteristics was also collected (age, 171 gender, profession) and practices, i.e. the frequency (always, often, sometimes, never) they 172 discuss with pupils each of nine different public health topics, including vaccination.

b) Qualitative data: focus groups

The focus groups followed an interview guide composed of open-ended questions exploring participants' (i) knowledge about HPV and HPV vaccination; (ii) attitudes, preferences and barriers regarding HPV vaccination; and (iii) views regarding the role of school in promoting HPV vaccination. The interview guide was developed through an informal consensus by the study group, based on its expertise in qualitative research regarding attitudes towards HPV vaccination and results from the literature. We planned to conduct face-to-face focus groups in some selected middle schools but 181 had to propose also one virtual meeting due to the Covid-19 pandemic (expected duration: 1h30). After an oral consent, 184 all the focus groups were recorded and transcribed