Parent, provider and vaccinee preferences for HPV vaccination

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Review

Parent, provider and vaccinee preferences for HPV vaccination: A systematic review of discrete choice experiments

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ABSTRACT

Objectives: To systematically review, appraise and evaluate available evidence regarding discrete-choice experiments (DCEs) for the human papilloma virus (HPV) vaccination in order to support policymakers in making reasonable and effective vaccination program implementation decisions.

Methods: A systematic literature review was conducted using the databases PubMed and Embase for DCEs in HPV up to May 2019. Extracted data was tabulated and two checklists were used for the quality appraisal of the included studies. All attributes were categorized in outcome, process or costs attributes and the relative importance of attributes was calculated using the range method.

Results: Out of 164 identified studies, 12 met the inclusion criteria. Eight were from high income countries (HICs) and four from low and middle-income countries (LMICs). Five studies each examined vaccinee and parent preferences, while only two assessed the providers' preferences. The studies were rather heterogeneous in terms of the populations investigated, the attributes included and the methodologic approach. Overall, outcome measures were the most prominent attributes and effectiveness consistently yielded high relative importance scores. But also process factors, such as the age at vaccination, played an important role for decision making. Discrepancies between HICs and LMICs were most prominent for cost attributes.

Conclusion: The heterogeneous preferences this review elicited highlight the importance of context when making decisions grounded on consumer preferences. Especially the lack of evidence from LMICs, where the burden of cervical cancer is highest, is worrisome. In order to increase uptake, close vaccination gaps and reduce current inequities in (reproductive) healthcare, policy makers need to understand the features that drive individual vaccination decisions and adapt national and clinical guidelines accordingly. Future research therefore needs to focus on LMICs in order to elicit preferences of those most vulnerable populations.

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1. Introduction

Globally, every two minutes, one woman dies of cervical cancer, resulting in more than 311,000 deaths (2018) annually [1]. Without a change in preventive and curative measures, this number is forecast to rise up to an estimated 428,000 in 2035 due to population growth, demographic and behavioral changes [1]. In addition, the large majority of the burden (85%) occurs in less developed regions of the world, where access to (secondary) preventive measures and treatment is limited [2]. To change this current situation WHO's Director General has announced the cervical cancer elimination initiative and a global strategy towards the elimination of cervical cancer has been developed to be adopted by the World Health Assembly in May 2020 [3]. Practically all cases of cervical cancer (99%) are linked to a genital infection with the human papillomavirus (HPV) [2]. To prevent the development of cancer and precancerous lesions, three highly efficacious vaccines are currently marketed throughout the world [2].

According to Gavi, the Vaccine Alliance [5] and WHO [3], the best strategy to tackle cervical cancer is immunization combined with sufficient screening and treatment. While in many high income countries (HIC) several primary and secondary preventive measures to forestall the majority of fatal cancer developments are available, many low and middle-income countries (LMICs) lack the resources for such comprehensive cervical cancer prevention and treatment programs, which is why the provision of vaccinations is especially fundamental in these regions [4]. Although licensed in most countries, not all have included the HPV vaccination into their publicly funded vaccination program [6,7]. Populations with the highest vulnerability (in terms of incidence and mortality) still remain largely unprotected [6]: by 2019 more than three quarters (79%) of HICs have introduced the vaccine, while only 58% of upper middle income countries, 26% of lower middle income countries and 21% of low-income countries were able to do so [8].

There are several access barriers inhibiting the adoption of the vaccination in the national immunization schedule in LMICs. Besides costs [9], especially reachability is a major issue since the vaccination is recommended for girls between the age of nine and 14 and therefore falls out of the infant vaccination schedule [10]. Further issues were reported about the vaccine infrastructure and delivery as well as the reputation and communication about the vaccination [11]. Unfounded and scientifically unproven statements about the safety and efficacy of the vaccine in the media and social networks, as well as rumors about it encouraging sexual promiscuity immensely influenced public opinion and therefore the willingness to get vaccinated [11,12]. Although access issues such as supply, and availability of vaccines are less significant in many HICs, the issues on the demand side are similar. Often, even when the vaccination has been introduced into the national immunization schedule, immunization rates are low because of lacking trust in vaccines in general, conflicting information about the vaccine and a lack of provider recommendation [13].

To tackle these barriers and to ensure a successful and efficient uptake of an HPV vaccination program, besides dealing with supply-side issues, decision-makers need to understand what features drive individual vaccination decisions. On the policy level, analyzing individual and societal preferences can inform decision-makers when making national guidelines and evaluations about what treatments have the potential to ensure maximum compliance and increase public health [14]. Moreover, preference analyses can help make forecasts about demand which can support the planning of public health programs [14].

One way to gather insight into vaccinees' preferences is the use of discrete choice experiments (DCEs). DCEs, a form of conjoint analysis (CA), are gaining more popularity in healthcare nowadays and have proven to be the gold standard for the elicitation and analysis of preferences [15,16]. DCE studies, which originated from marketing and environmental economics, reveal information about to what extent people are willing to trade-off certain attributes of one option against the other, when making decisions about complex, multi-attribute goods, such as healthcare [15]. By constructing hypothetical market scenarios and analyzing data from these settings, DCEs can mimic existing markets or elicit preferences for goods and services that do not exist yet [14]. DCEs can further be used to derive information about the willingness to pay (WTP) for a product which in turn can be used for cost-effectiveness assessments [15].

To conduct the analysis, study participants are usually asked to fill out a survey where they need to choose between hypothetical options in various choice sets [15]. All alternatives are described by a combination of different attributes, each being defined at a specific level. These levels describe the extent to which attributes vary across options [14,15]. Once generated, the data is analyzed in discrete choice models where preferred attributes can then be elicited according to their contribution to overall utility [15]. Because the approach is grounded on random utility theory, a strong theoretical background is given, providing the opportunity to create valid and reliable results [15].

In recent years, several DCEs have been conducted to assess vaccinee, parent or provider preferences for HPV vaccination. To our knowledge no systematic literature review of these studies is currently available. Systematically collecting and summarizing all available evidence about vaccine preferences has great relevance for decision-makers, since this allows for an evidence-based approach to policymaking that takes consumer input into account. This evidence is especially useful considering that many countries are currently planning the uptake of HPV vaccination into their national immunization schedule. Hence, this research paper aims to systematically review, appraise and evaluate available evidence regarding DCEs for HPV vaccination in order to support policymakers in making reasonable and effective vaccination program implementation decisions. More specifically, this study aims to assess the most important characteristics for HPV vaccination for vaccinees, parents and providers.

2. Methods

2.1. Eligibility criteria and search strategy

A systematic literature review was conducted following the guidelines published by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [17]. In order to generate an efficient but still comprehensive search strategy, search terms were chosen based on previously published reviews of DCEs [18,19]. Electronic searches of PubMed and Embase were conducted on the 9th of May 2019 using a combination of synonyms and related terms of the three categories: DCEs, cervical cancer and vaccination (see Appendix A).

Titles and abstracts screening, followed by full text assessment were done by two researchers (AL, MT). Any discrepancies between the two researchers were discussed until consensus was found. Similar to previous reviews, CAs or DCEs were included if they were published in English and if either vaccinees, parents or providers were asked about their preferences for HPV vaccination in a DCE or CA (see Appendix B for a description of eligibility criteria according to PICOS).

Studies that were not original research or not published in English were excluded. Since the vaccine entered the market in 2004, the publication timeframe for inclusion was set to the years 2000–May 2019. References of the included articles were then systematically screened, and a forward search of relevant literature was conducted in Web of Science to identify additional publications. Forward searching detects those studies that cited the selected publications which may also be applicable for the underlying review. To complement the systematic search, a search of grey literature, using platforms such as Google and ResearchGate was conducted, given the expected limited number of results. Eligibility criteria for this search remained the same.

For this study, a research protocol was written as thesis research proposal and approved by the research team. The protocol was not published.

2.2. Data extraction and analysis

To extract data and compare the results, the findings of each study were tabulated. This included general study characteristics such as information about the setting and sample sizes but also more in-depth information about the experimental design of the DCE, namely the attribute and level identification and selection methods, number and significance of attributes and information about the choice sets (see Appendix C).

All attributes were divided into one of three categories: costs, outcome or process. The latter refers to all activities related to the delivery and administration of care and treatments. Outcomes can range from protection against cervical cancer to side-effects or other forms of discomfort. If appropriate, further subcategories within the process and outcome categories were formed in order to group similar attributes (e.g. effectiveness) and allow for a more comprehensive synthesis of results. When the allocation of a certain attribute into a given category was unclear, a second researcher (MT) was consulted.

Within and across the categories, frequency and significance of the attributes were assessed to identify the most important characteristics. If studies provided the relative importance of attributes, these were used for assessment after checking the methodology and calculations for correctness. If the relative importance was unavailable, it was estimated using the range method as proposed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conjoint Analysis Good Research Practices Task Force [20]. Within this method, first, the range of attribute specific

levels is calculated by subtracting the lowest from the highest coefficient for the levels of each attribute. We then calculated the relative importance by dividing the attribute specific level range by the sum of all level ranges. The relative importance was calculated for each attribute and put into comparison per participant category (vaccinee, parent, provider).

To conduct a comparison between HICs and LMICs, the classification as published by the World Bank was used [21].

2.3. Quality appraisal

Two checklists were used to critically appraise the quality and risk of bias of the identified studies. A first assessment was done using the Purpose, Respondents, Explanation, Findings and Significance (PREFS) checklist [22]. Focusing on these five key elements, allows for a simple base evaluation of the publications. To enable a more comprehensive analysis, the checklist published by the ISPOR Good Research Practices for Conjoint Analysis Task Force was used in a second step to extend the quality appraisal. This checklist consists of 10 main elements relating to the research question: attributes and levels, construction of tasks, experimental design, preference elicitation, instrument design, data-collection plan, statistical analyses, results and conclusions, and study presentation [23]. The quality appraisal was done by two researchers (AL, MT).

3. Results

3.1. Study characteristics

The search strategy yielded 163 findings: 70 through PubMed and 93 through Embase. One additional article was found through other sources (see Fig. 1).

57 duplicates were removed and after the screening of titles, abstracts and of the full texts, 12 articles fulfilled our inclusion criteria and were thus included for analysis. The study conducted by Assefa was not published in a peer-reviewed journal, but on the website of the School of Public Health of Addis Ababa and was identified through the previously described search of grey literature. After careful examination of the methodologic quality of the study by two researchers (AL, MH), the decision was made to include it into the analysis, given the potentially valuable input from an LMIC setting. Neither the forward search nor the screening of references, provided any further results.

Study characteristics are provided in Table 1. Most studies ($n = 8$) were conducted in HICs, namely the USA ($n = 3$) [24–26], Hong Kong ($n = 1$) [27], the Netherlands ($n = 3$) [28–30] and Canada ($n = 1$) [31]. The remaining studies from LMICs were conducted in Vietnam ($n = 2$) [32,33], Thailand ($n = 1$) [34] and Ethiopia ($n = 1$) [35]. Almost all studies were published between the years 2010 and 2018, apart from the study of Raley et al. which was published in 2004 [26]. Interestingly, most studies were conducted before the vaccine's introduction into its respective (entire) country [36]. Exceptions are the studies conducted by Oteng et al. [31], Hofman et al. [28,29] and de Bekker-Grob et al. [30], the latter being published in the year of introduction.

Parental preferences were examined in five studies [25,27,29,32,34] as were vaccinee's [24,28,30,31,35], while two studies assessed the preferences of healthcare providers (e.g. nurses, physicians, etc.) [26,33] including fellows of the American College of Obstetricians and Gynecologists (ACOG) [26] and self-identified healthcare providers in a broader sense [33].

Three out of five studies regarding parental preferences focused on the mother as the primary decision maker for vaccination decisions [25,27,32], while two included both parents [29,34]. DCEs

Table 1
Study characteristics.

	Country	Vaccine introduction	Target group	Attribute & level identification/ selection	Vaccine profiles	Attributes	Levels	Quality appraisal				
								P	R	E	F	S
Asiedu et al. [33]	Vietnam (LMIC)	n/a	Providers	Unclear	12	3	2–3	X		X		X
Assefa [35]	Ethiopia (LMIC)	2018	Vaccinees (girls)	Literature search, pilot interviews, expert consultation	32 (2 questionnaires)	7	2	X		X	X	X
Ngorsuraches et al. [34]	Thailand (LMIC)	2017	Parents	Literature search	36 (6 questionnaires)	4	3–4	X		X		X
Poulos et al. [32]	Vietnam (LMIC)	n/a	Parents (mothers)	Literature search, expert interviews, pretests	36 (6 questionnaires)	3	3–4	X		X	X	X
Brown et al. [25]	USA (HIC)	2016	Parents (mothers)	Literature search, expert consultations, pretest interviews	32 (4 questionnaires)	4	2–4	X		X	X	X
Brown et al. [24]	USA (HIC)	2016	Vaccinees (girls)	Literature search, expert consultations, pretest interviews	32 (4 questionnaires)	4	2–4	X		X	X	X
De Bekker-Grob et al. [30]	Netherlands (HIC)	2010	Vaccinees (girls)	Literature review, expert interviews, focus groups	54 (6 questionnaires)	5	3	X		X	X	X
Hofman et al. [28]	Netherlands (HIC)	2010	Parents	Literature review, parent focus groups, expert interviews	54 choice sets (6 questionnaires)	4	3	X		X	X	X
Hofman et al. [29]	Netherlands (HIC)	2010	Vaccinees (girls)	Literature review	16	5	2–3	X		X	X	X
Oteng et al. [31]	Canada (HIC)	2009	Vaccinees (society)	Literature review, survey with parents, expert consultations	100 (10 questionnaires)	7	3–4	X		X	X	X
Raley et al. [26]	USA (HIC)	2016	Providers	Unclear	9	4	2–3	X		X	X	
Wong et al. [27]	Hong Kong (HIC)	n/a	Parents (mothers)	Literature review, interviews with local experts, pediatricians and mothers	16	4	4	X		X		X

with vaccinees included mostly girls between 11 and 18 years [24,28,30,35], except for Oteng et al. [31] who incorporated a sample of Canadian residents > 19 years (both male and female). All studies except for three [26,33,35] presented the participants with two vaccine profiles (i.e. a description of a [fictional] vaccine depending on the attributes/levels used in the study) and the option not to vaccinate (opt-out).

The quality appraisal revealed that every publication had some (minor) methodological flaws either in the reporting or the actual experimental design. All publications received either a three or four out of five when evaluated according to the PREFS checklist while quality scores from the ISPOR checklist varied between 19 [33] and 28 [28,34] out of 30. Sample sizes ranged from 181 [26] to 1,157 [31]. None of the included studies

Fig. 1. PRISMA flow-chart.

Fig. 2. Relative Importance of Attributes - Vaccinees.

Fig. 3. Relative Importance of Attributes – Parents.

reported serious conflicts of interest or had concerning affiliations or sponsorships.

3.2. Vaccine attributes

In order to identify and select attributes and levels, most studies combined a literature review with some qualitative assessment such as pretests and interviews with experts, parents or vaccinees [25,27,29,32,33]. While one study relied solely on a literature review [34], the methods for selection and identification remained unclear in two publications [26,33].

In half of the included studies, the DCE contained four attributes with two to four levels each [24–27,29,34]. Two studies each

reported three [32,33], five [28,30] and seven attributes [31,35] respectively, again with two to four levels.

Of the 54 reported attributes, 63% were classified as outcome, 22% as process and 15% as cost attributes. Cost attributes consisted exclusively of out-of-pocket costs and were reported in 8 studies. Outcome and process attributes on the other hand were more diverse depending on the study and setting.

The most frequently included outcome measure was vaccine efficacy against cervical cancer which was included in all, but one studies [33]. The second most included measure was the duration of protection ($n = 8$) [24,25,27–30,32,35] followed by side-effects ($n = 6$) [27–30,34]. It should be noted that vaccine effectiveness was phrased differently in different studies, namely degree of

Fig. 4. Relative importance of Attributes – Providers.

protection (%) [24,25,27–30,35], cervical cancer risk reduction (%) [31,32,34] or efficacy (%) [26]. In order to facilitate a comparison between studies, these terms were summarized as *effectiveness* in the subsequent analysis. If included, side effects were expressed in frequencies [27–31,34,35].

More than half of the included studies ($n = 7$) reported process attributes in their analysis [26,28–30,33,35]. The most common process attribute was the age at vaccination which was included in all of these studies. Other process attributes were less frequent and included the need for cervical smear testing [31], the number of doses [35] and the way of delivery [35].

3.3. Relative importance

All reported attributes were significant for at least one of the defined levels except for the attributes reported by Raley et al. which did not include any information on statistical significance [33]. Figs. 2, 3 and 4 give an overview of the relative importance of the attributes for vaccinees, parents and providers respectively.

3.3.1. Vaccinees

Five studies reported vaccinee preferences, including one from a low income country [35]. A wide range of attributes was used resulting in a very diverse distribution of relative importance. All studies included outcome attributes (especially effectiveness) while the majority (60%) also reported on cost coefficients. With one exception [24], process attributes were included in all studies.

Overall, effectiveness was identified as the attribute with the highest relative importance. Values ranged from 22% [31] to 60% [28], making it the most important attribute in 60% of the studies in this category. Cost was assessed in three studies where two studies revealed an important effect of costs ranging from 25% [31] to 47% [24]. However, in the LMIC setting (Ethiopia), cost had the lowest relative importance of only 0.25% [35].

Side effects were divided into serious and mild side effects and had similar values and ranges. We would like to stress that the term adverse events following immunization (AEFI) would have been a more appropriate expression in this context. However, since all authors used the more popular term side effects, this will be used in this review to avoid confusion. In addition to costs, effectiveness and side effects, duration of protection also accounted for a significant share of relative importance, ranging from 2% [35] to 20% [24].

Cross-protection against genital warts, though reported four times in total [24,25,31,34], was not given a high importance both in the studies conducted with vaccinees as well as parents.

3.3.2. Parents

Parents preferences were assessed in five studies including two publications from a LMIC setting, more specifically Thailand [34] and Vietnam [32]. The attributes and their importance varied substantially across studies and settings. All five studies included effectiveness [25,27,29,32,34], four included duration of protection [25,27,29,32], while only three included costs [25,27,34] and side effects [27,29,34]. Due to insufficient explanations on reported values, the cost attribute in the study of Poulos et al. [32] had to be excluded from the calculations shown.

The most important attributes were effectiveness [27,29,34], side effects [27] and costs [25]. Effectiveness expressed as the protection against cervical cancer or risk reduction was more important than duration of protection [25,27,29,32]. When side effects were considered, it was shown to have a more significant impact on parents' preferences than effectiveness in Wong et al.'s study [27] but were deemed less important than effectiveness in Hofman et al. [29] and Ngorsuraches et al.'s studies [34].

Cost was shown to be not important in Wong et al. [27] and Ngorsuraches et al. [34] while it was the most important attribute in Brown et al. [25]. Process attributes in general were only considered in the form of the age at vaccination and only reported in one study [29]. Even there, it was not reported to have a significant impact on vaccination decision-making.

3.3.3. Providers

Insights from healthcare providers were sparse, as only two studies (17%) included them into the experiment, one from Vietnam [33] and one from the USA [26]. Both studies included patient age and vaccine type (bivalent or quadrivalent) into the DCE and came to somewhat comparable importance scores. Yet, the most significant importance scores differed. While Asiedu et al.'s [33] study participants put most emphasis on the costs of the vaccination, in Raley et al.'s [26] study the approval by the ACOG was the most valued attribute. Interestingly, Asiedu et al. [33] were the only authors in this analysis that did not include effectiveness in their DCE.

4. Discussion

This study identified 12 DCEs that revealed preferences for HPV vaccination from both HICs and LMICs. The studies were rather heterogeneous in terms of the populations investigated, the attributes included and the overall methodologic approach. This led to very divergent results both within and across target populations, making a comparison difficult and stressing the importance of context when making decisions grounded on preferences or consumer input in general. Overall, outcome attributes such as effectiveness measures specifically were examined most often and were considered the most prominent vaccine attribute in terms of inclusion in the experiment as well as relative importance for both vaccinees and parents. In addition, perceptions about potential or supposed “side-effects”, costs and the duration of protection were shown to be important. Studies examining vaccinee preferences included more different attributes ($n = 12$) than those exploring parents’ ($n = 6$) and providers’ ($n = 5$). This also applied to the proportion of process attributes included. While both provider and parent studies mostly included outcome measures, in vaccinee studies half of the attributes were classified as process attributes. Specifically, the number of doses [35], the way of delivery [35] and the target group to vaccinate (only boys, only girls, both) [31] were shown to be important, but each only in one study. Some discrepancies between preferences were observed, by example for costs which had high relative importance values in some studies [24,25], but yielded results lower than 1% in others [27,34,35]. The large ranges within attributes can have multiple reasons. Firstly, the combination and number of attributes influences the reported importance as these are only relative values and are consequently dependent on the choice set. Therefore, a comparison of studies with different attributes needs to be undertaken with caution. Similarly, the definition of the levels, i.e. the extent to which attributes vary across options, can be a source of bias. Because values were calculated using the range method, large ranges likely imply a high relative importance, especially for linear attributes such as costs. Defining levels by using high or even unrealistic values can unintentionally impact the relative importance score. For instance, in the study published by Brown et al. [24] the cost attribute had a level range of US\$ 700, which may have overestimated the importance of this attribute, especially compared to the other studies in this category with ranges as low as US\$ 5 [35]. It is further important to mention that it can be assumed that vaccinees (adolescent girls) don’t actually have to pay for their vaccination themselves, as they are dependent on their parents or guardians. This needs to be kept in mind when interpreting the weight of this attribute and comparing it to other target groups.

Seven out of the 12 (58%) publications additionally calculated the willingness to pay (WTP) [24,25,27,31,32,34,35]. While these values are likely overestimated and do not constitute the real willingness or ability to pay in terms of the market price due to hypothetical bias [34,37], they provide the opportunity to manifest and test the DCE results and put them into a financial context. If one interprets the WTP as a cost-benefit analysis, it can be concluded that, if the WTP is higher than the current market price, parents/vaccinees realize net benefits when getting the vaccine, or in other words, they value the benefits of the vaccine more than its costs. This holds true for three of the studies that reported on vaccine profiles that are comparable to currently marketed vaccines [24,25,34], while one study suggested the opposite [27]. This conclusion is consistent with other cost-effectiveness analyses indicating that vaccines are cost-effective under certain market prices [38,39]. Differences between WTP and cost-effectiveness are likely attributable to the degree of cervical cancer awareness or fear thereof, socioeconomic factors and the current market price in the respective country.

The quality appraisal of the studies revealed several methodologic issues. First, the generalizability of the studies may partly be limited, especially in terms of the study sample’s socioeconomic and educational status (see Appendix C). This limitation has also been acknowledged by several authors. Because successful policy-decisions are dependent on reliable and representative evidence, future DCE studies should evaluate preferences in population samples that represent the greater population rather than a convenient target group. Second, in light of the large heterogeneity of the results, the importance of the selection of attributes and levels needs to be stressed. It is crucial that this is based on valid and current evidence which can be elicited through literature search or qualitative measures. While most studies used such (mixed) methods, it should be noted that several authors [27,32,34] referred to one study in particular [25] to select attributes for their own study. This may have resulted in important, to this date unidentified effects not being considered. Though not all studies followed extensive procedures to select attributes, all studies (except for Asiedu et al. [33] who did not disclose p -values) reported statistically significant results for all attributes on at least one level, meaning that they do have an effect on the vaccination decision and the participant’s utility. Nevertheless, the results from vaccinee studies suggest that process attributes, which were omitted in many publications, influence preferences and need to be assessed more in depth. It is therefore recommended that future researchers incorporate more consumer input in the identification and selection process, thereby attaining higher levels of validity and minimizing the distortion of results by unobserved confounders.

Across populations, evidence was sparse especially from LMICs. This is highly problematic especially because a large majority of the global burden of cervical cancer occurs in these regions. Only four DCEs from a LMIC setting could be identified which may not be sufficient to make well-informed, evidence-based decisions about policy, allocation or communication measures. Additionally, this made comparing preferences in HICs and LMICs difficult and only possible to a very limited extent. Yet, while costs played an important role in HICs, the three LMIC studies conducted with parents and vaccinees [32,34,35] had significantly lower relative importance values for the cost attribute. Although we acknowledge that the LMIC studies all had some limitations in generalizability (e.g. income levels, education) and therefore may not reflect the entire population’s preferences, these results are surprising and point towards the large differences in the preference distribution across settings. One potential reason for this distribution could be that LMICs, especially if they have qualified as GAVI eligible countries, may not pay the full rate for the vaccination but are able to purchase them for a highly reduced price. Thus, the application of the results from HICs in an LMIC setting is limited. In order to holistically address vaccine hesitancy amongst the most vulnerable populations and possibly contribute to a more equitable global distribution of cervical cancer care, future research therefore needs to focus more on LMICs.

Tailoring care to vaccinees or consumers more generally is not a new approach and the importance of incorporating patient input in health technology assessments and to aid in treatment adherence has been recognized by many healthcare players [40]. As this report has shown, for HPV vaccination consumer input data is still insufficient. Although other types of preference studies than solely DCEs exist, a scoping literature search of other qualitative and quantitative methods conducted in an earlier stage of this review, revealed only few additional relevant findings. While publications from low income countries, to an extent, assessed preferences for HPV vaccination, many focused on delivery strategies, such as the preferred place for vaccination rather than attributes of the vaccine itself [41,42]. These knowledge gaps also apply to

healthcare providers. Physicians, nurses and other healthcare professionals play a crucial role in vaccine delivery, demand and the general attitude towards medical and preventive care. It is therefore essential to take their preferences into account. Studies have shown that a recommendation to receive the vaccination by a physician or another healthcare worker, is one of the most important factors influencing the uptake decision [43–45]. The fact that this review only identified two studies that examined provider preferences [26,33], emphasizes the need for more research in this field.

The findings of this report could have important clinical and policy implications. As effectiveness was the most important attribute in half of the included studies, communication of the vaccine must stress the high efficacy of the currently marketed and future vaccines. This can be done both on a clinical level as well as on the broader policy scale when formulating vaccination recommendation guidelines. Moreover, process factors play an important role for vaccinee and parent decision making [35]. This needs to be recognized by all stakeholders involved, i.e. clinicians and policymakers but also manufacturers and research institutions who can tailor the development of new technologies to align with vaccinee needs. In this sense, the findings are also highly valuable for WHO's novel Country-led Assessment for Prioritisation on Immunisation (CAPACTI) approach, which aims to accelerate the development of next generation vaccine products that are adapted to specific immunization settings specifically in LMICs [46]. Providing clarity on preferred product characteristics (PPCs) is central to the success of this strategy and the realization of sustainable immunization programs in LMICs [46,47]. Synthesized evidence with regards to product preferences such as the current paper can hereby form an important foundation on which policy makers can base implementation and selection decisions upon. Recognizing DCEs especially may be valuable given that they allow for the elicitation of preferences for pipeline products which do not exist on the market yet.

Although this study applied measures to ensure high reporting quality as proposed by PRISMA [17], some potential limitations remain. First, we only focused on DCEs and not on other types of preference studies. Even though a scoping review of other preference studies did not reveal additional findings, a more qualitative approach to preference elicitation could be worth investigating. Second, the small number of included studies particularly from LMICs is a source of concern and in line with that another potential limitation is the fact that only English publications were included in the review. Yet neither the systematic search nor the search of grey literature identified relevant publications in other languages. Only incorporating 12 studies in total and thereof only four in LMICs may distort results especially considering that vaccine preferences are highly context and culture specific. The large heterogeneity amongst the included studies complicated the synthesis and comparison of relative importance even further. Lastly, while DCEs have proven to be a valid method to elicit preferences, the experiment does not constitute real market decisions but rather hypothetical scenario decisions which bear the risk for hypothetical bias [48]. This shortcoming is valid for all stated-preference studies and must thus also be acknowledged in this paper. However, by carefully examining the DCE methodology these quality constraints were, to an extent, accounted for. Yet, no study received a perfect score in the PREFS or ISPOR checklist suggesting at least some methodological or reporting flaws. Whilst this is a limitation of the respective study, it also confines the validity of the presented results.

5. Conclusion

The current study revealed that vaccinees, parents and providers have strongest preferences for outcome attributes of the HPV vaccination. However only few DCEs have been conducted

to date and with large levels of heterogeneity. While these studies show that effectiveness is very important, cost and process attributes cannot be overlooked when analyzing the effects of vaccine attributes on the respondent's decision-making and utility. Differences between LMICs and HICs were especially prominent when comparing cost attributes. Yet the lack of evidence available for vaccinee preferences and, as a consequence, the limitations of offering care that is tailored to vaccinee needs, is indisputable. This must be addressed especially in light of WHO Director General's recent call to eliminate cervical cancer and to reach global female vaccination coverage of 90% by 2030 [3]. To reach this goal, effective and evidence-based (policy) decisions which support the realization of high vaccine uptake and schedule compliance need to be made. Though supply challenges do play an important role in this context, demand in terms of vaccine acceptance and hesitancy also greatly impact immunization rates and hence deserve further attention and integration into the elimination strategy. Although some attributes consistently played a major role in decision-making, most characteristics are context specific and are thus difficult to synthesize. By continuing to incorporate consumer preferences into research activities, a clearer conclusion can be drawn about which characteristics really matter for both the recipients of the vaccinations as well as the providers in different settings. Targeting especially LMICs where the burden of cervical cancer is highest, is thereby an essential step towards the reduction of current inequities in (reproductive) healthcare across the globe and reaching universal health coverage for all.

6. Contributions

Alina Lack, Mickael Hiligsmann and Raymond Hutubessy were involved in the conception of the work. Alina Lack conducted the data collection, data analysis and interpretation and drafted the article. Maike Tünneßen supported the literature search and data collection. Mickael Hiligsmann, Paul Bloem and Raymond Hutubessy critically reviewed the article. All authors gave the final approval of the version to be published.

All authors attest they meet the ICMJE criteria for authorship.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Search term

("DCE" OR "discrete choice experiment" OR "conjoint analysis" OR "preference" OR "patient preference" OR "stated-preference") AND ("HPV" OR "human papillomavirus" OR "cervical cancer" OR "cancer uteri") AND ("Vaccination" OR "Immunization" OR "Vaccine"

Full electronic search strategy on Pubmed:

"DCE"[All Fields] OR "discrete choice experiment"[All Fields] OR "conjoint analysis"[All Fields] OR "preference"[All Fields] OR "patient preference"[All Fields] OR "stated-preference"[All Fields]) AND ("HPV"[All Fields] OR "human papillomavirus"[All Fields] OR "cervical cancer"[All Fields] OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("uterus"[MeSH Terms] OR "uterus"[All Fields] OR "uteri"[All Fields])) AND ("Vaccination"[All Fields] OR "Immunization"[All Fields] OR "Vaccine"[All Fields]) AND (("2000/01/01"[PDAT] : "2019/09/05"[PDAT]) AND English[lang])

Appendix B. Eligibility criteria (PICOS)

Eligibility criteria, according to PICOS are as follows:
Participants = Vaccinees, parents, providers

Intervention/comparison = HPV vaccination
Outcome = Preferences for vaccination attributes
Study design = CAs or DCEs

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
General Characteristics												
Country	Hong Kong	Netherlands	USA	Vietnam	Thailand	Vietnam	USA	Canada	Netherlands	Netherlands	Ethiopia	USA
Study's objective	to investigate the mothers' choices and decision making when contemplating the attributes of the HPV vaccination to determine local mothers' preferences and their WTP toward the HPV vaccination	to generate knowledge to improve information and organization strategies; to assess which vaccine characteristics were important for parents and girls when deciding about uptake and which trade-offs they're willing to make between these characteristics	to estimate how features of HPV vaccines affect mothers' perceived benefit and stated vaccine uptake for daughters	to assess the WTP for vaccines using a CA study and to estimate the tradeoffs mothers are willing to make between different attributes	to examine parents' preferences toward the attributes of HPV vaccines and to calculate their WTP	to compare Vietnamese health care providers' preferences and the tradeoffs that they are willing to make to recommend HPV vaccination with regard to patient age, type of HPV vaccine and cost	to examine the acceptability to gynecologists of HPV vaccination for their patients as function of physician preferences for key vaccine-related characteristics	to evaluate societal preferences for the different vaccination and screening strategies, to identify the properties of the vaccine that are important and to determine the willingness to pay for these attributes	to investigate the preferences of girls aged 12-16 years for HPV vaccination through a DCE	to assess which attributes of HPV vaccination have influenced preferences for HPV vaccination uptake after the media debates have ended and in the absence of reports of serious side-effects	to assess preferences of 15 -18 year old school-girls about HPV vaccine, to rank the contribution of the attributes for HPV vaccination and to measure WTP, trade-offs and choices of girls between risks and benefits of the vaccination in Addis Ababa	to measure adolescent girls' preferences over features of HPV vaccines in order to provide quantitative estimates of the perceived benefits of vaccination and potential vaccine uptake

Appendix C. Tabulated overview of the included studies and extracted data

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
Affiliation	Department of Family Medicine and Primary Care, Department of Paediatrics and Adolescent Medicine and School of Public Health, The University of Hong Kong; Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital	Department of Public Health Erasmus MC, University Medical Centre, Rotterdam	Centers for Disease Control and Prevention, Immunization Services Division, National Center for Immunization and Respiratory Diseases, Atlanta; RTI international	RTI; PATH; Hanoi medical University	Department of Pharmacy Administration, Faculty of Pharmaceutical Sciences, Prince of Songkla University; Department of Pharmacy Practice, College of Pharmacy South Dakota State University, Brookings	Department of Health Sciences Research, Division of Health Care Policy and Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester; Department of Radiology, Jackson Memorial Hospital/University of Miami; Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology, University of Oklahoma; Department of Gynecologic	Department of Obstetrics and Gynecology, Department of Epidemiology and Holden Comprehensive Cancer Center, University of Iowa; Department of Pediatrics, Indiana University School of Medicine, Indianapolis	University of British Columbia; British Columbia Center for Disease Control, Vancouver; Centre for Health Evaluation and Outcome Sciences, St. Paul's Hospital, Vancouver	Dept. of Public Health, Erasmus MC – University Medical Centre Rotterdam; Dept. of Business Economics, University, Rotterdam; Dept. of Obstetrics and Gynaecology, Erasmus MC – University Medical Centre Rotterdam; Dutch Association of Obstetrics and Gynaecology, Utrecht	Department of Public Health, Erasmus MC – University Medical Centre Rotterdam; Rijnmond, Rotterdam	School for Public Health, College of Health Sciences, Addis Ababa University, Ethiopia	CDC; RTI; Washington University St. Louis

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
						Oncology & Gynecologic Surgery, Mayo Clinic, Jacksonville						
Funding	The health and medical research fund, food and health bureau Hong Kong	Dutch Cancer Society	None declared	PATH and Bill & Melinda Gates foundation	No funding for the study	The Vietnamese American Medical Association and Tung Van Dinh, MD Memorial Travel Scholarship	None declared	None declared	Grant support by the Dutch Cancer Society	The Dutch Cancer Society	None declared	None declared
Target Population	Mothers of daughters between 8 and 17 years who have not received any HPV vaccination	Parents with daughters between 10 and 12 years	Mothers with at least one daughter between 13 and 17 who have not received the HPV vaccine	Mothers with daughters between 9 and 17 years	Parents with at least one daughter between 9 and 13 years	Healthcare providers	Fellows of the American College of Obstetricians and Gynecologists (ACOG)	"Society" (> 19 years currently residing in Canada and speaking English)	Girls between 12 and 16 years	Girls between 11 and 15 years	School girls between 15 and 18	Girls between 13 and 17 years
Generalizability	Limitations	Limitations (high education lvl)	Limitations	Limitations (high education lvl)	Limitations (income and education)	Limited (mostly females)	Ok	Limitations	Limitations (high education)	Ok (but more higher educated)	Ok	Limitations

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
DCE Characteristics												
Attribute and Level Identification	Literature review, interviews with relevant local experts	Literature review, parent focus groups, expert interviews	Literature search, expert consultations, pretest interviews	Literature search, expert interviews, pretests	Literature search	Unclear	Unclear	Literature review, survey with parents, experts consultations	Literature review, expert interviews, focus groups	Literature review (based on previously conducted study)	Literature search, pilot interviews, expert consultations	Literature search, expert consultations expert, pretest interviews
Attribute and Level Selection	Interviews with pediatricians and mothers	Literature review, parent focus groups, expert interviews	Literature search, expert consultations, pretest interviews	Literature search, expert interviews, pretests	Literature search	Unclear	Unclear	Literature review, survey with parents, experts consultations	Literature review, expert interviews, focus groups	Literature review (based on previously conducted study)	Literature search, pilot interviews, expert consultation	Literature search, expert consultations expert, pretest interviews
DCE Design	Orthogonal design	Efficient design maximizing d-efficiency	Statistically efficient fractional-factorial design	Fractional design	Orthogonal and level balanced	Full factorial design	Fractional factorial	Fractional factorial design, orthogonality, minimal overlap, level balance	Fractional factorial design, orthogonality, level balance	Efficient design (maximizing d-efficiency)	Fractional factorial design	Fractional design
No. vaccine profiles	16	54 choice sets (divided into 6 questionnaires ; block design)	32 (divided into 4 questionnaires)	36 (divided into 6 questionnaires)	36 (divided into 6 questionnaires)	12	9	100 (divided into 10 questionnaires)	54 (divided into 6 questionnaires)	16	32 (divided into 4 questionnaires)	32 (divided into 4 questionnaires)
Choice sets per respondent	8 + validity test	9 + validity test	8 + 2 validity tests	6 + validity test	6+1 validity test	12	9	10 + 2 validity tests	9 + validity test	16 + validity test	16	8+2 validity tests
options per choice set	2 + opt out	2 + opt out	2 + opt out	2 + opt out	2 + opt out	10 point likert scale	0-100 (scale)	2 + opt out	2 + opt out	2 + opt out	2	2 + opt out

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
Data collection												
Sample Size	428	294	307	258	314	244	181	1157	312	500	330	307
Mode of Survey	online questionnaire (with assistance)	Written questionnaires	online survey	face-to-face survey	written questionnaire	written questionnaires	written questionnaire	online questionnaire	written questionnaire	written questionnaire	written questionnaire	online questionnaire
Ethical Considerations	written consent	approval by medical ethics committee Erasmus MC	informed consent	verbal informed consent by each respondent + ethical approval by RTI's Institutional Review Board and PATH's Research Ethics Committee	approved by ethics committee of faculty of Pharmaceutical Sciences Prince of Songkla University	approved by a US institutional Review Board and the Director of Da Nang General Hospital; oral consent	approval by institutional review board of the University of Iowa	approved by the behavioral Research Ethics Board of the University of British Columbia	approval obtained by medical ethics committee erasmus MC university medical center Rotterdam	n/a	informed consent, approval by Addis Adaba University School of Public Health ethical clearance committee	no
Attributes and Relative Importance												
Number of Attributes	4	4	4	3	4	3	4	7	5	5	7	4
Levels	4 per attribute	3 per attribute	2-4 per attribute	3-4 per attribute	3-4 per attribute	2-3 per attribute	2-3 per attribute	3-4 per attribute	3 per attribute	2-3 per attribute	2 per attribute	2-4 per attribute
Relative Importance reported	no	no	no	no	no	yes	yes	no	no	no	no	no

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
Most important attribute (* = significant)	side effects*	Degree of protection*	Protection against cervical cancer*	effectiveness	effectiveness	cost of vaccination*	ACOG approval (32.2)	Target group*	Protection against cervical cancer*	Degree of protection*	degree of protection*	protection*
all attributes (* = significant)	protection against cervical cancer*, protection duration*, side effects*, out-of-pocket costs*	Degree of protection against cervical cancer*, duration of protection*, risk of serious side effects*, age at vaccination*	Protection against cervical cancer*, protection against genital warts*, duration of protection*, Out-of-pocket costs*	effectiveness*, duration of protection*, costs*	cervical risk reduction*, genital warts risk reduction*, common side-effects*, costs*	Patient Age*, vaccine Type (HPV2 vs. HPV4)*, Cost*	ACOG approval, efficacy, age of participant, targeted disease (cancer, warts, both)	Need for vaccine booster*, frequency of cervical smear testing*, target group to vaccinate*, frequency of side effects*, Cost*, Lifetime risk of cervical cancer*, Lifetime risk of genital warts*	Degree of protection against cervical cancer*, protect duration*, serious side-effects* (e.g. hospitalization), mild side effects* (e.g. nausea), age of vaccination*	Degree of protection against cervical cancer*, duration of protection*, risk of mild side effects*, age at vaccination*, number of doses*	degree of protection*, duration of protection*, age at vaccination*, number of doses*, serious side effects*, price, way of delivery*	degree of protection*, duration of protection*, genital warts protection*, Cost*
Attribute Categories												
Total	4	4	4	3	4	3	4	7	5	5	7	4
Outcome	3	3	3	2	3	1	3	3	4	3	3	3
Process		1				1	1	3	1	2	3	
Cost	1		1	1	1	1		1			1	1
Willingness to pay												

Study	Wong et al. (2018)	Hofman et al. (2014)	Brown et al. (2010)	Poulos et al. (2011)	Ngorsurach et al. (2015)	Asiedu et al. (2015)	Raley et al. (2004)	Oteng et al. (2011)	De Bekker-Grob et al. (2010)	Hofman et al. (2014)	Assefa (2017)	Brown et al. (2014)
Quadrivalent (gardasil-like) -> 70% cancer protection, 90% genital warts protection, 10 year duration	1619.89 HK\$ = USD 208	not reported	663 USD		21,189.9 Baht = 586.14 USD	not reported	not reported		not reported	not reported		456 USD (girls), 664 USD (mothers)
Bivalent (Cervarix-like) -> 80% cervical cancer protection, 0% genital wart protection, 10 year duration			560 USD		10,479.9 Baht = 289.9 USD							402 USD (girls), 560 USD (mothers)
ideal technology	100% protection, lifetime duration, 0% side effects -> 8975.72 HK\$ = USD 1129		100% cancer protection, 90% warts protection, lifetime duration -> 1086 USD	lifetime protection, 99% effectiveness -> 356 USD				not reported in a comparable way (WTP per attribute)			not reported in a comparable way, (WTP per attribute)	100% cancer protection, 90% warts protection, lifetime duration -> 805 USD (girls), 1,088 USD (mothers)

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