

Introduction of HPV vaccination in Kenya

Doctoral thesis submitted to the Faculty of
Medicine and Health Sciences
Ghent University

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CHMP	Committee for Medicinal Products for Human Use
DNA	Deoxyribonucleic Acid
DTP3	Diphtheria-Tetanus-Pertussis (toxoids/vaccine - 3 doses)
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
FGD	Focus Group Discussion
GAVI	Global Alliance for Vaccines and Immunization
HBM	Health belief Model
HIC	High-income Countries
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
KES	Kenyan shilling
LMIC	Low- and Middle Income Countries
SAGE	WHO Strategic Advisory Group of Experts
STI	Sexually Transmitted Infections
TPB	Theory of Planned Behaviour
UK	United Kingdom
USA	United States of America
USD	United States Dollar
VIA	Visual Inspection with Acetic acid
VILI	Visual Inspection with Lugols Iodine
WHO	World Health Organization

Part I

EXECUTIVE SUMMARY

Introduction Cervical cancer poses a serious health threat to sexually active women, especially in low and middle income countries (LMIC) where screening opportunities are often low and treatment remains inaccessible for most of the affected women. Primary prevention through human papillomavirus (HPV) vaccination may therefore provide a turning point in the battle against cervical cancer. However, prior to implementing large-scale vaccination programmes, several knowledge gaps need to be addressed. Therefore, formative research has been conducted measuring (hypothetical) acceptability and identifying potential barriers to successful implementation. In general, the vaccine is well accepted, with main reported barriers costs and fear of side effects.

The introduction of the HPV vaccine gave indeed rise to many studies gauging the public's perspectives, often applying health behaviour theories such as the Health Belief Model (HBM) to identify determinants of acceptability (i.e. susceptibility and severity of cervical cancer, barriers and benefits of the vaccine, self-efficacy, and cues to action). However, most of these studies took place in industrialized regions and did not measure HPV vaccine uptake. As such, several questions arise: 1) Is the HPV vaccine acceptable in low-income countries, where they can have most impact, and are the determinants similar? - 2) Does high acceptability always lead to high HPV vaccine uptake, i.e. the true outcome of interest? In order to answer them, a study with three objectives was set up.

Objectives

- Objective 1: To determine the acceptability and subsequent uptake of the HPV vaccine in the context of an HPV pilot vaccination programme in Eldoret, Kenya.
- Objective 2: To ascertain whether health behaviour theories can be effectively applied to predict HPV vaccination in Eldoret, Kenya.
- Objective 3: To identify factors that influence successful introduction of an HPV vaccination programme in Eldoret, Kenya.

Study design A longitudinal study was rolled-out, with baseline and follow-up taking place before and after the implementation of an HPV vaccination effort. The programme freely offered the HPV vaccine to girl pupils of primary schools in Eldoret: the vaccine was administered in the referral hospital but promotion was done at school by teachers. A cohort of randomly selected mothers of these eligible girls was set up and invited to participate twice in a quantitative interview regarding cervical cancer prevention. HPV vaccine acceptability was measured at baseline while uptake got reported at follow-up. This design allowed studying acceptability and uptake, including the relation between these two main outcomes. In addition, a qualitative component was implemented at follow-up, evaluating the programme from the perspective of key-informants.

Results The HPV vaccination programme took place from May 2012 until March 2013. Baseline and follow-up data were collected two months before and after the programme, in March 2012 and May 2013, respectively. Of the 287 women interviewed in 2012, 89.2 percent (256/287) agreed to be interviewed again the next year. Also focus group discussions were organized in May 2013, with fathers (3), teachers (4) and vaccinators (1).

While acceptability of the HPV vaccine among the mothers was very high at baseline (88 percent accepted), only 31 percent had eventually vaccinated their daughter, and 51 percent reported that they had wanted to vaccinate but had missed the opportunity. Results showed that among this latter group, 55 percent had not received information regarding the whereabouts of the programme. Finally, among those who had actively decided not to vaccinate (18 percent), 42 percent mentioned fear of side effects as barrier and 31 percent said the partner opposed to vaccinating the daughter against cervical cancer. In general, the majority of the participants reported that unknown side effects made them doubt about HPV vaccination and that they needed more information in order to make an informed decision.

No strong relation was found between HPV vaccine acceptability and vaccination. Also with regard to the applicability of the Health Belief Model (HBM), no associations were found between the constructs and uptake, except for self-efficacy which positively influenced vaccination. The predictive value of the model did increase after adding a variable reporting whether or not the mother had received adequate information; being well-informed led to higher vaccine uptake.

The qualitative data revealed that teachers and fathers had poor knowledge regarding cervical cancer and felt rather uncomfortable sharing information about it. This had also led to poor communication regarding the vaccination programme. Teachers also missed support of health care providers to address the questions of the parents as well as their own doubts. In general, HPV vaccination was not considered important given that cervical cancer was perceived as a consequence of a modern lifestyle with which the participants did not feel related. Finally, distrust towards (new) vaccines also hampered uptake: some thought it was an experiment while others had lost faith in vaccines during previous vaccination experiences. Suspicion did however fade away after a couple of months, once the community was convinced about the safety of the vaccine.

Discussion HPV vaccine acceptability was not a strong predictor of vaccine uptake. The translation of intention into behaviour was mainly hampered because information about the vaccination programme did not reach all parents. Limited knowledge regarding HPV and cancer and cultural taboo made it difficult for teachers and parents to discuss HPV vaccination. Therefore, direct communication of health care providers with caregivers seems crucial as the former is better positioned to discuss such topics. Moreover, failure of achieving such a contact moment did not only lead to poor uptake but also allowed the spread of rumours and doubts. Future programmes will need to have more attention for two-way communication, to address misbeliefs, as opposed to the top-down approach usually used.

So while HPV vaccine uptake was lower than expected, mainly due to organizational reasons, HPV vaccine acceptability reported at baseline might have been overestimated because of several factors. First of all, given that awareness regarding cervical cancer and HPV vaccination is generally low in Kenya, some participants were probably overtaken by the new information which interfered with their estimation of intention, tending to overvalue (also partly due to social desirability). In addition, people may overestimate their intentions - especially for new behaviours barriers are hard to predict - or express a desire rather than a true plan of action. Finally, given the novelty of HPV vaccination, it is not always clear who will take the final decision and as reported by the women in the quantitative study, in the end many fathers had an important role in the decision-making. As a result, women were not in control of the behaviour meaning that their intentions were no longer relevant as predictor for the vaccination status of the daughter.

Taken all together, the poor vaccine uptake, due to promotional flaws, combined with the high reported acceptability led to an imbalance in the relation acceptability-uptake which was mainly driven by low acceptability leading to non-uptake, rather than by acceptors fulfilling their own reported objectives.

Similar to acceptability, also the HBM constructs were poor determinants of uptake. Given that these measurements only assess personal beliefs and attitudes, and given the above-mentioned importance of programmatic strategies, adding variables beyond the personal perspective, at the organizational level, might improve the predictive value of the theory. In addition, also the value of each of the constructs can be questioned. Regarding the absence of a correlation of uptake with severity and susceptibility, this is not so surprising given the Kenyan context: access to high quality care is limited and diseases often remain untreated which makes them more life-threatening. Especially (cervical) cancer is considered deadly. As such, perceiving cervical cancer as a threat is common and, consequently, does not distinguish those who vaccinate against HPV and those who don't. With regard to foreseen benefits and barriers, one can wonder how reliable people's estimates can be regarding the advantages and disadvantages of a new, unknown vaccine. By meas-

uring users' and non-users' perspectives, more realistic determinants might be identified. Also trust in the vaccine or in the health system might be a stronger predictor, given that people rely on past, medical experiences. Also self-efficacy, which was positively associated with vaccine uptake, can be considered as trust, in oneself, to perform the desired behaviour.

By focussing promotion on increasing trust, but also by choosing a delivery platform that instils confidence and convenience, vaccine uptake could thus potentially increase. A carefully designed programme should indeed take into account vaccine confidence, complacency and convenience and address them by both tailored promotion and adequate vaccine delivery. In the context of the HPV vaccination programme in Eldoret however, none of the three C's seemed to be properly fulfilled: some people distrusted the vaccine and the health providers in the referral hospital, cervical cancer was not always seen as a threat (whereas the vaccine had potential side effects) and offering the vaccine in a health centre was not considered the most convenient approach. School-based vaccination seemed more preferred but good cooperation between health staff and the teachers corpse will be crucial to obtain good coverage.

Conclusion Measuring HPV vaccine acceptability and its determinants is not sufficient to predict uptake. More attention should go to other important factors such as vaccine confidence or more broadly, vaccine hesitancy. In addition, variables beyond personal control contribute significantly to vaccine uptake pointing out the need to complement formative research - mostly conducted prior to implementation and based on personal health behaviour theories – with monitoring vaccination programmes and assessing users' and non-users' perspectives.

Deel II

SAMENVATTING

Inleiding Baarmoederhalskanker vormt een ernstig gezondheidsrisico voor seksueel actieve vrouwen, in het bijzonder in ontwikkelingslanden waar de mogelijkheden tot opsporing ervan vaak beperkt zijn en waar de meeste vrouwen geen toegang hebben tot behandeling. Primaire preventie door middel van vaccinatie tegen het humaan papillomavirus (HPV) kan daarom een kantelpunt vormen in de strijd tegen baarmoederhalskanker. Vooraleer er echter grootschalige vaccinatieprogramma's kunnen worden opgezet, dienen er wel een aantal kennishiaten weggewerkt worden. Met het oog hierop wordt er formatief onderzoek gevoerd om naar de (hypothetische) aanvaardbaarheid te peilen en om potentiële barrières voor een succesvolle implementatie te identificeren. Daaruit blijkt dat het vaccin in het algemeen goed aanvaard wordt en dat de kosten en de vrees voor bijwerkingen de vaakst gerapporteerde barrières zijn.

De introductie van het HPV vaccin leidde dus tot veel studies die de publieke opinie ten opzichte van het vaccin willen meten. Dergelijke studies maken vaak gebruik van het Health Belief Model (HBM) om determinanten van aanvaarding na te gaan (nl. vatbaarheid voor en ernst van baarmoederhalskanker, de voor- en nadelen van HPV-vaccinatie, eigen-effectiviteit en prikkels of 'cues' die aanzetten tot actie). De meeste van deze studies vonden echter plaats in ontwikkelde regio's en omvatten geen informatie omtrent de opname van het HPV-vaccin. Dit leidt tot meerdere vragen : 1) Is het HPV-vaccin ook aanvaardbaar in lage-loonlanden, waar het de grootste impact kan genereren, en zijn de determinanten vergelijkbaar? - 2) Leidt een hoge aanvaarding altijd tot een hoge opname van het HPV-vaccin, wat uiteindelijk de werkelijk beoogde uitkomst is? Om deze vragen te kunnen beantwoorden, is een studie opgezet, die drie doelstellingen omvat.

Doelstellingen

- Doelstelling 1: Bepalen van de aanvaardbaarheid en de daaropvolgende opname van het HPV-vaccin in de context van een HPV-piloot-vaccinatieprogramma in Eldoret, Kenia.
- Doelstelling 2: Nagaan of theorieën omtrent gezondheidsgedrag effectief kunnen toegepast worden om HPV-vaccinatie in Eldoret, Kenia, te voorspellen.

- **Doelstelling 3:** Identificeren van factoren die een invloed hebben op een succesvolle introductie van een HPV-vaccinatieprogramma in Eldoret, Kenia.

Opzet van de studie Een longitudinale studie werd opgezet, met baseline en opvolging net voor en na de implementatie van een HPV-vaccinatieprogramma. Het programma bood gratis HPV-vaccinatie aan meisjes leerlingen van basisscholen in Eldoret: het vaccin werd toegediend in het referentieziekenhuis, maar de promotie gebeurde op de scholen, door leerkrachten. Via willekeurige selectie werd een cohorte opgezet van moeders van de meisjes die in aanmerking kwamen voor het vaccin. De moeders werden tweemaal uitgenodigd om deel te nemen aan een kwantitatief interview over preventie van baarmoederhalskanker. De aanvaardbaarheid van het HPV-vaccin werd gemeten op baseline, en de vaccinatiestatus werd gerapporteerd bij de vervolgmeting na afloop van het programma. Deze aanpak liet toe om aanvaarding en opname van het HPV-vaccin te bestuderen, alsook de relatie tussen deze twee eindvariabelen. Daarnaast werd een kwalitatieve component toegevoegd aan de opvolgingsstudie, waarbij het programma werd geëvalueerd door sleutelfinformatanten.

Resultaten Het HPV-vaccinatieprogramma vond plaats van mei 2012 tot en met maart 2013. Baseline- en opvolgingsdata werden verzameld, respectievelijk twee maanden voor en na het programma. Van de 287 vrouwen geïnterviewd in 2012, ging 89,2 percent (256/287) het jaar nadien akkoord om opnieuw geïnterviewd te worden. Daarnaast werden focusgroepdiscussies georganiseerd met vaders (3), leraars (4) en vaccinatoren (1).

Waar de aanvaarding van het HPV-vaccin bij de moeders op baseline zeer hoog was (88 percent), liet uiteindelijk slechts 31 percent hun dochter vaccineren; 51 percent rapporteerde dat ze haar hadden willen laten vaccineren, maar de kans daartoe toch gemist hadden. De resultaten toonden aan dat bij deze laatste groep, 55 percent geen praktische informatie had ontvangen over het programma. Bij degenen die bewust beslist hadden niet te vaccineren (18 percent), had 42 percent angst voor bijwerkingen en gaf 31 percent aan dat hun partner zich had verzet tegen het vaccineren van hun dochter. In het

algemeen gaf de meerderheid van de deelnemers aan dat ongekende bijwerkingen hen hadden doen twijfelen over HPV-vaccinatie en dat ze meer informatie nodig hadden om een doordachte beslissing te kunnen nemen.

Er werd geen sterk verband gevonden tussen aanvaarding van het HPV-vaccin en vaccinatiegedrag. Wat betreft het HBM, werden er evenmin verbanden gevonden tussen de constructen en opname van het vaccin, behalve voor zelf-effectiviteit, wat een positieve invloed had op vaccinatie. De voorspellende waarde van het model verhoogde wel nadat een variabele werd toegevoegd die aangaf of de moeder al dan niet adequate informatie had ontvangen; goed geïnformeerd zijn leidde tot een hogere vaccin opname.

De kwalitatieve data toonden aan dat leerkrachten en vaders een zwakke kennis hadden over baarmoederhalskanker en zich niet comfortabel voelden bij het delen van informatie daaromtrent. Dit had ook geleid tot beperkte communicatie omtrent het vaccinatieprogramma. Voor leraars ontbrak het ook aan steun van gezondheidswerkers om een antwoord te kunnen bieden op vragen van ouders, en om hun eigen twijfels weg te nemen. In het algemeen werd HPV-vaccinatie niet belangrijk geacht, gezien baarmoederhalskanker werd beschouwd als een gevolg van een moderne levensstijl die, volgens de deelnemers, niet van toepassing was op hen. Tot slot werd opname van het vaccin ook gehinderd door wantrouwen ten opzichte van (nieuwe) vaccins: sommigen dachten dat het om een experiment ging, terwijl anderen hun vertrouwen in vaccins reeds verloren hadden bij vorige ervaringen met vaccinatie. Na een paar maand werd die achterdocht echter minder, eens de gemeenschap overtuigd was van de veiligheid van het vaccin.

Discussie Aanvaarding van het HPV-vaccin leidde niet steeds tot vaccinatie. De omzetting van intentie naar gedrag werd voornamelijk gehinderd doordat de informatie over het vaccinatieprogramma niet alle ouders bereikte. De communicatie over HPV-vaccinatie tussen leerkrachten en ouders werd bemoeilijkt door de gebrekkige kennis over HPV en kanker en door het culturele taboe. Directe communicatie tussen een gezondheidswerker en de ouders lijkt daarom cruciaal, gezien de gezondheidswerker beter geplaatst is om dergelijke

onderwerpen te bespreken. Het niet verwezenlijken van een dergelijk contactmoment, leidde niet alleen tot een lage opname, maar liet ook toe dat er geruchten en twijfels omtrent HPV-vaccinatie verspreid werden. Toekomstige programma's zullen meer aandacht moeten geven aan tweerichtingscommunicatie, ten opzichte van de gebruikelijke top-down benadering.

Terwijl de opname van het HPV-vaccin lager was dan verwacht, vooral omwille van organisatorische redenen, is het ook mogelijk dat de aanvaardbaarheid van het vaccin, gerapporteerd op baseline, te hoog werd ingeschat omwille van diverse factoren. Ten eerste, sommige deelnemers werden wellicht overweldigd door nieuwe informatie, gezien de kennis omtrent baarmoederhalskanker en HPV over het algemeen vrij laag is in Kenia. Dit beïnvloedde hun eigen inschatting van intentie waarbij ze geneigd waren om een hogere intentie te rapporteren (ten dele ook te wijten aan het geven van sociaal wenselijke antwoorden). Daarnaast werden eigen intenties misschien overschat omdat het moeilijk is om barrières voor nieuw gedrag te voorspellen, of misschien werd er eerder een wens dan een werkelijk actieplan gerapporteerd. Uiteindelijk is het bij nieuw gedrag ook niet steeds duidelijk wie de uiteindelijke beslissing zal nemen. Uit de kwantitatieve studie met de moeders bleek inderdaad dat het de vaders waren die vaccinatie soms hadden tegengehouden. Gezien vrouwen dus niet steeds de controle hadden over het al dan niet vaccineren van de dochter, kunnen hun intentieverklaringen als minder relevant beschouwd worden voor de uiteindelijke vaccinatie-status van de dochter.

Men kan dus stellen dat de lage opname van het vaccin, omwille van falende promotie, gecombineerd met hoge gerapporteerde aanvaarding, leidde tot een onevenwicht in de relatie aanvaarding-opname. Die relatie werd namelijk voornamelijk gestuurd door niet-aanvaarding die tot niet-opname leidde, eerder dan door aanvaarders die hun eigen gerapporteerde doelstellingen verwezenlijkten.

Net zoals aanvaarding, bleken ook de variabelen van het HBM zwakke determinanten van vaccinatie te zijn. Gezien deze factoren enkel persoonlijke overtuigingen en attitudes weerspiegelen, en

gezien het hogervermelde belang van programmatische strategieën, zou de voorspellende waarde van de theorie verhoogd kunnen worden door het toevoegen van variabelen op hogere niveaus dan het persoonlijke perspectief. Daarnaast kan ook de waarde van elk van de factoren van de theorie in vraag gesteld worden. Zo is de afwezigheid van een correlatie tussen opname van het vaccin, en vatbaarheid en ernst niet echt verrassend, rekening houdend met de Keniaanse context: toegang tot een kwalitatieve gezondheidszorg is beperkt, en aandoeningen worden vaak niet behandeld, zodat ze meer levensbedreigend worden. Zeker (baarmoederhals)kanker wordt als dodelijk beschouwd. Baarmoederhalskanker als een bedreiging beschouwen is dus een algemene manier van denken en maakt bijgevolg geen onderscheid tussen diegenen die vaccineren tegen HPV en diegenen die dat niet doen. Wat betreft de voorziene voordelen en barrières, men kan zich afvragen hoe betrouwbaar iemands inschatting kan zijn over de voor- en nadelen van een nieuw, ongekend vaccin. Door het nagaan van de denkbeelden van gebruikers en niet-gebruikers, kunnen mogelijk meer realistische determinanten geïdentificeerd worden. Ook vertrouwen, in het vaccin of in het gezondheidssysteem, zou een sterkere voorspeller kunnen zijn, gezien mensen verder bouwen op voorbije, gelijkaardige ervaringen met vaccinaties of met gezondheidszorg. Daarenboven kan ook zelf-effectiviteit, wat een positieve determinant was van vaccinatie, beschouwd worden als vertrouwen, in zichzelf, om het gewenste gedrag uit te voeren.

De opname van het vaccin zou verhoogd kunnen worden door zowel via promotie als via een geschikt vaccinatieplatform het vertrouwen in vaccinatie te stimuleren en de toegankelijkheid te verhogen. Een zorgvuldig ontworpen programma zou inderdaad vertrouwen en toegankelijkheid moeten garanderen, alsook de nadruk leggen op de noodzaak van vaccineren. Binnen de context van het HPV-vaccinatieprogramma in Eldoret, waren echter geen van deze voorwaarden volledig vervuld: sommige mensen wantrouwden het vaccin en de gezondheidswerkers in het referentieziekenhuis, baarmoederhalskanker werd niet altijd als risico gezien (terwijl het vaccin wel als potentieel gevaarlijk werd beschouwd) en het vaccin aanbieden in een ziekenhuis werd niet gezien als de meest geschikte, toegankelijke benadering. Vaccinatie op school leek meer geprefereerd, maar een goede samenwerking tussen gezondheidswerkers en het le-

rarenkorps zal dan cruciaal zijn om een goede vaccinatiedekking te bereiken.

Conclusie Het meten van HPV-vaccin aanvaarding en de determinanten ervan is niet voldoende om opname van het vaccin te voorspellen. Meer aandacht dient te gaan naar andere belangrijke factoren zoals vertrouwen in vaccins of, meer algemeen, een aarzelende houding t.o.v. vaccineren. Gezien de vele variabelen die vaccinatie beïnvloeden, maar die niet steeds onder de individuele controle vallen, is het noodzakelijk om formatief onderzoek – dat veelal wordt uitgevoerd vóór een vaccinatieprogramma van start gaat en gebaseerd wordt op persoonlijke gedragstheorieën – aan te vullen met het monitoren van vaccinatieprogramma's en het nagaan van de perspectieven van de gebruikers.

Part III

INTRODUCTION

Chapter 1

HPV infections and the burden of related diseases

Human papillomaviruses (HPV) cause a serious health threat to men and women worldwide. Among the sexually transmitted infections (STI), genital HPV infections are most common, hence the heavy burden on global health. In this first chapter, HPV infections will be discussed, more particularly their transmission mode and the process from infection to malignant lesions such as cervical cancer. Stipulating when most infections occur and which tend to be persistent will also help clarifying the pathway of cancer development. Secondly, cervical cancer incidence will be presented, with special attention to the situation in Sub-Sahara Africa given that the study presented in this thesis took place in Kenya. Finally, both secondary and primary prevention techniques will be addressed, pointing out their strengths and weaknesses.

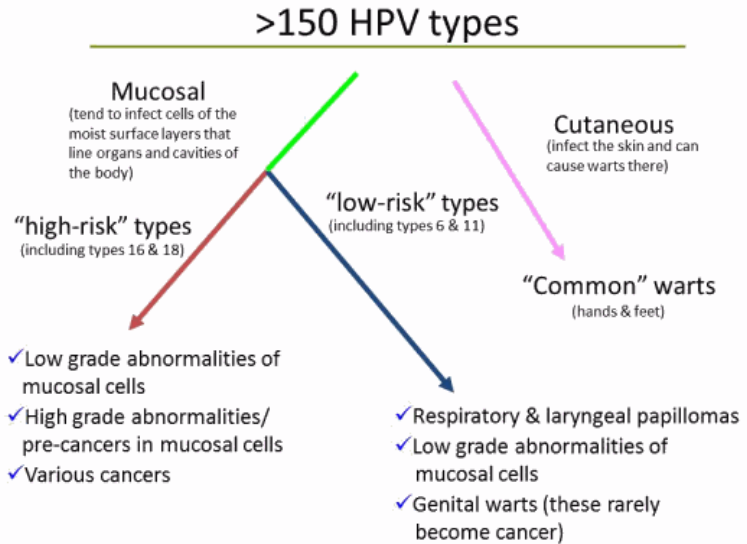
1.1 Human Papillomavirus infections

Human papillomaviruses (HPV) are a group of small, non-enveloped, double-stranded DNA viruses belonging to the family Papovaviridae. There are over 150 different HPV types divided in five major HPV genera: alphapapillomavirus, betapapillomavirus, gammapapillomavirus, mu papillomavirus and nu papillomavirus. They are perfectly

adapted to invade oral mucosa or skin (representatives of all five genera) or epithelial cells in genital mucosa (alphapapillomaviruses only) [1].

While most of the HPV types are harmless, some types induce malformations and even cancer. The causal link between these viruses and cervical cancer was first established in 1991 by Harald Zur Hausen, a German scientist [2], while more recent research also provides evidence of their role in the pathogenic process of anogenital cancers (vagina, vulva, anus and penis) and head and neck tumours, including oropharyngeal malignancies. Furthermore, several benign lesions of the skin are associated with HPV infections (warts, among others) (figure 1.1) [3]–[8]. In this thesis, I will focus on genital HPV infections, especially cervical ones.

Figure 1.1: HPV types: mucosal and cutaneous infections



source: The American Cancer Association 2014

1.1.1 Transmission and risk factors

Genital HPV infections are primarily transmitted through sexual contact, most commonly vaginal and anal intercourse (other routes such as digital and oral genital contact are also seen, yet less frequently). Simulations have suggested that HPV is more infectious than the Human Immunodeficiency Virus (HIV) or herpes simplex 2, with a median per-act transmission probability of 40 percent [9], [10]. Factors that enhance the risk of HPV acquisition are early sexual onset - due to an enlarged transformation zone during puberty - and having multiple partners; other STI are potentially cofactors as opposed to just markers. In addition, immunodeficiency disorders also increase the chance of HPV infections. More particularly, they inhibit clearance and may thus lead to multiple infections and/or speed up the progress of malignancy [10].

Studies have demonstrated a similar effect of smoking [11], [12] yet others have failed to do so [10], [13], [14]. Smoking might thus alter one's susceptibility for HPV infections or either be a proxy of sexual risk behaviour. Likewise, the use of hormonal contraceptives is linked with HPV infections but whether it is a causal relation or a confounding effect remains unclear [10], [14], [15]. Finally, condom use and male circumcision may significantly reduce HPV acquisition, however, research results are not conclusive. Nevertheless, it is clear that condoms will never provide full protection since HPV may still infect the not-covered areas [10], [14], [16], [17].

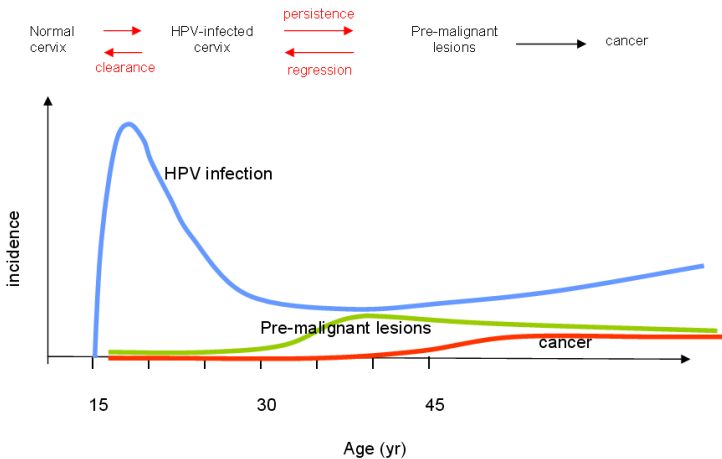
1.1.2 Stages of cervical HPV infections

Cervical infections with HPV are very common and typically happen between the age of 15 and 20 years, i.e. the period of sexual debut. Usually, incidence then steadily decreases although some studies show a stabilization or even a second peak among middle-aged women (figure 1.2). This observation is found all over the world but seems to be more prominent in Africa and Central and South America. Possible explanations for the occurrence of more HPV infections in later life are reactivation of old, latent infections due to hormonal changes or dropped immune defence. Additionally, the peak might also originate from new, unprotected sexual relations

(from the partner) at older age [10], [14], [18].

Up to 80 percent of all women worldwide will become infected with high-risk HPV once in their lifetime but most of them clear or suppress the infection naturally within one or two years. Only persistent infections may lead eventually to malignant lesions, which can take up to 10 years and more. Natural regression remains possible even after pre-malignant lesions are formed; only invasive abnormalities are a point of no return (figure 1.2). The risk of evolving towards precancerous lesions and ultimately to cancer depends on many factors: higher age and impaired immunity seem to increase the risk of persistent infections. As mentioned above, also tobacco use and hormonal family planning methods may interfere with one's capacity to ward off a persistent infection. The most important factor however, might be the type of HPV with which one is infected. HPV 16, for example, is known to progress rapidly [8], [10], [14].

Figure 1.2: Progression of HPV infections



source: Trottier 2006

1.1.3 Type distribution

As previously mentioned, HPV can induce several types of abnormalities but while there are over 150 types of human papillomaviruses, only a small subset is considered to be high-risk, with HPV 16 and 18 as most known oncogenic types (table 1.1)

Table 1.1: Risk classification of alpha HPV types

Risk level	HPV types
High-risk or oncogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probable high-risk	26, 30, 34/64, 53, 66, 68, 67, 69, 70, 82, 85
Low-risk or non-oncogenic	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

source: Bzhalava 2013

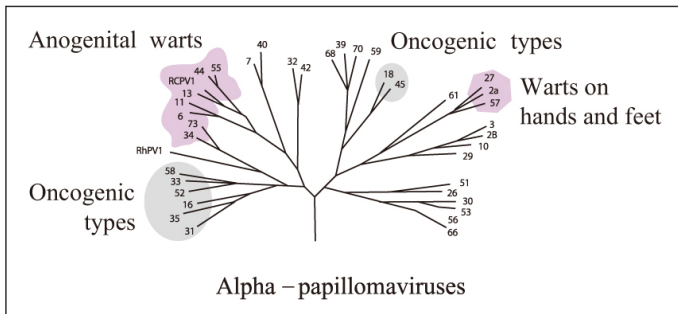
Among women with normal cervical cytology, up to 11.7 percent are HPV positive, with the highest prevalence found in Sub-Sahara Africa (24.0 percent). HPV 16 and 18 are consistently in the top three of most frequent infections in women without cytological abnormalities among all continents (worldwide prevalence of 3.2 percent and 1.4 percent, respectively) [6], [19], [20].

With regard to HPV types detected in lesions, HPV 6 and 11 account for 90 percent of genital warts while HPV 16 and 18 are found in over 70 percent of invasive cervical cancers worldwide. The contribution of HPV 16 and 18 increases from low-grade cervical lesions (16-32 percent), to high-grade (41-67 percent), up to invasive cancer. Following HPV types cause another 25 percent of the cases: 31, 33, 35, 45, 51, 52 and 58 [21]–[23]. Similarly, HPV 16 and 18 are predominantly found in penile and anogenital cancer (figure 1.3)[24], [25].

Again there is little or no variation in the distribution of HPV types in cervical cancer around the world. However, some studies do show small deviations, e.g. HPV 35, 45 and 52 have been

more reported in invasive cervix cancers in Sub-Sahara Africa compared with worldwide presence [26]–[29]. More research is needed to confirm this yet there is already evidence that the current HIV epidemic might be at the root of this deviation. HIV positive women have more often multiple HPV infections, including HPV types less frequently detected in women with single infections [26], [27], [30]–[32].

Figure 1.3: HPV types linked with warts and tumours



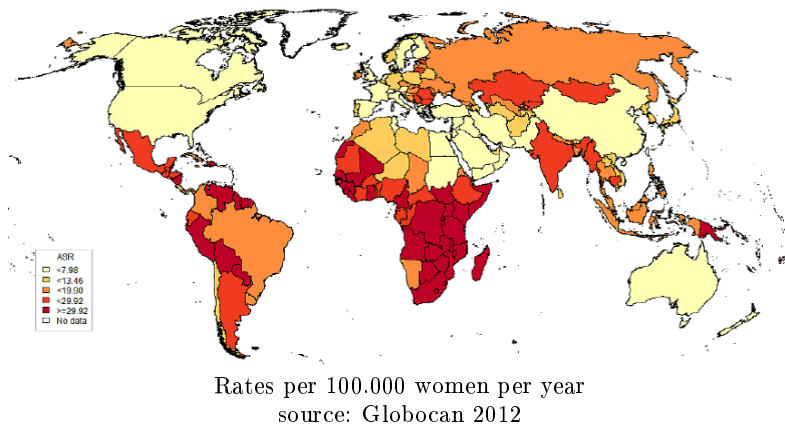
source: Kim 2008

1.2 Cervical cancer

1.2.1 Cervical cancer worldwide

Crude incidence rates show that cervical cancer is the fourth most common cancer among women worldwide, with over 500,000 new cases each year. Similarly, cervical cancer is the fourth most lethal cancer in the world with an estimated 265,653 deaths in 2012. The burden of disease differs however greatly among regions, depending heavily on the level of development as can be seen in figure 1.4. Indeed, around 70 percent of the yearly new cases occur in the low and middle income countries (LMIC) where age-standardized mortality rates can rise up to 27.6/100,000 (East Africa) compared with 2/100,000 in Western Europe. The main reasons for this striking health inequality are mainly the lack of screening and treatment opportunities [24], [33].

Figure 1.4: Age-standardized incidence of cervical cancer worldwide; estimation for 2012



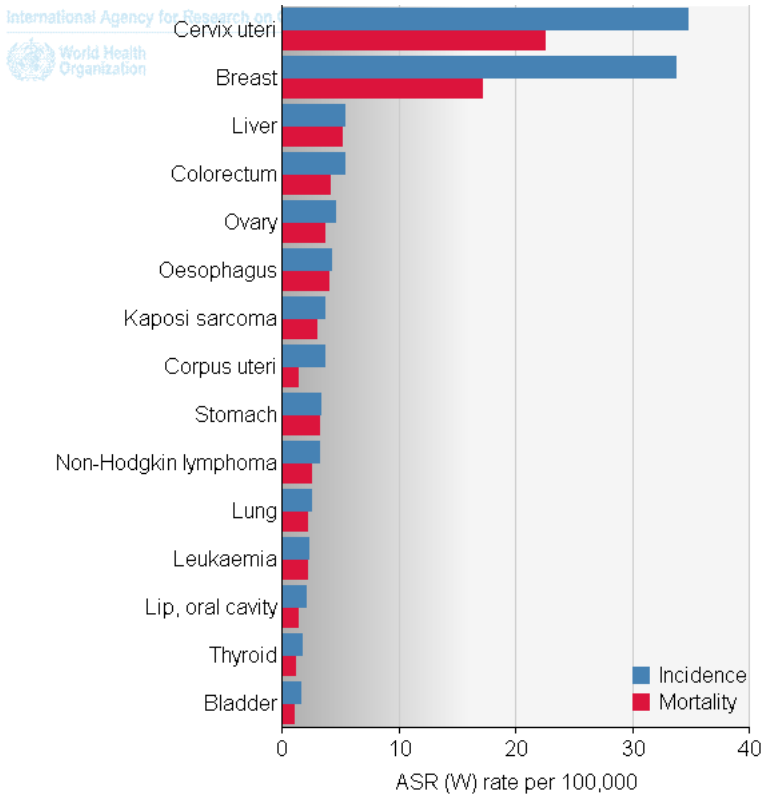
1.2.2 Cervical cancer in Sub-Saharan Africa

The world's region most affected by cervical cancer is Sub-Saharan Africa. With age-standardized incidence and mortality rates of 34.8/100,000 and 22.5/100,000 respectively, it is the cancer which causes the highest health burden among women (figure 1.5)(crude incidence of breast cancer is however slightly higher). In addition, projections are not hopeful: due to the current population growth, the number of yearly new cases may double by 2030 (from 93,225 cases in 2012 to 160,163 in 2030) [33]. Other competing health priorities, such as HIV/AIDS, malaria and tuberculosis, have led to lack of attention while poor cancer registries have led to an underestimation of the problem. Better cancer registration is needed to obtain a more detailed understanding of the presence of the disease in different regions [30].

Besides the aforementioned shortage of adequate health services to detect and treat (precursors of) the disease, knowledge is often very poor resulting in low screening coverage even if programmes are in

place. Also, some of the risk factors, such as early age at first sexual intercourse and pregnancy, or other STI infections are still far too common in Sub-Sahara Africa and contribute substantially to the high incidence of cervical cancer [27], [30], [31]. High mortality on the other hand is also explained by poor general health (e.g. co-morbidity with nutrition deficiencies, anaemia or malaria), delay in presentation and abandonment of treatment due to poverty related barriers [31].

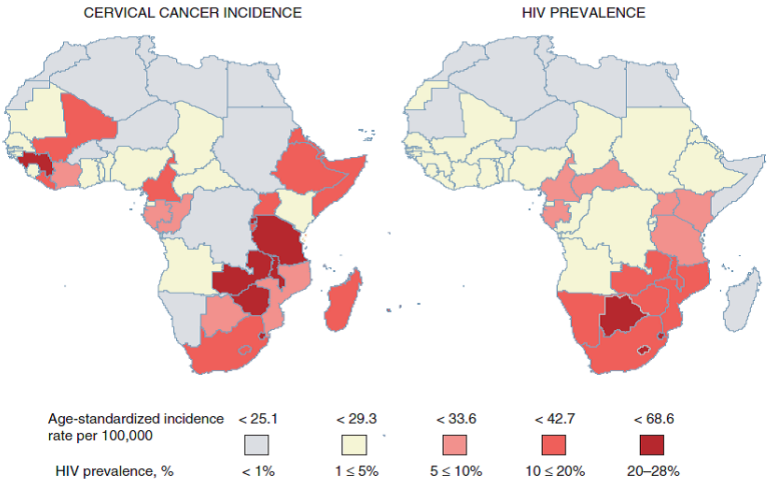
Figure 1.5: Cancer among women in Sub-Sahara Africa: age-standardized incidence and mortality rates; estimation for 2012



source: Globocan 2012

Whether the current HIV epidemic has also influenced the number of new cases of cervical cancer remains unclear as in some countries there has been no increased incidence reported since the beginning of the HIV outbreak. However, it is known that HIV positive women are more susceptible to HPV infections and seem to clear them less easily due to their impaired immune system. Therefore, cervical cancer is even more common among HIV positives in Sub-Sahara Africa and since 1993 it is included in the list of AIDS-defining clinical conditions (figure 1.6) [22], [27], [30], [31]. It is yet to be seen if access to antiretroviral therapy (ART) will affect the current epidemic: a longer life might provide the time needed to develop malignant lesions while a restored immune defence might help clearing HPV infections [27], [30].

Figure 1.6: Age-standardized (world) incidence rates of cervical cancer and HIV prevalence in Africa



source: Louie 2009

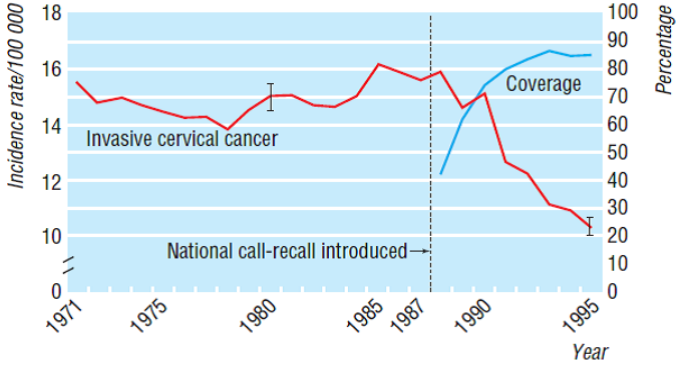
1.3 Prevention of cervical cancer

1.3.1 Screening: secondary prevention

Cervical cancer is sometimes called "the silent killer" given the slow and often asymptomatic progression of lesions into malignant abnormalities (figure 1.2). But because of this time-taking process, malformations can be detected and treated or removed before the disease becomes terminal. Cytological screening is based on this principle and allows trained health providers to detect abnormal cell formations: cervical cells are sampled by removing epithelial cells with a brush and revised under the microscope (i.e. pap smear). While the technique has limited sensitivity (59 percent), it has good specificity (94 percent). However, due to the low negative predictive value in the general population it needs to be repeated frequently. Even though the technique itself is cheap, it is labour intensive and requires high-trained staff and rigorous quality control [34]–[36].

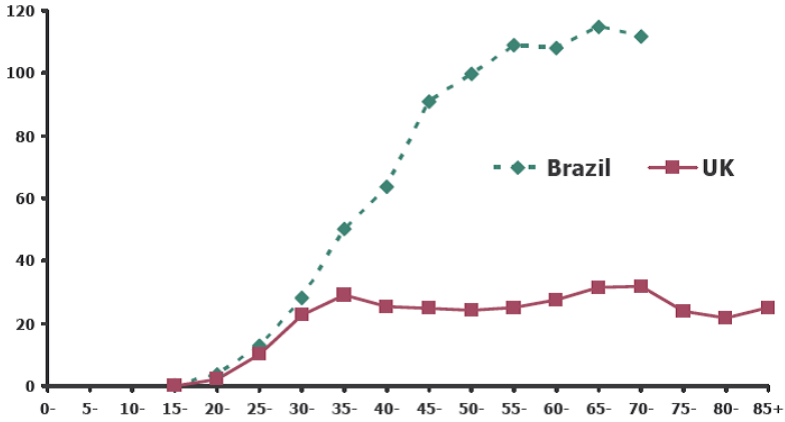
Reduced cervical cancer incidence in industrialized countries is mainly due to high screening coverage (63 percent on average), either achieved by organized programmes or through opportunistic screening (figure 1.7). Women in LMIC are much less screened (13 percent) hence the higher incidence rates (figure 1.8) [34], [37]–[40]. In the past ten years, a lot of effort has been put into evaluating alternative screening methods to get around the above-mentioned barriers of cytological screening. Approaching most-at-risk groups and targeting one or two screening episodes in a lifetime, are considered first steps towards improved cervical cancer control. Furthermore, alternative technologies have been assessed and pushed forward: VIA and VILI (visual inspection with acetic acid and visual inspection with Lugol's iodine, respectively) are feasible options to offer screening in regions where cytological screening is difficult to implement, even though sensitivity and specificity are lower. Both techniques rely on the fact that abnormal cells colour differently after applying either acetic acid or iodine on the cervical epithelium. Additionally, screen-and-treat programmes, using cryotherapy as immediate relieve, are promoted in order to reduce the number of visits and thus loss-of-follow-up [34], [35], [41]–[43].

Figure 1.7: Age-standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-1995



source: Quinn 1999

Figure 1.8: Age specific incidence of cervical cancer in 2 countries with and without centralized and widespread screening programmes



source: Bosch 2006

Finally, therapeutic vaccines and molecular tests are being developed [42], [44], [45]. Especially HPV DNA-tests are currently under debate, in terms of quality but also with regard to practical issues such as informing and follow-up of HPV positive patients [42]. In this discussion, also other sample types are considered, such as self-sampled vaginal swaps. A meta-analysis by Arbyn et al. (2014) showed that sensitivity and specificity of HPV testing on self-samples was however lower compared with clinician-taken samples. Nevertheless, offering women the opportunity to screen by self-sampling might be a good approach to include those who do not attend regular screening programmes [46]. Similarly, detecting HPV DNA in (first void) urine has been proposed, based on the high correlation that was found between urinary HPV DNA and infections of the lower genital tract, including cervical infections. DNA detection in urine is however conditional on correct sampling, good storage conditions and sample preparations, and lab techniques used. But since these steps can be optimized and standardized, detecting HPV in urine offers a very valuable alternative for vaginal/cervical samples given that it only requires an easy-to-collect, non-invasive sample. Besides the fact that this might be again more acceptable in some subgroups, it also creates the use of new viral endpoints for clinical trials of HPV vaccines [47]–[50].

1.3.2 Vaccination: primary prevention

The vaccines

Since 2006-2007, two prophylactic HPV vaccines are on the market. In 2006, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) granted Gardasil (Merck) marketing authorization. Later on Cervarix (GlaxoSmithKline Biologicals S.A.) was also approved by the EMA and the FDA in 2007 and 2009, respectively. While Cervarix was designed to prevent precancerous lesions in and cancer of the cervix only, Gardasil protects also against condylomata acuminata or genital warts. The former is indeed a bivalent vaccine containing purified major capsid (L1) L1 proteins for HPV 16 and 18, two highly oncogenic HPV types, in contrast with the quadrivalent Gardasil which also includes

L1 proteins for HPV 6 and 11, the causal agents of genital warts. At the moment, Gardasil and Cervarix are also recognized as primary prevention methods against HPV lesions of the vulva and the vagina. In addition, Gardasil's protection against anal lesions and cancer is also acknowledged (even though studies have indicated protection offered by cervarix as well) [51]–[55].

Both vaccines are ideally administered before sexual onset, given that efficacy is highest among HPV-naïve people. Therefore young adolescents are targeted but catch-up vaccination might be given to older adolescents and young adults. It is also worth mentioning that both vaccines induce higher antibody levels among young adolescents versus adolescents and young adults [56], [57]. As a result, the original administration schedules are adapted: upon approval, vaccination consisted out of three doses within six months. After re-evaluation, a two-dose schedule given six months apart to girls nine to fourteen or nine to thirteen for Cervarix and Gardasil respectively, has been approved [58]–[61]. Cervarix is only licensed to be given to girls; Gardasil can be used among both males and females.

An important difference between the vaccines is the use of a strong, novel adjuvant (adjuvant system 04, AS04) in Cervarix compared to the aluminium salt adjuvant of Gardasil. This strong adjuvant might be the reason why Cervarix clearly offers cross-protection against non-vaccine HPV types (i.e. 31, 33, 45, 51) [62]–[65]. In terms of duration of protection, both vaccines sustain high immunogenicity and efficacy up to 8 years [66]–[69]. However, some studies show a decreased anti-HPV 18 titer after five years among 15-26 year old women vaccinated with Gardasil [68], [70], [71]. In general, Cervarix tends to induce higher immune response which may have consequences for the duration of protection against HPV 16 and 18 [72]. Whether this will have clinical implications or whether the vaccines will also provide protection due to immune memory or low, undetectable titers remains to be investigated through long-term follow-up studies. Finally, none of the vaccines are currently linked with serious adverse side effects (table 1.2) [67]–[69].

Table 1.2: Prophylactic HPV vaccines

	GARDASIL	CERVARIX
HPV types	HPV 6, 11, 16, 18	HPV 16, 18
Cross-protection	HPV 31	HPV 31, 33, 45, 51
Adjuvant	aluminium hydroxyphosphate sulphate	AS04 - aluminium hydroxide and 3-deacylated monophosphoryl lipid A
Injection place	Intramuscular	Intramuscular
Schedule	0, 2, 6 months	0, 1, 6 months
Approved for	Boys and girls, nine years or above	Girls, nine years or above
Storage	2°C - 8°C	2°C - 8°C

Impact and the way forward

Given the time it takes to develop cervical cancer and the fact that the vaccines are less than ten years on the market, it is too early to detect changes in incidence rates in vaccinated populations. Impact on other HPV-related endpoints are however documented, e.g. in Australia where many studies have reported the impact on genital warts. While the national HPV vaccination programme was launched in 2007, results were already noticed in 2009 by investigating trends in diagnoses of genital warts in 2004-2009. A decline was noted for young women, not for older groups, and evidence already hinted towards herd protection for young, heterosexual men [73]. In 2013, boys were included in the programme and later on, more studies showed the protective effect of the vaccine, either direct or through herd protection, by comparing pre- and post-vaccination data on cases of genital warts. Besides detecting large effects for young, heterosexual women and men, they also confirmed that the reductions are similar for indigenous and non-indigenous populations, and for people living in disadvantaged versus less-disadvantaged areas [74]–[76]. In addition, a small decline among men who have sex with men has been observed yet it is not clear whether this could be attributed to HPV vaccination [77].

Similar results are detected in a meta-analysis by Drolet et al. (2015), including also data from other countries. A first tendency described is a decrease in vaccine HPV-types (i.e. HPV 16 and 18) and anogenital warts, both in populations with high and low vaccine coverage (more or less than 50 percent uptake among girls younger than twenty years of age, respectively). Furthermore, among the populations with high uptake, results from clinical studies are confirmed: cross-protection against HPV 31, 33 and 45 is detected and herd-effects are noted through a decrease of anogenital warts in older women and men. These results need to be interpreted with caution due to several biases, such as potentially more doctor visits for genital warts post-vaccination or lack of control for changes in sexual behaviour after the vaccines were introduced. In addition, the protective effect of the vaccine might fade out over time if immunogenicity does not hold. On the other hand, vaccinated girls have often not yet entered the age-period when HPV infections and anogenital lesions peak, offering the possibility to detect an even larger impact in the upcoming years. Finally, given that the results are drawn from studies in high-income countries (HIC), different HPV epidemiology or sexual behaviour, or co-factors such as HIV prevalence might inhibit correct extrapolation to resource-limited regions [78], [79].

Several studies have also noted a decrease in high-grade cervical abnormalities, which are the closest surrogates for cervical cancer [80]–[83]. Again in Australia, the incidence of high- and low grade cervical abnormalities was compared before and after the introduction of the vaccine. A decrease in high-grade lesions was found among girls younger than 18 years of age, which was significantly different from the trend before the onset of the vaccination programme [81]. Also, when comparing vaccinated versus non-vaccinated women, a significant reduction in cervical abnormalities was detected already five years after the start of the vaccination programme [80]. Further evaluation of the results of these studies is however warranted. For example, some results are not controlled for screening behaviour or are only applicable for younger women [81]–[83]. Similarly, it is yet to be seen if the same protective effect will be registered among subgroups such as HIV positive people or whether the vaccine will be equally protective against HPV related cancers other than

cervical tumours [84]–[86]. Also more research is needed to monitor type replacement by nonvaccine types. Results from a Finnish studies suggested a competitive advantage for HPV 33 among the unvaccinated population [87].

In 2014, a nonavalent vaccine containing HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antigens was licensed by the US FDA, followed by the European Committee for Medicinal Products for Human Use (CPMH) in 2015. Together, these nine HPV types cause almost 90 percent of cervical cancers [61], [88]. Again, results of clinical trials are promising but close follow-up will be necessary to verify the population based effect.

Chapter 2

HPV vaccination programmes worldwide

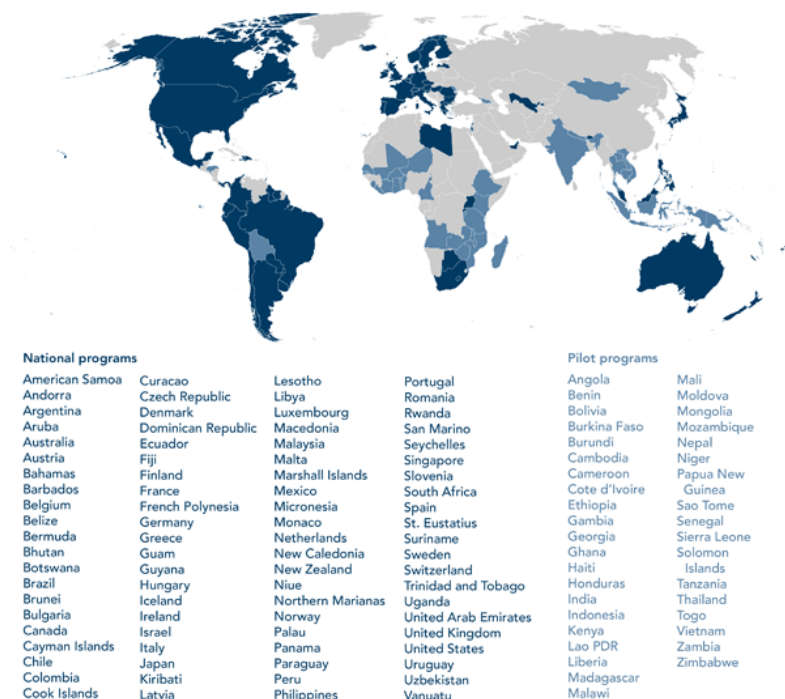
Several kinds of HPV vaccination programmes are currently implemented all over the world, applying various designs, targeting entire countries or just some localities, launched as a long-term component or as a pilot project. The following sections will describe different types of vaccination programmes that have been rolled out, as well as the uptake rates that have been reached so far. More particularly, the first section will address national HPV vaccination programmes, describing the state of affairs in HIC and in low- and middle income countries. A second section is dedicated to the pilot HPV vaccination programmes or 'demonstration programmes' that have been implemented in LMIC as to prepare national roll-out, pointing out some shortcomings of these small-scale vaccination projects.

2.1 National HPV vaccination programmes

Since the introduction of the HPV vaccines in 2006-2007, many countries have incorporated cervical cancer vaccination in their immunization scheme and have implemented programmes. While in 2010 national programmes were still limited to Mexico, Panama and most HIC (USA, Canada, Australia, New-Zealand and North- and West-Europe), by 2015 most Latin-American countries had followed

(figure 2.1) [89]. However, these reports need to be interpreted with caution, e.g. while Suriname has a national programme, it is mainly focussed on the capital-city, meaning that many people in rural areas still have limited access. Similarly, the programme in South-Africa offers HPV vaccination to girls in public schools only, leaving behind those in private institutions and non-school going girls [90].

Figure 2.1: Implementation of HPV vaccination programmes, February 2015



source: Cervical Cancer Action

2.1.1 High-income countries

Uptake of the HPV vaccine varies among countries and regions. In Europe, reported three dose coverage ranges from over 75 percent in Belgium-Flanders (2012), Denmark (2011), Portugal (2011) and the UK (2015), to less than 30 percent (Belgium-Wallonia-2015, France-2008 and Luxembourg-2009) [91]–[98]. Also outside Europe discrepancies are found, even within countries: in the USA uptake can vary between 15 and 70 percent [94], [95], [99]–[103] and also in Canada differences are found (80 to 85 percent in eastern provinces against 59 percent in Ontario (2010)) [94], [104]. In Australia, a country that has been one of the pioneers in HPV vaccination, coverage of around 70 percent is reported consistently from 2009 to 2013 [95], [105]. Finally, it is important to mention that studies in various countries have showed that people of low economic status or ethnic minorities report less uptake compared to the general population, lowering the potential of the vaccine to reduce health inequality [100], [101], [103], [106]–[112].

Organizational factors that have been identified to influence HPV uptake are mainly the delivery platform and the financing methods. In general, school-based vaccination is more successful than health centre-located programmes [113], [114] and, given the high cost of the vaccines, publicly funded programmes or societies with high medical insurance coverage are more likely to reach high uptake [91], [95], [100], [101].

2.1.2 Low- and middle-income countries

As can be seen in figure 2.1, national programmes in LMIC are mainly located in Latin America, with some exceptions in Asia (e.g. Singapore and Bhutan) and Africa (e.g. Rwanda and South-Africa). Good results have been achieved through various implementation schemes and delivery platforms. In Mexico for example, a gradual roll-out, starting with mobile health clinics in the most deprived communities in 2008, has grown into a nationwide programme in 2012, applying an adapted scheme of 2 doses in 6 months and a booster dose 5 years later. In 2009, a coverage of 67 percent was reached for the second dose. Panama on the other hand uses a mixed

approach of both clinic and school based vaccination, reaching a 67 percent coverage for the third dose in 2010 [94].

Especially the high cost of the vaccines (up to more than 100 USD per dose in HIC) is a major barrier for LMIC to organize large-scale HPV vaccination programmes. Rwanda and Bhutan were able to do so thanks to multi-year donations from Merck [94]. In Rwanda, a combination of school-based vaccination and community involvement to identify out-of-school girls led to a successful three dose uptake of 93 percent in 2011 [115]. Other countries can obtain HPV vaccines at reduced prices thanks to the Pan American Health Organization's Revolving Fund (14 USD a dose) or the Global Alliance for Vaccines and Immunization (GAVI; 4.5 USD a dose). The latter committed itself in 2011 to offer HPV vaccines to eligible countries, i.e. countries with a DTP3 threshold of 70 percent national coverage, and that can demonstrate the ability to deliver HPV vaccine to adolescent girls. Demonstrated ability is defined as "prior experience in delivering multi-dose vaccines to at least 50 percent of a target population of 9-13 year old girls in an average-sized district". Currently, Rwanda, Lesotho and Uganda are the only African countries eligible for national HPV vaccine introduction support. Nations lacking experience can apply for support to conduct small-scale demonstration projects in order to gain the experience necessary to apply for national roll-out [94], [116]–[120].

2.2 Demonstration programmes

At this moment, most experience regarding HPV vaccination in LMIC comes from demonstration projects, i.e. the pilot programmes conditional to become eligible for GAVI support for national roll-out (see above). Nepal, Vietnam, Peru and Uganda were the first countries to implement small-scale HPV vaccination efforts with the guidance of Path, an American NGO (2008-2010). Vaccines were provided to Path by Merck (USA) and GlaxoSmithKline (UK). Different delivery platforms were tested among the different countries and districts: school-based (selection of eligible girls either by age or grade), health centre-based, incorporation of HPV vaccination in an existing programme (i.e. the Child Days Plus Programme

in Uganda), or a mixed approach. All countries showed positive results: with exception of the district in Uganda where HPV vaccination was incorporated in the Child Days Plus Programme (uptake was not higher than 61 percent), coverages were mainly above 80 percent (ranging from 68 to 98 percent). [120], [121].

After these four initial pilots, many more demonstration projects have followed or are currently ongoing [122]–[127]. Especially in East-Africa efforts are made to gradually introduce the HPV vaccines (figure 2.1). Given the large burden of disease in this region, this is extremely urgent. Regarding the success rates of such programmes, a review by Ladner et al. (2014) provided insight in uptake rates of 21 Gardasil Access Programs (pilot programmes made possible through donations of Merck). Between 2009–2013, these pilots, taking place in 14 countries and using different delivery methods, all achieved high coverage (minimum 69 percent) [122].

In contrast with these successful demonstration projects, one pilot programme did however not end well: in India, a demonstration programme of Path was suspended after various human rights groups, women’s groups and academics asked for a re-evaluation of the vaccine’s safety and efficacy. Besides questioning the vaccine itself, people were not convinced about the need or priority given to introduce (an expensive) vaccine against cervical cancer. Finally, the vulnerability of the potential participants led to fear for exploitation. The non-responsiveness of the government on these concerns resulted in more pressure and ultimately suspension of the programme [128], [129].

2.2.1 Limitations of demonstration projects

While results are encouraging - high uptake of the HPV vaccine in LMIC seems possible - it is not always entirely clear how this was achieved. Only some countries have thoroughly reported on how demonstration projects were carried out and what their impact was in terms of HPV vaccine uptake, acceptability and knowledge (the Path projects in Uganda, Peru, Nepal and Vietnam are well described) [115], [121]–[127], [130]–[142]. For example, few programmes have documented how promotion took place or what types

of messages were spread through what media. Nonetheless, those studies that did investigate factors influencing uptake showed that knowledge is an important predictor [133], [136] or found that exposure to community influencers was of great importance and highly related to vaccination [134]. Also, in Tanzania and Vietnam, vaccine refusers reported side-effects as one of the main reasons for not vaccinating against cervical cancer, indicating the need for more (convincing) sensitization [130], [132].

Besides community outreach and mobilization, Tsu et al. (2014) also identified service delivery operations as defining for the success rate of a programme, referring to types of vaccination platforms or venues used, definition of the target group (eligibility criteria) and timing of vaccination. [138]. Understanding the advantages and disadvantages of different delivery strategies is of course crucial to improve or maintain high uptake of the HPV vaccine yet projects usually don't report more than the venue where vaccination took place.

More efforts are thus needed in documenting HPV vaccination programmes with respect to different service delivery operations and promotional strategies in order to provide lessons learned and good practices. In addition, such results may shed light on whether or not it will be possible to scale-up pilot programmes into national vaccination efforts: is the used design feasible nationwide and can it lead to similar or more successful results? Indeed, for many countries the sustainability of and the possibility to expand the demonstration projects remain unclear [118].

Chapter 3

Conceptual frameworks to understand vaccination behaviour

With the introduction of new methods comes along formative research to evaluate the health system's capacity to include the newly developed tool. Besides assessing whether the health system can offer high quality health services, also the population's readiness to take up the new behaviour is generally measured. To do so, acceptability studies are carried out to identify factors that hamper uptake and to determine strategies to maximize coverage. This is not different for the HPV vaccine: given the potential health benefit that high coverage of the vaccine may offer, a lot of efforts goes to studying whether the vaccine is well-received and if not, what causes its rejection.

The following chapter will thus describe HPV vaccine acceptability studies. Extra attention will go to 1) determinants of vaccine acceptability that are often investigated or discussed, 2) the state of the art regarding acceptability studies in Sub-Saharan Africa, and 3) the health behaviour theories used to study vaccine acceptability and uptake. Furthermore, a critical evaluation of HPV vaccine acceptability studies is presented as to identify points of improvement.

Finally, the more recently introduced concept of 'vaccine hesitancy' - as opposed to vaccine acceptability - is presented, describing the different definitions and forms of usage of the last couple of years.

3.1 HPV vaccine acceptability studies

HPV vaccine acceptability is often determined by using the word 'would' in questions like "Would you agree to vaccinate..." or "Would you accept..." or "How likely would you vaccinate..." [143]. These type of questions are in a large majority of the acceptability studies directed to (young) women, given that they are presumably the main decision-takers when it comes to vaccination against cervical cancer (being part of the target group or in their role as (future) mother). Indeed, during early adolescence, most children remain dependent on their parents for basic needs such as transportation and they have not yet begun to test the authority of their parents and other adults. Consequently, young adolescents may be most likely to comply with parental advice regarding vaccination [144]. In addition, a caregiver's consent is often required prior to vaccination.

In general, (childhood) vaccines are broadly accepted and also many HPV vaccine acceptability studies report that the vaccine is received positively by many people. The primary driver for vaccination is protection against cervical cancer. Health care professionals are considered the most trusted person to advice on HPV vaccination, therefore, their recommendation is crucial and helps counteracting doubts while stressing the importance of cervical cancer prevention [95], [100], [101], [145].

Nonetheless, studies have showed that willingness-to-vaccinate should not be taken for granted and might vary strongly among different (sub)populations [95], [146]–[149]. In the Netherlands for example, Protestants were less likely to accept the vaccine as opposed to Roman Catholics or people without religion [150], [151]. It is known that Orthodox Protestants, living in the so called Dutch Bible Belt, are suspicious about vaccination; combined with a more traditional lifestyle, rejection of the HPV vaccine is not truly surprising. In Canada on the other hand, in-school HPV vaccination was refused

by Catholic schools in Calgary. They banned the vaccine inspired by the Roman Catholic bishop of Alberta who objected because "the vaccine implies that early sexual intercourse is allowed" [152]. So Roman Catholics in the Netherlands and Canada held up a different point of view with regard to HPV vaccination. 'Religious' reasons of vaccine refusal are often not more than a reflection of personal concerns shared by a certain community [153]. For example, conservative wings in the USA have boycotted HPV vaccination, based on moral concerns (they believe the vaccine promotes risky sexual behaviour) [154], [155].

In addition, variance in acceptability has been documented among ethnic groups. Non-Caucasians had lower awareness and a less positive attitude towards the vaccines than Caucasians in Canada [156], while in the UK, Marlow et al. (2009) found that ethnicity and religion were highly associated with acceptability: white women reported higher acceptability compared to African, Caribbean or South Asian, and Muslims accepted less as opposed to those with no religion [157]. These results clearly demonstrate that cultural factors and underlying concerns influence people's intentions to vaccinate their daughter [153]. By studying acceptability and its determinants researchers try to find pathways to increase acceptability, if needed, and eventually HPV vaccine uptake.

3.1.1 Determinants of acceptability

As stated, measured HPV vaccine acceptability is often high but, as with most vaccines, concerns related to safety and efficacy do exist. Especially fear of side effects seems to lower vaccine uptake rates [91], [95], [101]. Concerns may arise from the fact that the vaccine is newly developed (or newly introduced) and that it prevents an STI by targeting young adolescent girls prior to sexual debut [146], [158]–[161]. Also practical issues can temper willingness to vaccinate, such as the high cost of the vaccine or the time and effort it takes to accompany the daughter, up to three times, to the health care provider. Finally, awareness of cervical cancer is low in certain communities meaning that people may doubt the usefulness of the vaccine [160], [161]. These and other determinants are discussed in the following paragraphs.

Awareness as primary condition

Being aware of cervical cancer and the possibility to vaccinate against it is a first condition to accept the HPV vaccine. More in-depth knowledge often increases acceptability [112], [148], [154], [162]–[165] yet not all studies confirm this [149], [158], [166], while others even show that also without detailed knowledge acceptability can be high [165], [167]–[184]. In any way, since the vaccines were introduced in 2006-2007, public awareness regarding cervical cancer and HPV has improved thanks to promotional campaigns and media attention [149], [185]–[187]. Unfortunately, knowledge remains generally inadequate: worldwide, the causal link between HPV and cervical cancer is still poorly understood and the vaccine remains rather unknown. In addition, information received is not always complete or correct and as a result people might reject the vaccine, e.g. when pilot vaccination programmes are considered as part of a clinical trial, the vaccine’s safety will obviously be an issue [148], [162], [188].

If interest fades away, knowledge and awareness might even more decrease. A systematic review by Trim et al. (2012) showed indeed a slight drop in 2010 after an increase in 2008 and 2009 [185]. In addition, knowledge varies greatly, both in country and between countries [95], [112], [147], [149], [188] and worrisome, under-served or disadvantaged groups are more likely to have limited knowledge [146], [154], [161], [189].

More information is frequently requested by participants of acceptability studies as to enable them to make an informed decision [163]. Given that lack of information or misunderstandings also allow instigation of doubts and impinges the ability to feel confident about a decision, it is clearly important for vaccination programme designers to answer this request and to transfer information correctly and convincingly. Surprisingly, few studies have evaluated the impact of promotional campaigns and those that did do not always show improved knowledge [133], [190]. Various reasons might cause this failure, going from organizational factors, poorly tailored messages or lack of capacity among the target group to correctly interpret information. As such, health literacy might be an important factor to

take into account, however, until now it has not been a major point of discussion in HPV vaccine related research. This might be partly due to a poor understanding of the concept.

Table 3.1: Matrix with four dimensions of health literacy applied to three health domains

	Health care	Disease prevention	Health promotion
Obtain health information	Ability to access information on medical or clinical issues	Ability to access information on risk factors	Ability to update oneself on determinants of health
Understand health information	Ability to understand medical information and derive meaning	Ability to understand information on risk factors and derive meaning	Ability to understand information on determinants of health and derive meaning
Process health information	Ability to interpret and evaluate medical information	Ability to interpret and evaluate information on risk factors	Ability to interpret and evaluate information on determinants of health
Apply health information	Ability to make informed decisions on medical issues	Ability to make informed decisions on risk factors	Ability to make informed decisions on health determinants

source: Sorensen 2009

The concept of health literacy has greatly evolved during the last years: while the original, more narrow interpretation indicated the ability to handle words, terms and numbers in the context of medical care, it has broadened up to a set of skills which enables people to use health information in decision making and carrying out the preferred action. Sorensen et al. (2012) introduced a new definition, based on a review of all definitions and frameworks that have been used in the past: *"Health literacy is linked to literacy and entails people's knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgements and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course"*. With this definition, twelve dimensions are introduced, formed out of four competences (access, understanding, pro-

cessing and applying information) and three domains (health care, prevention and promotion) (table 3.1) ([191]). When it comes to decisions regarding preventive actions such as HPV vaccination, obtaining and rightly evaluating information on especially risk factors seem to be important skills in the process of decision-making, as opposed to the more traditionally evaluated factors such as 'having heard of', in this case cervical cancer, HPV and the HPV vaccine.

Safety and efficacy

Thanks to the success of childhood vaccinations, vaccines are considered some of the most effective methods to prevent diseases by health policy makers and providers but also by the general public. Therefore, a lot of people have faith in the HPV vaccine when it comes to safety and efficacy, but others do worry: doubts are mostly related to the novelty of the vaccines, i.e. can we exclude already long-term side-effects and will the induced protection be long-lasting? Such fears are known to have a negative effect on HPV vaccine acceptability [146], [154], [163].

Some people are particularly worried about the HPV vaccine's potential interference with fertility. Specially in more traditional or patriarchal communities targeting only girls against an STI raises extra concerns [146]. In these settings, vaccinating both boys and girls might boost the vaccine's credibility. Also, given the faith people put in physician's advice, they are in place to counteract doubts and provide correct information [95], [100], [101], [145].

Influence on sexual behaviour

Due to the sexual nature of cervical cancer, the HPV vaccine is also believed to encourage early sexual onset, promiscuity or unsafe sex according to some societies [95], [112], [146]–[149], [154], [159], [160], [162], [182], [183], [185]. Offering protection against an STI could be interpreted by the targeted young girls as an approval to become sexually active or could result in risk compensation. In Denmark, for instance, young women mentioned that due to the vaccine a false sense of security might be created among vaccinated people, which could lead to more high-risk sexual behaviour [192]. In gen-

eral however, these concerns are only reported by a minority, often concentrated among conservative, religious affiliations. Nonetheless, it does jeopardize acceptability and subsequently coverage and herd immunity. Until this moment, a number of studies have shown no increase in sexual activity among those vaccinated [193], [194].

Related to this is that some people worry about stigmatization: vaccinating against an STI is openly saying that the girl is or will soon become sexually active. This might be the reason that acceptability tends to rise if the vaccines are offered to older girls. Seemingly, for some people it is more acceptable to vaccinate adolescent girls and young women against cervical cancer as opposed to young adolescents [95], [112], [147], [149], [154], [159], [183], [185].

Practical barriers

Time and money constraints obviously also interfere with HPV vaccination intentions. Especially the latter barrier is often mentioned, which is of great concern: the capacity of the vaccine to close the gap of health inequality when it comes to cervical cancer, is jeopardized when people refuse to vaccinate based on cost or insurance status. Both in high- and low-income countries, cervical cancer will remain ‘a disease of the poor’ when the vaccine is not (sufficiently) subsidized [95], [146], [160], [195]. Acceptability and subsequent uptake of the vaccine will thus highly depend on programmatic decisions reducing investments to be made by the target group, such as transport, both financial and in terms of time. Also, different vaccination schedules, and more particularly reducing the need for several doses, can significantly lessen the burden and thus help increasing willingness to vaccinate [168].

Similarly, and linked with the above-mentioned importance of awareness, acceptability of the HPV vaccine is highly influenced by health professionals’ recommendation. As such, access to health care and contact moments to discuss HPV vaccination with a physician are identified as important determinants [95], [100], [101], [145]. While this is of course strongly related to the quality and coverage of the local health care system, willingness to invest personal time to visit a health centre will again play a role. Additionally, in order

to reach the target group with crucial information regarding cervical cancer and HPV vaccination, as well as to inform them on practical issues such as cost, possible reimbursements or the whereabouts of the vaccination effort, other promotional activities than face-to-face client-provider visits could also enhance the flow of information.

3.1.2 HPV vaccine acceptability studies in Sub-Saharan Africa

Several HPV vaccine acceptability studies were implemented in HIC even before the vaccines were approved. The bulk of studies is still carried out in industrialized regions but over the last five years, LMIC and more importantly countries with high cervical cancer incidence are also studying their population's readiness towards HPV vaccination [121], [126], [146], [168]–[184], [196]–[205]. While the main results are similar - high acceptability is reported as well as fear of side effects - some context specific factors emerge. An important conclusion is that general awareness is even lower and the aetiology of cervical cancer is practically unknown. Although this does not always impede high acceptability, it does contribute to myths and rumours. Terminology issues - e.g. cervix is not always translatable in the local languages - add to this problem [178], [181].

In addition, in Sub-Saharan African communities, distrust towards the vaccines might not only originate from the novelty of the vaccine but also from a generally more suspicious attitude towards the health system. According to formative research in low-resource settings (Vietnam, Peru, Uganda and India), people question the vaccinators' ability to safely administer the vaccines, doubt they will use clean needles or are afraid expired vaccines will be used. Additionally, vaccines are believed from lower quality than those used in HIC or, people tend to believe that Western companies use their communities to experiment with unapproved medicines [146]. Again it is yet to be seen if this can be overcome or if this will hamper vaccination behaviour eventually.

Another factor that might be more pronounced in Sub-Saharan African studies is the difference in involvement or attitude of men and women regarding HPV vaccination. While women tend to know

more about cervical cancer - are more targeted in sensitization programmes - and are often hold responsible for the health of family members, they might lack decisive power or financial liberty [169], [180], [184], [206]. In addition, women in Uganda have reported a non-supportive role of their partners when it comes to vaccination [206].

Finally, HPV vaccine refusal based on fear for sexual inhibition or fertility interference might be more present in African settings, where perceptions are often traditional and diverse and a moralistic or paternalistic approach towards young girls is common. Also stronger religious convictions might play a role here. Some studies have indeed already reported concerns related to vaccinating young girls against an STI but it is not clear if this will actually inhibit vaccine uptake [170], [176].

However, while these factors can lead to lower HPV vaccine acceptability, there might also be an extra driver in Sub-Sahara Africa compared with HIC. People are still more conscious about the impact of vaccines on child health as opposed to people in HIC who have not experienced the threat of childhood diseases [206]. As such, African communities can value more the benefit of prevention over treatment.

3.1.3 Theoretical frameworks: Health behaviour theories

The Health Belief Model

The main interest of acceptability studies is to find predictors and barriers for acceptability and consequently for behaviour. Frequently these studies apply health behaviour constructs that include a variety of psychological factors (e.g. attitudes, beliefs, perceived barriers) to associate them with acceptability. A proven health behaviour theory to predict vaccination is the **Health Belief Model** (HBM) (table 3.2) [207], [208], which is also commonly used in HPV vaccine acceptability studies [143], [158], [183]. The authentic HBM indicates that for an individual to take action (e.g. to have one's daughter vaccinated), this person would have to (1) perceive the

disease at least as moderately severe; (2) perceive a susceptibility or vulnerability by the disease; (3) believe that there are benefits in taking the preventive action; (4) not perceive major barriers obstructing the action. Self-efficacy (one’s perceived ability to undertake the action) and cues-to-action (triggers such as multimedia advertisement or a physician’s recommendation) were added later in order to improve the theoretical model [209].

Table 3.2: Constructs of the Health Belief model

BELIEF	DEFINITION
Perceived susceptibility	What chance individuals believe they have of getting a specific health condition
Perceived severity	How seriously individuals believe a certain condition will affect their life situation
Perceived benefits	The benefits individuals believe there are in taking action to address the health condition
Perceived barriers	The road blocks or threats individuals anticipate in trying to address the health condition
Cue to action	External or internal factors that stimulate individuals to act (based on their perceptions)
Self-efficacy	The level of confidence individuals have in their ability to act

Brewer et al. (2007) and Cunningham et al. (2014) have reviewed HPV vaccine acceptability studies focussing on the HBM constructs in the USA and Africa respectively [158], [183]. The former review included twenty eight studies, the latter fourteen (among ten countries). Perceived susceptibility reported in African studies was not always high which might have been caused by misunderstandings such as believing the disease is inherited. In general, own risk was considered lower than a daughter’s risk of HPV infection or cervical cancer. While studies in the USA revealed a positive relation with acceptability [158], Cunningham et al. (2014) reported either no correlation [169] or also a positive one ([170], [183]). Among all studies, the majority of the participants agreed that cervical cancer is a serious illness (perceived severity) [158], [183]. While two studies, in

Botswana and Ghana [169], [170], detected an association between HPV vaccine acceptability and perceived severity, the other studies were not conclusive [158], [183]. Perceived effectiveness of the HPV vaccine was the main benefit investigated while in terms of barriers cost and safety concerns were discussed, among others. The link with acceptability remains again unclear for both constructs: reported barriers do not necessarily deter acceptability and trusting the vaccine's efficacy does not always lead to higher willingness to vaccinate [158], [183]. Finally, cues to action indicated by American studies included physician's recommendation and school requirement, and although this was only reported by few studies, a positive association with acceptability was found [158]. In the African studies, cues to action also enclosed endorsement from the government and acknowledgement by community members (associations with acceptability were not investigated) [183].

The indecisiveness of the mixed results reported above induces the idea that the HBM is not always applicable in the context of HPV vaccine acceptability. Given that the reviews are based on studies in different countries and settings (rural, urban, clinics) and include different participants (adolescents, young women, students and parents), it might however be that the model only predicts HPV vaccine acceptability in certain situations. In addition, the constructs used are not standardized and are thus measured in different ways which may also affect the predictive value of the model in each study.

Finally, and more importantly, the original HBM stipulates associations of constructs with a certain action, and not with acceptability or any other precursor of behaviour. A theory that does include an antecedent such as acceptability is the **Theory of Planned Behaviour**. This other well-known model estimates the occurrence of a certain action under the assumption that the action was intentional: the three main constructs (attitude, subjective norms and perceived behavioural control) are correlated with intention, which is considered the final predictor of the actual behaviour. Some studies, applying the TPB, did indeed find a relation between intention and vaccination behaviour, or support for the TPB in general [210]–[212].

So although the HBM constructs were not originally thought of as determinants of precursors, many researchers do verify their correlations with acceptability or willingness to vaccinate similar to the idea of the TPB that actions are preceded by intentions. Thoroughly investigating whether the HBM constructs actually predict acceptability and/or HPV vaccine uptake seems necessary in order to justify the use of the model in HPV vaccine acceptability studies.

3.1.4 Limitations of acceptability studies

As mentioned above, HPV vaccine acceptability studies are mainly carried out in Western settings, while research in LMIC, i.e. where the vaccines can have the greatest impact, is still scarce. Furthermore, due to convenience sampling, the majority of the studies focus mainly on white, Caucasian people in urban settings. Participants are often recruited at colleges or health centres and very few studies have tried to identify cultural variations [103], [143], [158]. Acceptability studies in resource limited regions or targeting different groups of populations might give new insights on the vaccine decision-making process.

The results of HPV vaccine acceptability studies are also limited due to methodological issues. For example, the context in which HPV vaccine acceptability is measured, i.e. whether the vaccine is already accessible, will influence the measurement greatly. In addition, the cross-sectional character of most studies inhibits investigating the entire pathway of decision making, i.e. the translation of acceptability into actual behaviour. Furthermore, the majority of the studies only gauge personal opinions - sometimes driven by 'traditional' cognitive health behaviour theories at that level - excluding many other important determinants related to vaccine uptake. These major limitations and possible solutions are further discussed below.

Acceptability as precursor of behaviour

By measuring acceptability one obtains an estimate of the potential coverage rate that could be reached with an ideal implementation design. However, various acceptability studies were conduc-

ted before the HPV vaccine was actually on the market, gauging acceptability, barriers and attitudes in a purely hypothetical situation. As such, actual behaviour and encountered hindrances might be different from those foreseen. But also in situations where the HPV vaccine is not yet widely available or accessible for the general population, participants might report fairly conjecturally given the novelty of the vaccine and the little experience they have with it. Consequently, assessed willingness to vaccinate might be a poor predictor for subsequent behaviour; once the opportunity to vaccinate against cervical cancer actually occurs, people can react differently or can be influenced by experiences (from thirds) [213]. Indeed, a review by Trim et al. (2012) showed that in HIC reported intention was highest in 2005, i.e. before the vaccines were licensed, then dropped a bit, to rise again until 2008 and from then on decline onwards [185]. Introduction of the HPV vaccine may have caused these shifts in measured acceptability. Therefore, extra attention should go to users' perspectives, exploring how people choose and gathering feedback on how they experienced vaccination, rather than solely trying to gauge acceptability at a certain moment in time [213].

Another step would be to implement longitudinal studies, to assess both the precursor and the actual action itself, and to investigate to what extent the precursor truly estimates the behaviour [214]. Unfortunately, the majority of the HPV vaccine acceptability studies now are cross-sectional, measuring acceptability through quantitative or qualitative research methods, and do not implement a follow-up round to assess actual uptake. To our knowledge, very few studies - and all in HIC - have compared expressed acceptability and/or intention to vaccinate to actual HPV vaccine uptake through longitudinal surveys and those that did found contradictory results regarding the correlation between the antecedent and the actual vaccination behaviour [210], [211], [215]–[219]. More longitudinal research is necessary to get a better understanding of the link between HPV vaccine acceptability and behaviour in different contexts.

A last remark regarding the methodology used in quantitative acceptability studies, is that they often rely on (univariate) correlations to investigate determinants of acceptability. While these asso-

ciations are often wrongly interpreted as causal links, they also don't take into account the more complex pathway of decision-making. Mediating analysis such as structural equation modelling should be considered in order to better understand underlying mechanism of behaviour [220].

Acceptability versus structural factors

While acceptability might be a first step towards HPV vaccination, there are of course several factors that may impede the intention and thus the translation towards behaviour. Many of these variables might be related to community or organizational characteristics. For example, the importance of community influencers to reach high uptake reported in the post-vaccination studies of the demonstration projects in Uganda and Vietnam imply that people reach out to others in order to make a decision [121], [130]. Refusal of community chiefs might thus hamper vaccination regardless of one's own (initial) intention. Also, as mentioned above, even if HPV vaccination is accepted and considered a priority, programmatic design can impose too much when it comes to time and financial investments. As such, studies which only take into account personal drivers and barriers are limited and might oversee important organizational hindrances [121]. Unfortunately, the majority of the HPV vaccine acceptability studies don't investigate factors other than at individual level.

Also the application of health behaviour theories often encourages the use of personal factors only: while theories provide a framework for guiding the study and help researchers putting the problem in a certain perspective, directing the design of the study in line with this perspective, they also might blind the researcher for important determinants other than the constructs. In the case of applying the Health Belief Model in the context of HPV vaccination, indeed only personal attitudes are investigated.

Although it is possible that in certain contexts personal opinions are indeed the main components of action, this might be different in other situations. By reviewing evaluations of HPV vaccination programmes in LMIC and interviewing key informants, Wigle et al. (2013) found that besides sociocultural barriers, health systems and

political barriers are at least as important [118]. So besides studying acceptability, attention should also go to those factors beyond personal opinion.

Finally, rigorous testing of behavioural theories in several (cultural) contexts regarding different preventive techniques is seldom done [214], [220]. Since the development of many theories is Western based and validation has also mainly been carried out in HIC, one can question the applicability of behavioural theories in other settings. The findings that health system barriers might be more important than sociocultural barriers with regard to HPV vaccine uptake in LMIC [118], indicate that theories at a personal level might not be that applicable in settings where the quality of the health services is not guaranteed. It is therefore important to test and compare constructs and health behaviour theories in order to understand the efficacy of these theories in predicting health behaviour in different settings.

3.2 Vaccine hesitancy

During the past few years, the term vaccine hesitancy has popped up in vaccination literature regarding reluctance towards immunization, which is documented in both **LMIC and HIC**. However, definition and usage - as attitude, behaviour or decision making process - were not always consistent. Therefore, the WHO Strategic Advisory Group of Experts (SAGE) established a Working Group on Vaccine Hesitancy in 2012 to define and review vaccine hesitancy. In the following years, reports and publications showed the results of their work, among which following definition and determinants of vaccine hesitancy: [221]–[223].

VACCINE HESITANCY *"Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines."* [223].

3.2.1 Determinants of vaccine hesitancy

Contextual, individual and group, and vaccine/vaccination specific influences

In terms of determinants of vaccine hesitancy, the SAGE Working Group proposed two models. A first model they developed is a more complex model arranging identified determinants in three categories: contextual, individual and group, and vaccine/vaccination specific influences (figure 3.1). While doing so, they reviewed literature and noticed that, like in HPV vaccine acceptability research, determinants are often linked with the core constructs of popular social cognitive models, which are however limited and miss important factors [221], [222], [224]–[226].

Figure 3.1: SAGE Working Group Determinants of Vaccine Hesitancy Matrix

<p><u>CONTEXTUAL INFLUENCES</u> Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors</p>	<p>a. Communication and media environment b. Influential leaders, immunization program gatekeepers and anti- or pro-vaccination lobbies. c. Historical influences d. Religion/culture/ gender/socio-economic e. Politics/policies f. Geographic barriers g. Perception of the pharmaceutical industry</p>
<p><u>INDIVIDUAL AND GROUP INFLUENCES</u> Influences arising from personal perception of the vaccine or influences of the social/peer environment</p>	<p>a. Personal, family and/or community members' experience with vaccination, including pain b. Beliefs, attitudes about health and prevention c. Knowledge/awareness d. Health system and providers-trust and personal experience. e. Risk/benefit (perceived, heuristic) f. Immunisation as a social norm vs. not needed/harmful</p>
<p><u>VACCINE/ VACCINATION-SPECIFIC ISSUES</u> Directly related to vaccine or vaccination</p>	<p>a. Risk/ Benefit (epidemiological and scientific evidence) b. Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine c. Mode of administration d. Design of vaccination program/Mode of delivery (e.g., routine program or mass vaccination campaign) e. Reliability and/or source of supply of vaccine and/or vaccination equipment f. Vaccination schedule g. Costs h. The strength of the recommendation and/or knowledge base and/or attitude of healthcare professionals</p>

source: SAGE Working Group 2014

Vaccine confidence, complacency and convenience

A second model that was identified was a framework that was actually introduced by the WHO EURO Vaccine Communications Working Group in 2011, presenting the "three C's", which stand for vaccine confidence, complacency and convenience, as influencing factors of vaccine hesitancy.

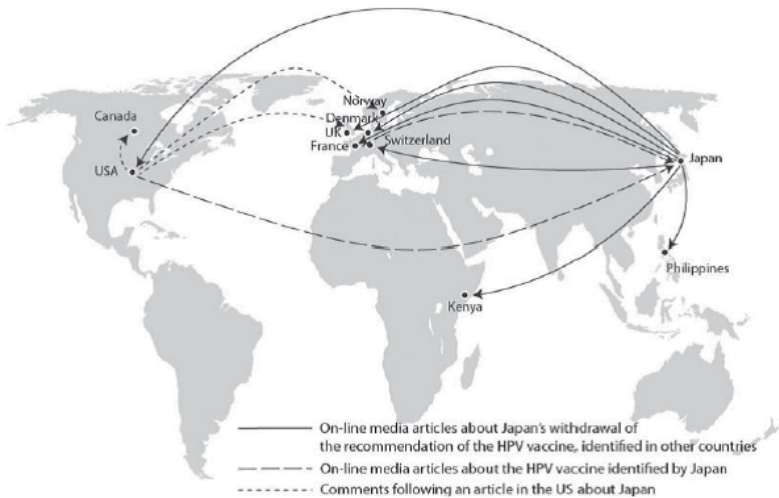
VACCINE CONFIDENCE *"Trust in the effectiveness and safety of vaccines and in the system that delivers them, including the reliability and competence of the health services and health professionals and having trust in the motivations of the policy makers who decide which vaccines are needed and when they are needed. Vaccination confidence exists on a continuum, ranging from zero to 100 percent confidence. Vaccination confidence is only one of a number of factors that affect an individual's decision to accept a vaccine."* [221]

VACCINE COMPLACENCY *"Vaccine complacency exists where perceived risks of vaccine preventable diseases are low and vaccination is not deemed a necessary preventive action. Besides perceptions of the threat of disease severity and/or transmission, complacency about a particular vaccine or about vaccination in general can be influenced by under-appreciation of the value of vaccine (effectiveness and/or safety profile) or lack of knowledge. Immunization programme success may result in complacency and ultimately, hesitancy, as individuals weigh risks of vaccines against risks of diseases that are no longer common as a result of immunization."* [221])

VACCINE CONVENIENCE *"The quality of the service (real and/or perceived) and the degree to which vaccination services are delivered at a time and place and in a way that is considered appealing, affordable, convenient and comfortable, also affects the decision to vaccinate. Vaccination convenience and complacency are also determined by the priority that an individual places on vaccination."* [221]

Vaccine confidence is probably by far the most documented determinant. Especially in the last decade, several vaccine boycotts have increased the interest in trust in vaccines, in particularly in vaccine safety and effectiveness. In Nigeria, for example, the polio vaccine was brought in discredit in 2003-2004, leading to outbreaks across three continents. Similarly, the H1N1 vaccine caused a lot of disturbance during the pandemic in 2009-2010, while more recently, the HPV vaccine was rejected in Spain, Greece, the Netherlands, Cameroon, India and Japan. In all countries, a drop in HPV vaccine acceptability and uptake was seen after incomplete messages regarding non-associated adverse effects were circulated by the media [127], [128], [150], [227]–[231]. In the latter country, where the government stopped actively recommending the vaccine, coverage rates even dropped from 70 percent to 5 percent. In addition, rumours were rapidly picked up by media from other countries resulting there also in confidence loss (figure 3.2) [128], [230], [231].

Figure 3.2: Global transmission of HPV related reports and rumours from and towards Japan in 2014



source: Larson 2014

Also anti-vaccination groups - who believe that vaccines hamper (the development of) the immune system, cause diseases such as autism and autoimmune disorders, and are introduced out of financial interest of the pharmacy - spread their messages quickly and far-out by (social) media. Research showed that the majority of Youtube videos regarding HPV vaccination were negative in tone and that videos disapproving the vaccines were more viewed [232]. Through these channels they can directly influence people's beliefs about vaccines and consequently vaccination coverage. Generally, (social) media tend to publish more over-simplified, negative messages which endangers vaccine trust and induces loss in confidence and thus vaccine hesitancy [194], [233], [234].

In general, both models - the matrix and the three C's - include many factors that are traditionally addressed in vaccine acceptability studies, such as fear for side effects or perceived severity. This is not entirely surprising given that vaccine hesitancy can be defined as a continuum between full acceptance and outright refusal of a vaccine.

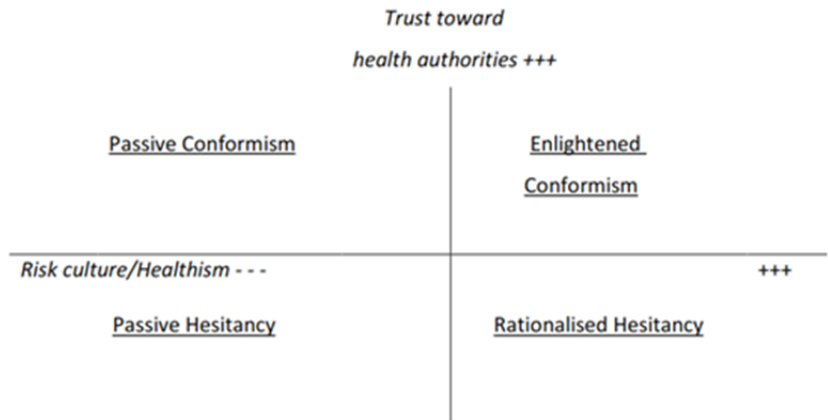
3.2.2 Vaccine hesitancy as a decision-making process

Peretti-Watel et al. (2015) further elaborated on the work of the SAGE Working Group and developed a theoretical framework to further minimize ambiguous notions. They argued that while vaccine hesitancy is often conceived as a temporary attitude of individuals who are situated in an anti/pro continuum, this does not imply that they are against or in favour of vaccination in general, but rather that they endorse intermediate feelings regarding one or more vaccines in particular. As such, it might be more appropriate to define vaccine hesitancy as a decision-making process. This process can be simple (without hesitancy), for people with strong pro-vaccine or anti-vaccine convictions, or difficult (with hesitancy) for those with doubts. Additionally, there is a third group, namely people who have little interest in the vaccine. So while this latter group shares the same behaviour as those who are doubting, i.e. delaying vaccination, and while they are also positioned in the intermediate of the anti/pro continuum, they are not committed to look for information to make a balanced decision [235]. Defining vaccine hesitancy as a

process rather than an attitude, i.e. a position on a pro/anti vaccination continuum, thus shifts the focus from an outcome of interest, i.e. vaccine uptake, delay or refusal, towards the pathway by which this behaviour is reached.

Finally, Peretti-Watel et al. (2015) created a framework in which four groups are identified - passive conformism, passive hesitancy, enlightened conformism and rationalized hesitancy - by combining two major factors of vaccine hesitancy: trust in authorities, and risk/culture and healthism, i.e. exerting autonomy over and supervising health (figure 3.3). People with low trust might thus shift, for example after being exposed to promotion, from passive to rationalized hesitancy; lately this is observed in some high-educated subgroups, merely in HIC [235]. This approach clearly allows for more differentiation than more traditional divisions of vaccinated vs. non-vaccinated, or acceptors vs. non-acceptors of vaccines.

Figure 3.3: Vaccine hesitancy along two axes: commitment to risk culture/healthism (horizontal) and distrust/trust toward health authorities



source: Peretti-Watel et al. 2015

3.3 Rationale

Cervical cancer imposes a huge health threat on women in Sub-Saharan Africa and the burden will only increase - due to the current demographic explosion - if no extra effort is undertaken. The development of primary prevention techniques, i.e. HPV vaccines, can however induce a turning point in the process of eradicating HPV infections and the associated cancers.

Prior to introducing the HPV vaccine in national immunization programmes, acceptability studies are encouraged in order to estimate a population's readiness for this new preventive method. However, even though a lot of effort is put into measuring HPV vaccine acceptability, it is not guaranteed that

- from a public health perspective it is justified to measure acceptability: is acceptability a major determinant of uptake or not?
- we use the correct theories to identify determinants of vaccine acceptability and uptake.
- acceptability studies cover the most important factors leading to successful vaccination programmes.

Few studies have indeed investigated whether high HPV vaccine acceptability really leads to high uptake. Similarly, pilot vaccination projects provide limited insight in how they reached good coverage: to what extent are personal beliefs important and at what point do organizational decisions play a role in achieving high uptake? In order to inform countries on how to introduce HPV vaccination successfully, a critical reflection on the usefulness of acceptability studies is necessary, as well as evidence based lessons learned from demonstration projects.

Part IV

OBJECTIVES

General objective

The general objective of this doctoral research is to contribute to the understanding of factors influencing HPV vaccine introduction.

Specific objectives and research questions

Objective 1: To determine the acceptability and subsequent uptake of the HPV vaccine in the context of an HPV pilot vaccination programme in Eldoret, Kenya.

1. What are determinants of HPV vaccine acceptability and uptake - is acceptability a predictor for uptake?
2. Which barriers to vaccinate do people foresee and which are eventually encountered during a vaccination programme?

Hypotheses: Acceptability will be high yet uptake will be somewhat less: both outcomes will be related to each other, but precursors of behaviour such as acceptability are not always translated into action. Knowledge will be associated with acceptability and uptake, but HPV vaccination will also be influenced by practical barriers. Finally, fear for side effects will be a major reason for refusing the vaccine as opposed to conservative attitudes towards vaccinating young girls against an STI; for many, protection against cervical cancer will be the convincing driver.

Objective 2: To ascertain whether health behaviour theories can be effectively applied to predict HPV vaccination in Eldoret, Kenya.

1. Do the constructs of the Health Belief Model predict uptake?
2. Do the constructs of the Health Belief Model predict acceptability?

3. What is the added value of a precursor of behaviour, such as acceptability or intention, in the Health Belief Model?
4. What is the added value of mediating and moderating personal characteristics?

Hypotheses: Most constructs of the Health Belief Model will predict uptake but associations with acceptability will be higher. As such, adding a precursor of behaviour will increase the predictive value of the theory. Socio-demographic factors will have a substantial, direct impact on behaviour and will hence improve the model.

Objective 3: To identify factors that influence successful introduction of an HPV vaccination programme in Eldoret, Kenya.

1. How were people mobilized - which factors defined the success of the promotional strategy, taking into account determinants of vaccine hesitancy (figure 3.1):
 - Contextual influences, such as the communication environment and religious or cultural characteristics?
 - Individual and/or group influences, such as knowledge and beliefs about cervical cancer, vaccine related experiences and health literacy?
 - Vaccine/vaccination-specific issues, such as health care providers' capacities to promote, and attitude towards the vaccine and the programme?
2. Did people have a good understanding of HPV and cervical cancer after the programme had finished?
3. How did the service delivery operations, i.e. the vaccination strategy, influence vaccine uptake, taking into account determinants of vaccine hesitancy (figure 3.1):
 - Contextual influences, such as socio-economic or logistic barriers?
 - Individual and/or group influences, such as trust in the health system?

- Vaccine/vaccination-specific issues, such as the administration schedule or novelty and reliability of the vaccine?

Hypotheses: Awareness will improve but correct understanding of HPV and cervical cancer will still be limited; this will not influence vaccine uptake. Programmatic design, such as assuring absence of logistic barriers and clear communication regarding the availability of the vaccine will be strong determinants of vaccine uptake. Therefore, direct communication and recommendations of health care providers with the caregivers of the girls will be crucial. Failure of achieving such contact moments will lead to poor uptake and will allow the spread of rumours. In addition, given the novelty of the HPV vaccine, hesitancy towards the vaccine will be common, mainly due to lack of confidence.

Part V

**STUDY SETTING AND
METHODOLOGY**

Chapter 4

Study setting

4.1 HPV infections and the burden of cervical cancer in Kenya

4.1.1 Cervical cancer

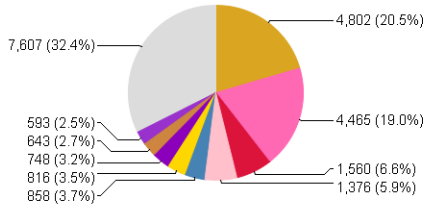
Kenya has one of the highest incidence rates in the world for cervical cancer. With a crude incidence of 22.4/100,000 a year and age-standardized of 40.1/100,000, it is the most common female cancer in Kenya, leaving even breast cancer behind. Likewise, cervical cancer is also the most lethal cancer among Kenyan women (mortality of 11.5/100,000 a year; age-standardized 21.8/100,000) (see figure 4.1). Age specific incidence and mortality rates are similar to those of other Eastern African countries and of course far above the world averages (figures 4.2 and 4.3) [236].

Figure 4.1: Cancer incidence and mortality among women in Kenya; estimations for 2012

International Agency for Research on Cancer



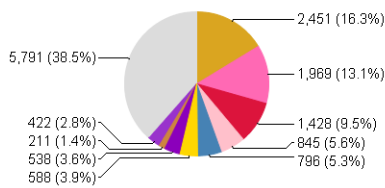
Incidence



International Agency for Research on Cancer



Mortality



- Cervix uteri
- Breast
- Oesophagus
- Kaposi sarcoma
- Stomach
- Colorectum
- Ovary
- Corpus uteri
- Non-Hodgkin lymphoma
- Other and unspecified

source: Globocan 2012

Figure 4.2: Age specific incidence rates of cervical cancer in Kenya, Eastern Africa and the world; estimations for 2012

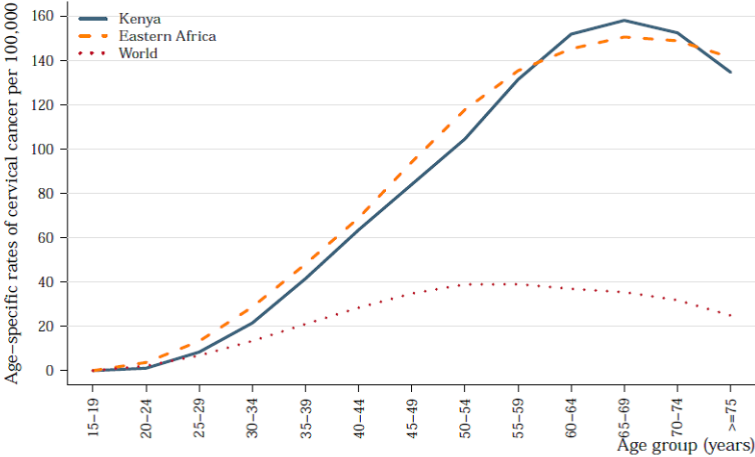
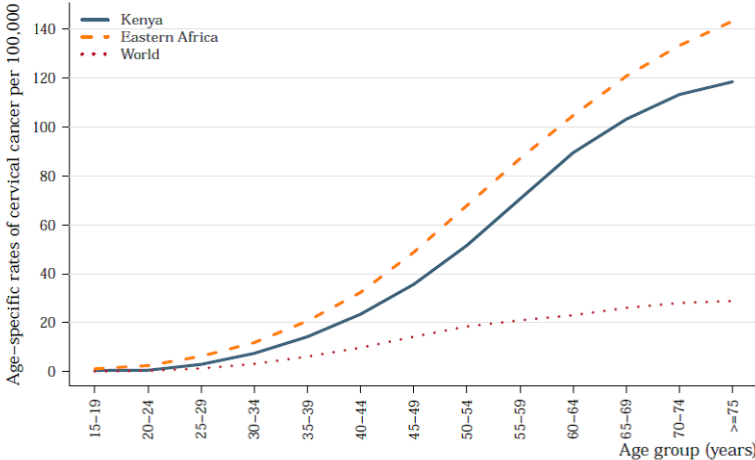


Figure 4.3: Age specific mortality rates of cervical cancer in Kenya, Eastern Africa and the world; estimations for 2012



source: Human Papillomavirus and Related Diseases Report - KENYA - 2015

As a result of the high incidence and the poor prognosis of most patients, cervical cancer poses a high burden on the Kenyan health system. The low survival chances are often due to late detection and limited prevention and treatment options. Data on cervical cancer screening is scarce but clearly shows inadequate usage. According to the WHO Household survey of 2002, only 4 percent of urban women and 2.6 percent of rural women had been screened in the last ten years [236]. A more recent study (2007-2009) by Rositch et al. (2012) in Nairobi measured that 14 percent of the female participants had ever had a pap smear and only 18 percent recognized screening as the most conventional method to prevent cervical cancer [237]. In Kisumu, on the other hand, only 6 percent of the women visiting health facilities reported to be screened previously (2007) [238].

Also, while the disease is highly prevalent and has a devastating impact on the reproductive health of many women, knowledge remains low in Kenya. For example, a study among women in health facilities near Kisumu showed that only 22 (15 percent) of them had ever heard of cervical cancer [168]. Older studies also present low knowledge rates and one study showed that even among cervical cancer patients only 52 percent had heard about the disease (2003-2005) [239], [240].

In addition to low awareness and limited health services, which inhibits people to look for preventive medicine, there are many more factors that stimulate the expansion of this epidemic. Onset of sexual activity at young age and unsafe sexual practices, both recognized as risk factors for cervical cancer, are rather common in the Kenyan community. According to the latest Demographic and Health Survey, 12 percent of women age 20-49 years had their sexual debut before the age of 15 and about half of them before they were 18 years old. Regarding safe sex, only 24 percent of women reported condom use at first sexual encounter, and among the sexually active women age 15-24, 33 percent had engaged in higher-risk intercourse during the last 12 months [241].

4.1.2 HPV infections

In Kenya, various studies have defined the prevalence of HPV. A study in Mombasa showed a prevalence of 42.3 percent of infection with any type of HPV. Of those infected, 46 percent had a multiple infection and the most prevalent types were HPV 58, 16, 53, 18 and 6 (decreasing order) [242]. Another study in Nairobi found 44.3 percent of cervical samples positive, with HPV 52, 16, 35 and 66 as most present types (decreasing order). HPV 16, 52 and 35 were frequently detected in high-grade lesions [243]. Among HIV negative and HIV positive women with invasive cervical cancer, the same distribution of HPV types is reported for both groups: HPV 16 and/or 18 were found in over 60 percent of the cancers. Multiple infections were, as expected, also more present among the HIV positive women [244]. Finally, in a study among female sex workers in Mombasa, HPV 16 and/or 18 did not seem the most present types: of the screened women, 22.8 percent was positive for HPV 16 and/or 18 while almost 50 percent was infected with other HPV types. Of all women, 35.2 percent was HIV infected and co-infection with HPV was seen among one fourth of them. Among the HIV positive women, cervical abnormalities were more present [245].

In conclusion, even though not all studies detected HPV 16 and 18 as most present HPV types, both viruses clearly contribute to the spread of cervical cancer in Kenya. Therefore, we can conclude that the application of the HPV vaccines would have a major impact if adequate coverage rates is reached.

4.2 The HPV vaccination demonstration project in Eldoret, Kenya

Through the GARDASIL Access Program (GAP), the Moi Referral and Teaching Hospital was granted 9,000 doses of the quadrivalent vaccine to vaccinate young girls in Eldoret, Kenya. The vaccines were used to pilot HPV vaccination focusing both on completion of the scheme (three doses in six months) and safety. Hospital-based vaccination was chosen to reduce the costs of the programme.

In order to avoid excess demand, promotion of the programme was originally restricted to a limited number of government primary schools. Only schools within the Eldoret Municipality were considered to avoid non-uptake due to transport issues. Up to ten schools (out of forty-two) were randomly selected until a total of about 4,000 eligible girls was reached, expecting a coverage of around 75 percent (3000/4000). However, if eligible girls who were not enrolled in these schools showed up at the vaccination site (i.e. the hospital), they were not refused.

The vaccines were offered to girls in classes 4 to 8, approximately 9 to 14 years old. The teachers were sensitized by health staff and through providing leaflets, and were subsequently asked to instruct students and parents. To do so, some schools organized parent meetings, other schools distributed letters while others just asked the students to inform their parents about the upcoming vaccination programme.

Vaccination took place on Saturdays and Wednesdays, from May 2012 to March 2013. After consent was obtained from an adult caregiver, nurses from the hospital vaccinated the girls for free. Given that a three dose schedule was planned, a vaccination card with a next appointment was given after the first and second dose. Additionally, nurses called the caregiver to remind them about the second and third dose if they had not showed up on the scheduled day.

Because of the low response during the first three months of the programme, other schools in the County, government and private, were also invited to participate from August 2012 onwards, and a local radio announced the vaccination opportunity as well. Consequently, sufficient demand was created and in September 2012, the programme stopped administering the first dose after reaching 3,000 girls in order to guarantee sufficient vaccines for the following doses.

Chapter 5

Study design

A mixed-method approach was chosen: quantitative data was collected, primarily to address the research questions related to specific objectives one and two (studying the gap between acceptability and uptake, and testing the HBM). A qualitative component, more specifically focus group discussions (FGD) with key stakeholders, was organized to answer the research questions of specific objective three (identifying factors that influenced the success rate of the programme).

5.1 The quantitative component: a longitudinal study

Given the dearth of longitudinal studies measuring HPV vaccine acceptability and uptake, a cohort study was set up. The study participants were mothers from eligible girl pupils who were enrolled in one of the ten initially selected schools of the HPV vaccination programme in Eldoret. The women were interviewed before the onset of the programme, assessing HPV vaccine acceptability (March 2012) and once it was finished, recording reported HPV vaccine uptake (May 2013). Through including mothers of eligible girls in the targeted schools, we assured that all participants would have had the option, in theory, to fully vaccinate their daughter against cervical cancer through the demonstration programme.

5.1.1 Recruitment of participants

Baseline After obtaining permission of the head teachers of the ten initially included schools, girls were randomly selected from the class lists of classes 4-8: the number of selected girls per school was proportional to the total number of girls in standard 4-8 of the ten selected schools, and the number of selected girls per class was proportional to the total numbers of girls in the classes 4-8 of that particular school. A short informative talk was given to teachers present, and in all schools leaflets were left behind to inform all teachers about the longitudinal study and the upcoming vaccination programme. Teachers were asked to hand out invitation letters to the selected girls. Through these letters, directed to the mother or female guardian, potential participants were invited to attend a face-to-face, informative session and interview regarding cervical cancer prevention, the next Saturday at school. If they were not able to make it but were willing to participate, they could return the invitation letter leaving us their telephone number so that we could reach out to them and schedule another appointment. They were given the choice to be interviewed at school or any other place they would prefer. Given the study context, all participants were mothers/guardians of young, teenage girls, living in an urban/semi-urban area.

Follow-up At the start of the baseline interview, it was made clear to the invited women that we intended to contact them again one year later, to ask for their final decision and actions regarding vaccinating their daughter against cervical cancer. Once agreed on, contact information was collected, including telephone numbers of the participant and people close to them, as well as a description of how to reach their house. These data were used to contact and invite the same women the year after for the follow-up interview. Again, interviews took place at school, at home or any other place of their choice. If women were unable to attend a face-to-face interview, some key questions regarding the uptake of the HPV vaccine were asked over the phone.

Sample size calculation To estimate the relation between baseline acceptability and vaccine uptake reported at follow-up, sample size for comparing two proportions was calculated, expecting acceptability among 75 percent of the participants and uptake among 60 percent of the non-acceptors and among 80 percent of the acceptors (power 80 percent). Anticipating non-participation and loss to follow-up, we doubled the required sample size of 234, thus aiming at distributing 468 invitation letters for the baseline study.

5.1.2 Procedures and measurements

Baseline A structured questionnaire was developed, using the HBM and the TPB as main frameworks to assess HPV vaccine acceptability, intention to vaccinate, and attitudes towards cervical cancer and HPV vaccination. In addition, socio-demographics and knowledge and awareness were assessed. Furthermore, the baseline interview included an informative session in order to allow the interviewee to make informed decisions about HPV vaccination. Leaflets with comprehensive facts and pictures about cervical cancer and HPV vaccination assisted the interviewer during these talks and assured consistency. Also the upcoming HPV vaccination programme was mentioned during this informative moment in order to ensure that women understood that the vaccine would soon be freely available at the hospital. Information was shared after gauging knowledge and awareness but before assessing willingness to vaccinate and theory related constructs.

Follow-up During the follow-up interview, participants were asked whether or not their daughter had received the HPV vaccine and if yes (i.e. had received at least one dose), what difficulties they had encountered in doing so. Women who had not vaccinated their daughter were asked to explain what had stopped them or why they had actively refused the HPV vaccine for their daughter. Finally, also the promotion of the programme was evaluated, i.e. whether or not the women had received information about HPV vaccination and the whereabouts of the programme - other than what they had received during the baseline interview - and whether this information had been useful to them.

5.1.3 Data management and analysis

In a first step of the analysis, determinants of HPV vaccine acceptability and uptake were identified using bivariate and subsequently multivariate logistic regression. While doing so, also the relation between these two outcome variables was investigated. Given the survey design, adjusted odds ratios were calculated taking into account the schools as primary sampling unit and using weights to adjust for discrepancies between the sample and the population. This post-stratification corrected for differences in the distribution of women invited per school compared with the proportion of girls in classes 4 to 8 of each school on the total number of girl pupils in these classes among the ten schools. In addition, a descriptive analysis of the follow-up data was carried out to gain insight in the barriers women had encountered while trying to vaccinate their daughter or reasons why they had refused to do so.

Secondly, the HBM was tested applying structural equation modelling. This pathway analysis allowed to verify the mediating and/or moderating effect of the constructs on HPV vaccine uptake as well as of socio-demographic variables. The predictive value of the model expanded with willingness to vaccinate, as precursor of vaccine uptake, was also measured.

5.2 The qualitative component: focus group discussions

At follow-up, the quantitative data was complemented with FGD with key stakeholders. More particularly, fathers of eligible girls were invited as to understand the perspective of the male guardian related to HPV vaccination of young girls. Furthermore, teachers and vaccinators were included to obtain their view on the HPV vaccination programme and to evaluate their tasks, i.e. promoting HPV vaccination and administering the vaccines respectively. The FGD were coded and analysed openly and subsequently the results were shared with the programme coordinator as to obtain his view on the course and the evaluation of the programme.

5.2.1 Recruitment of participants

Fathers of eligible girls were contacted using the contact information of themselves and their partners gathered during the baseline study. Teachers were invited by visiting the schools and, after obtaining approval of the head teacher, addressing them and scheduling a FGD. In addition, leaflets with invitations were left behind for those teachers who were not present at the moment of the research team's visit. Finally, the vaccinators were notified of the FGD by the head nurse of the hospital who also had been in charge of organizing the work of the vaccinators during the vaccination programme.

5.2.2 Measurements

Both fathers' and teachers' knowledge regarding cervical cancer and HPV prevention was assessed, as well as their attitudes towards the HPV vaccine. In all FGD, awareness regarding the HPV vaccination programme that had taken place was evaluated, while also the strengths and weaknesses of the programme were discussed and possibilities on how to improve future programmes were explored. Also the course of the programme was discussed, mainly with the vaccinators and the programme coordinator.

5.3 Research ethics

Ethical approval was obtained for both baseline and follow-up study, and the FGD by the ethical boards of Ghent University, Belgium, and Moi University, Kenya. Written and oral informed consent was obtained from the participants of the longitudinal study for the baseline and follow-up surveys, respectively. With exception of the women who were interviewed by phone, all interviewees of the follow-up survey received 200 KES (approximately 1.5 euro). In addition, signed consent forms were requested from all participants of the FGD and all received 200 KES (approximately 1.5 euro).

All field workers who assisted in this study were trained concerning three aspects: 1) basic knowledge and understanding of cervical cancer and HPV vaccination, 2) apprehension of the questionnaire or interview guide, and 3) awareness of the rights of, and skills to

approach (potentially vulnerable) participants. As such, interviewers were prepared to provide information when necessary and to explain potential participants that participation was voluntary and independent from their view regarding HPV vaccination.

Part VI

RESULTS

Outline

The results section is divided into three parts, following the objectives of the thesis. Each objective and its corresponding research questions are mainly addressed in one paper, although some are answered throughout the papers.

paper 1: published Vermandere H, Naanyu V, Mabeya H, Vanden Broeck D, Michielsen K, Degomme O. Determinants of Acceptance and Subsequent Uptake of the HPV Vaccine in a Cohort in Eldoret, Kenya. *PLoS One*. 2014;9(10):e109353. doi:10.1371/journal.pone.0109353.

paper 2: submitted - currently under review Vermandere H, van Stam MA, Naanyu V, Michielsen K, Degomme O, Oort F. Uptake of the Human Papillomavirus Vaccine in Kenya: testing the Health Belief Model through structural equation modeling on Cohort Data. *Globalization and Health*.

paper 3: published Vermandere H, Naanyu V, Degomme O, Michielsen K. Implementation of an HPV vaccination program in Eldoret, Kenya: results from a qualitative assessment by key stakeholders. *BMC Public Health*. 2015;15(1):875. doi:10.1186/s12889-015-2219-y.

Chapter 6

Determinants of Acceptability and Subsequent Uptake of the HPV Vaccine in a Cohort in Eldoret, Kenya

Paper 1: HPV vaccine acceptability and uptake In this first paper, the results of the longitudinal study are presented, i.e. HPV vaccine acceptability at baseline and HPV vaccine uptake at follow-up. While there are many acceptability studies - and the number is still growing, definitely in LMIC - only few have been able to also report the subsequent behaviour, i.e. vaccination. To our knowledge, this is the first cohort study in Sub-Saharan Africa covering determinants of both acceptability and uptake of the HPV vaccine, and the relation between these two outcome variables. At the same time, the paper reports on the perspectives of female caregivers of young girls towards the HPV vaccine and the demonstration programme, more particularly the barriers they foresaw and encountered.

Participation rates in the cohort study

Table 6.1 gives an overview on how invitations and subsequent participation rates led to the final study cohort: Aiming at 468 invitations, we eventually invited 472 mothers of girls in standard 4-8 of the ten schools initially targeted by the programme. Among these, 287 (60.81 percent) and 256 (89.20 percent) participated in the baseline and follow-up study respectively.

Table 6.1: Participation rates per school (10) and weights applied to adjust for the survey design

	Girls in school (proportion)	Girls invited (proportion)	Baseline participation (rate)	Weights adjusting diff. part. rates*	Post-stratification weights**	Follow-up participation (rate)
1	778 (0.14)	57 (0.12)	38 (66.67)	21.61	1.14	37 (97.37)
2	617 (0.11)	63 (0.13)	41 (65.08)	17.95	0.82	33 (80.49)
3	278 (0.05)	28 (0.06)	9 (32.14)	15.72	0.83	9 (100.00)
4	527 (0.09)	43 (0.09)	32 (74.42)	11.23	1.02	25 (78.13)
5	608 (0.11)	52 (0.11)	37 (71.15)	14.61	0.97	33 (89.19)
6	291 (0.05)	24 (0.05)	16 (66.67)	8.08	1.01	13 (81.25)
7	470 (0.08)	41 (0.09)	25 (60.98)	15.28	0.96	24 (96.00)
8	1087 (0.19)	93 (0.20)	44 (47.31)	47.72	0.97	42 (95.45)
9	240 (0.04)	20 (0.04)	15 (75.00)	5.00	1.00	14 (93.33)
10	769 (0.14)	51 (0.11)	30 (58.82)	26.38	1.26	26 (86.67)
Total	5665 (1.00)	472 (1.00)	287 (60.81)	-	-	256 (89.20)

* proportion girls in school/proportion girls invited)*(nr of girls invited - baseline participation

** Weights adjusting for difference in proportions 'number of girls in school' and 'number of girls invited' (proportion girls in school/proportion girls invited)



Determinants of Acceptance and Subsequent Uptake of the HPV Vaccine in a Cohort in Eldoret, Kenya

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Abstract

The development of Human Papillomavirus (HPV) vaccines provides new opportunities in the fight against cervical cancer. Many acceptability studies have revealed high interest in these vaccines, but acceptance is only a precursor of behavior, and many factors, at personal, community and provider level, may inhibit the translation of willingness to vaccinate into actual uptake. Through a longitudinal study in Eldoret, Kenya, HPV vaccine acceptability was measured before a vaccination program ($n=287$) and vaccine uptake, as reported by mothers, once the program was finished ($n=256$). In between baseline and follow-up, a pilot HPV vaccination program was implemented via the GARDASIL Access Program, in which parents could have their daughter vaccinated for free at the referral hospital. The program was promoted at schools: Health staff informed teachers who were then asked to inform students and parents. Even though baseline acceptance was very high (88.1%), only 31.1% of the women reported at follow-up that their daughter had been vaccinated. The vaccine was declined by 17.7%, while another 51.2% had wanted the vaccination but were obstructed by practical barriers. Being well-informed about the program and baseline awareness of cervical cancer were independently associated with vaccine uptake, while baseline acceptance was correlated in bivariate analysis. Side effects were of great concern, even among those whose daughter was vaccinated. Possible partner disapproval lowered acceptance at baseline, and women indeed reported at follow-up that they had encountered his opposition. In Kenya, women prove to be very willing to have their daughter vaccinated against cervical cancer. However, in this study, uptake was more determined by program awareness than by HPV vaccine acceptance. School-based vaccination might improve coverage since it reduces operational problems for parents. In addition, future HPV vaccination campaigns should address concerns about side effects, targeting men and women, given both their involvement in HPV vaccination decision-making.

Citation: Vermandere H, Naanyu V, Mabeya H, Vanden Broecke D, Michiels K, et al. (2014) Determinants of Acceptance and Subsequent Uptake of the HPV Vaccine in a Cohort in Eldoret, Kenya. *PLoS ONE* 9(10): e109353. doi:10.1371/journal.pone.0109353

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. Data have been deposited to Figshare: <http://dx.doi.org/10.6084/m9.figshare.1124187> and are also available from Ghent University: <https://biblio.ugent.be/publication/5644148>.

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Competing Interests: The vaccines were donated to Moi Teaching and Referral Hospital by Axios Healthcare Development (AHD) as part of the Gardasil Access Program, which was made possible by a pledge from Merck & Co., Inc. This donation was used for the study presented in this manuscript. Above mentioned statements do not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

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Introduction

Cervical cancer, caused by the oncogenic Human Papillomavirus (HPV), continues to be life-threatening for women worldwide. Especially in resource-limited settings, where screening is rare and high-quality treatment is either unavailable or unaffordable, health outcomes for infected women are poor. As a result, 85% of the 530,000 new cases annually occur in developing countries. Kenya is no exception and has one of the highest incidence and mortality rates associated with cervical cancer across the globe. [1–3]

With the introduction of HPV vaccines, primary prevention against HPV 16 and 18 has become a possibility. Given that the vaccines are most effective in HPV-naïve populations, young girls are the primary target group, with the aim of vaccinating before

sexual debut and as such avoiding potential infections. [4–7] Before implementing large-scale vaccination programs, however, various knowledge gaps need to be addressed [8]; in Kenya, for example, little is known about people's attitudes towards the vaccines and different vaccination strategies should be tested. [9,10]

Acceptability studies, primarily conducted in Western countries and some, more recently, in low- and middle-income countries (LMICs), generally indicate a high interest in these vaccines, but safety, cost and certain socio-cultural factors are often identified as obstructions. These concerns arise from the fact that the vaccines are relatively new and that it may be considered inappropriate to target young adolescent girls to prevent infection with a sexually transmissible virus. [11–16] Sub-Saharan African studies found similar results although cervical cancer awareness and knowledge

is often very poor. [9,10,15–29] A study in Ghana also reported a high willingness to vaccinate; yet, many participants were concerned about side effects, such as influencing the girls' fertility and unsafe administration of the vaccine (i.e. using unclean needles). [16] In Kisumu, West-Kenya, Becker-Dreps et al. initially found high acceptance (95%), but this rate dropped when mentioning that vaccination requires three shots (31%). [9] Moreover, acceptance has been suggested to vary among ethnic, religious and socio-economic groups. [30–32]

A recent review by Wigle et al. showed that in LMICs, health system and political barriers may impede the development of sustainable, successful programs more than socio-cultural obstacles do. For example, reaching the target population has proved to be challenging. [33] Adolescent care is often lacking or not prioritized in health centers, and while school-based delivery is mostly successful, it remains conditional on high attendance. [33,34] In addition, post-vaccination studies have revealed that vaccine uptake can be affected by program-related issues, such as community sensitization and involvement of the government. [35–38] Research should therefore go beyond the study of hypothetical acceptability and explore the entire pathway leading to vaccine uptake.

To this end, this longitudinal study aims to survey the acceptability, subsequent uptake and encountered barriers from the perspective of the mothers of young girls, in the context of a pilot HPV vaccination program in Eldoret, Kenya. This design enables us 1) to determine demographic predictors of baseline acceptability and uptake at follow-up, 2) to investigate to what extent acceptance itself is a predictor of behavior, and 3) to identify the barriers that were actually encountered as opposed to those foreseen. To our knowledge, this is the first longitudinal study measuring HPV vaccine acceptance and subsequent uptake in Africa.

Methods

The GARDASIL Access Program

This longitudinal study took place before and after the implementation of a pilot vaccination program. Through the GARDASIL Access Program (GAP), the Moi Referral and Teaching Hospital was granted 9,000 doses of the quadrivalent vaccine to vaccinate young girls in Eldoret, Kenya. [39] In order to avoid excess demand, promotion of the program was restricted to a number of randomly selected government primary schools, although other girls from the community were not refused if they showed up at the vaccination site (i.e. the hospital). A hospital-based vaccination was chosen to reduce the costs of the program. In order to avoid non-uptake due to transport issues, only schools within the Eldoret Municipality were considered.

The vaccines were offered to girls in classes 4 to 8, approximately 9 to 14 years old, from ten primary schools in Eldoret Municipality. These schools were randomly selected until a total of about 4,000 eligible girls was reached, expecting a coverage of around 75% (3000/4000). [38,40–42] The teachers were sensitized by health staff and through providing leaflets, and were subsequently asked to instruct students and parents.

Vaccination took place on Saturdays and Wednesdays, from May 2012 to March 2013. After consent was obtained from an adult caregiver, nurses from the hospital vaccinated the girls for free. Given that a three dose schedule was planned, a vaccination card with a next appointment was given after the first and second dose. Additionally, nurses called the caregiver to remind them about the second and third dose if they had not showed up on the scheduled day.

Because of the low response during the first 3 months of the program, other schools in the County, government and private, were also invited to participate from August 2012 onwards, and a local radio announced the vaccination program as well. In September 2012, the program stopped administering the first dose after reaching 3,000 girls in order to guarantee sufficient vaccines for the following doses.

Recruitment of study participants

Two months before the start of the vaccination program (March 2012), a random selection of mothers from girls in classes 4 to 8 from the ten selected schools were invited for a face-to-face interview: after randomly selecting girls from class lists in each school, invitation letters for the baseline interview, addressed to their mothers, were given to the girls. The number of invitation letters per school was proportional to the total number of girls in classes 4 to 8 of the ten schools. Two months after the vaccination program was closed (May 2013), the same mothers were invited for a follow-up interview by using the contact information they had provided during the baseline interview. If women were unable to participate again, yet reachable by phone, they were asked to answer a few key questions regarding uptake over the phone.

To estimate the relation between baseline acceptance and vaccine uptake reported at follow-up, sample size for comparing two proportions was calculated, expecting acceptance among 75% of the participants and uptake among 60% of the non-acceptors and among 80% of the acceptors (power 80%). Anticipating non-participation and loss to follow-up, we doubled the required sample size of 234, thus aiming at distributing 468 invitation letters for the baseline study.

Procedures

The interviews were conducted in Swahili or English, according to the interviewee's preference, and took place at school, work or home, again as chosen by the participant. To verify clarity and correct wording of the questionnaire, pilot tests were performed for the baseline and follow-up surveys (n = 4, n = 9, respectively). During the baseline interview, all women separately received basic information from the interviewer regarding cervical cancer, screening and HPV vaccination. Leaflets with comprehensive facts and pictures were used to assure consistency. In addition, the participants were also informed about the upcoming vaccination program and were made aware of the fact that they would be invited for a follow-up interview once the vaccination program was finished. Interviewers emphasized that participation in the baseline and follow-up study, should not affect the decision to have their daughter vaccinated.

Measures at baseline

Before the participants were provided with basic information as mentioned above, socio-demographic characteristics were collected, and their awareness concerning cervical cancer was assessed. Once the participants had been informed, their attitudes towards the HPV vaccine were investigated: 1) *Acceptability* was evaluated by asking the participants to score the question 'would you vaccinate your daughter against cervical cancer?' on a 5-point Likert scale, and 2) *Perceived barriers*, were assessed by first using an open question and subsequently giving reasons why not to vaccinate with which the participants could agree or disagree (5-point Likert scale). Acceptance was defined as '(very) likely to vaccinate your daughter' (scores 4–5). Potential barriers, derived from literature [9,16,29,30,43,44], comprised a lack of information, concerns about efficacy, side effects, infertility and unsafe administration (i.e. using unclean needles), worries about encour-

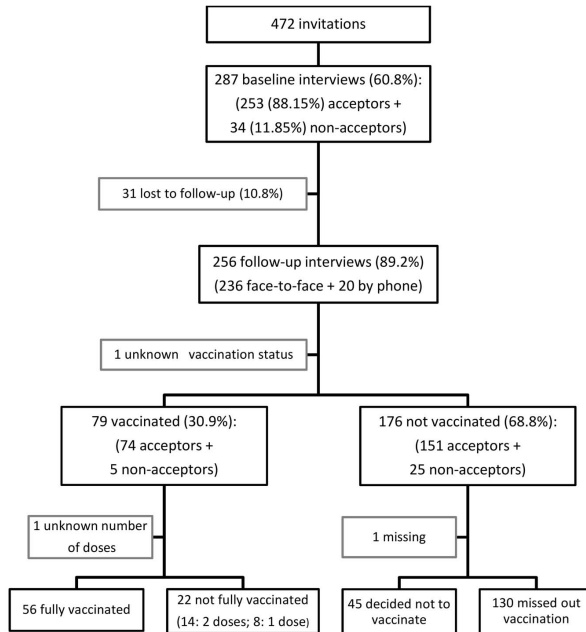


Figure 1. Flow diagram of participation in a longitudinal study, measuring baseline acceptance and subsequent uptake of the HPV vaccine.

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aging unsafe sexual activity, a perception of the daughter as too young, disapproval by the partner, time constraints and the inconvenience of three doses.

Measures at follow-up

The vaccination status of the daughter was verified by asking the mother. Participants whose daughter was not vaccinated were asked, regardless of their reported baseline acceptance, whether they had actively decided not to vaccinate (refusers) or whether they had wanted to vaccinate but had failed to do so. Initiation of vaccination (i.e. having received at least one dose) was considered as 'being vaccinated' in further analysis. Additionally, participants were asked whether they had received information regarding the HPV vaccination program.

In terms of barriers, all problems encountered were documented: mothers from vaccinated girls were asked which difficulties they had had to overcome (open and closed yes/no questions), while the others were asked why they had refused the vaccine (open question) or why they had not managed to have their daughter vaccinated as they had intended (open, and closed yes/no questions). Closed questions measuring reasons for not vaccinating included lack of time, transport costs, disapproval of somebody, refusal of daughter, fear of side effects and not knowing where and when to go for vaccination, and were obtained from literature. [35,38,45,46]

Analysis

In the analysis of the surveys, answers to open questions were grouped, and emerging themes were identified. The baseline characteristics and attitudes of non-respondents and respondents from the follow-up study were compared based on the Mann-Whitney-Wilcoxon test and chi-square analysis. For this purpose, perceived barriers were converted from a 5- into a 3-point scale, combining scores 1-2 and 4-5. In logistic regressions, baseline barriers were entered as continuous variables.

We used bivariate logistic regressions to examine correlates of baseline HPV vaccine acceptance and vaccination status. Given the small variation in baseline participation rate per school, adjusted odds ratios were calculated: weights were applied to take into account the missing observations. Additionally, schools were considered as a primary sampling unit; thus, we corrected for clustering at school level.

For each outcome variable (i.e. acceptance and uptake), three multivariate logistic regression models were developed with baseline variables. In the first model, the participants' characteristics were included, whereas in the second, all perceived barriers were incorporated. Independent items measuring the same barrier were grouped together - conditional on high internal consistency (i.e. Cronbach's alpha > 0.75) - to avoid multicollinearity. Lastly, the third model comprised baseline variables which were selected through backward stepwise regression. For the outcome variable uptake, an additional model was created by adding acceptance

Table 1. Baseline characteristics, perceived barriers and acceptance of the HPV vaccine; comparing respondents and non-respondents of the follow-up study.

	TOTAL BASELINE (n = 287)	FOLLOW-UP RESPONDENTS (n = 256)	NON-RESPONDENTS (n = 31)	
BASELINE CHARACTERISTICS				
	Median (IQR)	Median (IQR)	Median (IQR)	p-value
Participant age at baseline	35 (32–40)	35 (32–40)	35 (39–40)	0.43
Range (years)	21 – 59	21 – 59	23 – 56	
Age of daughter at baseline	12 (11–14)	12 (11–14)	12 (11–13)	0.68
Range (years)	8 – 18	8 – 18	8 – 17	
Years of education of participant	8 (7–12)	8 (7–12)	8 (6–11)	0.35
Range (years)*	0 – 13+	0 – 13+	0 – 13+	
Housing characteristics**	5 (4–5)	5 (4–5)	5 (4–6)	0.04
Range	1 – 7	2 – 7	3 – 7	
	n (%)	n (%)	n (%)	p-value
Marital status of participant				
With partner	217 (75.6)	194 (75.8)	23 (74.2)	
Without partner	70 (24.4)	62 (24.2)	8 (25.8)	0.85
Religious affiliation of participant				
Protestant	226 (79.3)	204 (80.3)	22 (71.0)	0.48
Catholic	46 (16.1)	39 (15.3)	7 (22.6)	
Muslim	13 (4.6)	11 (4.3)	2 (6.4)	
Origin of participant***				
urban	171 (60.2)	153 (60.2)	18 (60.0)	0.98
rural - outside Kenya	113 (39.8)	101 (39.8)	12 (40.0)	
Ever heard of cervical cancer?				
No – don't know	117 (40.9)	102 (40.0)	15 (48.4)	0.37
Yes	169 (59.1)	153 (60.0)	16 (51.6)	
BASELINE BARRIERS: if you would decide not to vaccinate, why would that be?				
Need more information?				0.40
(strongly) disagree	98 (34.6)	84 (33.3)	14 (45.2)	
neutral	17 (6.0)	15 (5.9)	2 (6.4)	
(strongly) agree	168 (59.4)	153 (60.7)	15 (48.4)	
Doubt the vaccine works?				0.36
(strongly) disagree	197 (70.1)	174 (69.6)	23 (74.2)	
neutral	24 (8.5)	20 (8.0)	4 (12.9)	
(strongly) agree	60 (21.3)	56 (22.4)	4 (12.9)	
Fear of side effects?				0.26
(strongly) disagree	149 (52.5)	129 (51.0)	20 (64.5)	
neutral	27 (9.5)	26 (10.3)	1 (3.2)	
(strongly) agree	108 (38.0)	98 (38.7)	10 (32.3)	
Fear of interference with fertility?				0.43
(strongly) disagree	171 (60.4)	149 (59.1)	22 (71.0)	
neutral	45 (15.9)	41 (16.3)	4 (12.9)	
(strongly) agree	67 (23.7)	62 (24.6)	5 (16.1)	
Afraid of unsafe administration?				0.07
(strongly) disagree	203 (71.7)	177 (70.2)	26 (83.9)	
neutral	17 (6.0)	14 (5.6)	(9.7)	
(strongly) agree	63 (22.3)	61 (24.2)	2 (6.4)	
It might encourage unsafe sex				0.94
(strongly) disagree	238 (84.7)	212 (84.8)	26 (83.9)	
neutral	23 (8.2)	20 (8.0)	3 (9.7)	

Table 1. Cont.

	TOTAL BASELINE (n = 287)	FOLLOW-UP RESPONDENTS (n = 256)	NON-RESPONDENTS (n = 31)
(strongly) agree	20 (7.1)	18 (7.2)	2 (6.4)
Daughter is too young for vaccine against an STI?			0.91
(strongly) disagree	250 (88.3)	222 (88.1)	28 (90.3)
neutral	9 (3.2)	8 (3.2)	1 (3.2)
(strongly) agree	24 (8.5)	22 (8.7)	2 (6.4)
Partner won't approve?			0.70
(strongly) disagree ****	221 (78.4)	196 (78.1)	25 (80.6)
neutral	30 (10.6)	28 (11.2)	2 (6.4)
(strongly) agree	31 (11.0)	27 (10.8)	4 (12.9)
Vaccination takes a lot of time			0.75
(strongly) disagree	275 (96.8)	245 (96.8)	30 (96.8)
neutral	6 (2.1)	5 (2.0)	1 (3.2)
(strongly) agree	3 (1.1)	3 (1.2)	0 (0.00)
Inconvenience of 3 doses needed			0.08
(strongly) disagree	265 (96.0)	236 (96.3)	29 (93.5)
neutral	6 (2.2)	6 (2.4)	0 (0.0)
(strongly) agree	5 (1.8)	3 (1.2)	2 (6.4)
BASELINE ACCEPTANCE			
Would you vaccinate your daughter against cervical cancer?			0.69
very unlikely	6 (2.1)	6 (2.3)	0 (0.0)
unlikely	3 (1.0)	3 (1.2)	0 (0.0)
neutral	25 (8.7)	21 (8.2)	4 (12.9)
likely	80 (27.9)	73 (28.5)	7 (22.6)
very likely	173 (60.3)	153 (59.8)	20 (64.5)

IQR = interquartile range.

*13+; those who studied in higher education i.e. college (middle level) and/or university.

**housing: continuous variable constructed by scoring aspects of the living place: material of the roof, walls and floors, and toilet and water facilities.

*** women were asked where they had lived for most of the time up to 12 years of age.

**** includes participants without a relationship.

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and being well-informed about the HPV vaccination program to the third model. The adjusted F-Wald test was used to measure goodness-of-fit. Potential interactions among the variables in these models were explored.

Ethics statement

The study was approved by the ethical boards of Ghent University, Belgium, and Moi University, Kenya. Written and oral informed consent from all participants were obtained for the baseline and follow-up surveys respectively. With exception of the participants who were interviewed by phone, all interviewees of the follow-up survey received 200 KES (approximately 1.5€). The ethics committees of Ghent University (Belgium) and Moi University (Kenya) approved this consent procedure.

Results

Preliminary analysis

Of the 472 women invited, 287 agreed to participate (60.8%), of which 256 (89.2%) were interviewed during follow-up (figure 1). There were no differences between those who did and those who

did not participate in the follow-up study, except for the quality of their housing (Table 1).

A strong correlation was identified between four baseline barriers inherent to vaccination (i.e. doubting efficacy, fear of side effects, of infertility and of unsafe administration; $\alpha = 0.90$). In addition, two baseline barriers related with time constraints were also correlated (i.e. vaccination takes time, and three doses are inconvenient; $\alpha = 0.79$). Therefore, average Likert scale scores were calculated, creating two new variables used in multivariate analysis.

Baseline acceptance and perceived barriers

Among all participants ($n = 287$), 60.3% and 27.9% said it was respectively 'very likely' and 'likely' that they would have their daughter vaccinated. Up to 59.4% considered a lack of information as potentially preventing them from vaccinating their daughter. Concerns about side effects were expressed by 38.0% (interference with fertility was indicated by 23.7%), and almost one out of four was afraid that the vaccine would not be administered safely. In addition, over one-fifth of the participants doubted the efficacy of the vaccine (Table 1).

Table 2. Bivariate logistic regression with acceptance and uptake of the HPV vaccine as outcomes.

VARIABLE	BASELINE ACCEPTANCE			UPTAKE				
	n	Acceptance (%)	AOR	[95% CI]	n	Uptake (%)	AOR	[95% CI]
BASELINE CHARACTERISTICS								
Participant age at baseline	286		1.05*	[1.01–1.08]	254		1.01	[0.97–1.04]
Age of daughter at baseline	285		1.14	[0.85–1.54]	253		1.03	[0.86–1.23]
Years of education of participant	279		0.10	[0.88–1.23]	247		1.05	[0.99–1.11]
Housing	287		0.81	[0.61–1.08]	255		1.12	[0.74–1.70]
Marital status of participant	287				255			
With partner		188/217 (86.6)				57/193 (29.5)		
Without partner			0.53	[0.15–1.84]		22/62 (35.5)	0.75	[0.43–1.32]
Religion of participant	285				253			
protestant		202/226 (89.4)				58/203 (28.6)		
Catholic		41/46 (89.1)	1.07	[0.23–4.88]		17/39 (43.6)	1.92*	[1.19–3.09]
Muslim		8/13 (61.5)	0.20	[0.04–1.09]		4/11 (36.4)	1.42	[0.48–4.18]
Origin of participant	284				253			
Urban		155/171 (90.6)				56/153 (36.6)		
Rural - outside Kenya		96/113 (85.0)	0.61	[0.19–1.94]		22/100 (22.0)	0.48	[0.21–1.10]
Ever heard of cervical cancer?	286				254			
No - don't know		107/117 (91.4)				24/102 (23.5)		
Yes		145/169 (85.8)	0.55	[0.22–1.37]		55/152 (36.2)	1.93*	[1.16–3.19]
BASELINE BARRIERS: if you would decide not to vaccinate, why would that be?								
Need for more information?	283		1.00	[0.84–1.20]	251		1.02	[0.89–1.17]
Doubt the vaccine works?	281		0.75*	[0.59–0.97]	249		0.98	[0.76–1.26]
Fear of side effect?	284		0.69*	[0.52–0.91]	252		1.00	[1.76–1.31]
Fear of interference with fertility?	283		0.71*	[0.53–0.96]	251		0.94	[0.71–1.25]
Afraid of unsafe administration (i.e. using unclean needles)	283		0.76**	[0.64–0.91]	251		1.04	[0.78–1.40]
It might encourage unsafe sex	282		0.80	[0.53–1.20]	250		0.81	[0.52–1.26]
Daughter is too young for vaccine against an STI?	283		0.54**	[0.38–0.76]	251		0.94	[0.61–1.43]
Partner won't approve?*	282		0.44***	[0.31–0.61]	250		0.87	[0.68–1.09]
Vaccination takes a lot of time	284		0.51	[0.24–1.12]	252		0.86	[0.60–1.21]
Inconvenience: 3 doses needed	276		0.67	[0.36–1.24]	244		0.94	[0.57–1.55]
ACCEPTANCE - WELL-INFORMED								
Would you vaccinate your daughter? (Baseline)					255			
neutral - (very) unlikely						5/30 (16.7)		

Table 2. Cont.

VARIABLE	BASELINE ACCEPTANCE		UPTAKE		AOR	95% CI
	n	Acceptance (%)	n	Uptake (%)		
(very) likely						[1.11–5.94]
Were you well-informed about the cervical cancer vaccination program at the hospital? (at follow-up)	235		74/235 (32.9)		2.57*	
No			10/88 (11.4)		–	
Yes			68/147 (46.3)		6.37**	[2.21–18.36]

AOR: adjusted odds ratio – CI, confidence interval.

* participants without a relationship are included in category 'strongly disagree'.

* p<0.05 ** p<0.01, *** p<0.001.

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Few women refused the vaccine thinking that it would encourage their daughter to have unprotected sex (7.1%) or that she was too young (8.5%). Considering vaccination as time-consuming or perceiving three doses as inconvenient was hardly mentioned (1.1% and 1.8% respectively), but 11.0% of the women believed that the partner would not approve of the HPV vaccination (Table 1). The open questions did not reveal other barriers than those probed for with closed questions.

Determinants of baseline acceptance

From all baseline characteristics of the participants, only age was correlated with acceptance in bivariate analysis, with older women more likely to accept. Regarding the barriers perceived at baseline, those referring to negative health consequences (i.e. side effects, infertility and unsafe administration of the vaccine) lowered acceptance, as did doubting the efficacy of the vaccine. 'Considering the daughter too young' and 'thinking the partner would not approve' were also negatively correlated with acceptability (Table 2).

Through multivariate analysis (Table 3), both acceptance and uptake were predicted 1) by the baseline characteristics of the participants (model 1) and 2) by the baseline barriers (model 2). In these models, acceptance was higher among older participants while negatively correlated with perceiving the partner as a potential barrier and with religion (Muslims accepted less). Backward stepwise regression with all variables led to the selection of three predictors of acceptance (model 3): the barriers 'foreseeing the partner's disapproval' and 'considering the daughter too young', and baseline cervical cancer awareness. In this final model, the aforementioned barriers had a negative impact on vaccine acceptance.

HPV vaccine uptake

Only 31.1% of the girls initiated vaccination during the pilot program (n = 254), of which 70.9% received three doses. Among the women whose daughter did not receive the vaccine (176/254), 45 had refused (17.7%), and 130 (51.2%) said that, although they had wanted to, their daughter was not vaccinated (Table 4 – figure 1).

Of the participants who did not accept the vaccine at baseline, none of the daughters received the vaccine, although two women (22.2%) claimed that in the end they had wanted to have their daughter vaccinated. Of the acceptors, 52.7% failed to have their daughter vaccinated, and 14.3% changed their mind and were no longer interested when the program rolled out. Of those who were indecisive at baseline, 23.8% had their daughter vaccinated, 28.6% chose not to, while the majority (47.6%) missed out even though they had decided to accept the vaccine (Table 4).

Determinants of HPV vaccine uptake

In bivariate logistic analysis, acceptance was associated with uptake (AOR:2.57), but being well-informed about the program (62.5%; 147/235) increased the odds of vaccination even more (AOR:6.37). Few baseline characteristics of the participants were correlated with uptake: having heard of cervical cancer at baseline predicted uptake, and Catholic participants had higher vaccination rates than Protestants. None of the barriers had any predictive value for uptake (Table 2).

In multivariate analyses, these results were confirmed as uptake was positively associated with 'ever heard of cervical cancer' (model 1), but with none of the baseline barriers (model 2). For both models, the adjusted Wald test showed a poor fit. Through backward stepwise regression, three predictors of uptake were identified and included in the third model: having heard of

Table 3. Multivariate logistic regression with acceptance and uptake of the HPV vaccine as outcomes.

	ACCEPTANCE - AOR [95% CI]			UPTAKE - AOR [95% CI]			
	Model 1 n = 270	Model 2 n = 278	Model 3 n = 280	Model 1 n = 239	Model 2 n = 246	Model 3 n = 247	Model 4 n = 227
ACCEPTANCE - WELL-INFORMED							
Would you vaccinate your daughter? (Baseline)							
(very) likely (ref: neutr. –(very) unlikely)							3.36 [0.80–14.1]
Were you well-informed about the vaccination program? (at follow-up) Yes (ref: No)							6.37** [2.24–18.1]
BASELINE CHARACTERISTICS							
Age of participant at baseline	1.06* [1.00–1.12]			1.003 [0.96–1.04]		nw	
Age of daughter at baseline	1.05 [0.77–1.44]		nw	1.088 [0.86–1.37]		nw	
Years of education of participant	0.98 [0.89–1.08]		nw	1.051 [0.97–1.14]		nw	
Housing	0.90 [0.64–1.26]		nw	0.972 [0.60–1.56]		nw	
Marital status of participant							
Without partner (ref: with partner)	0.56 [0.15–2.00]		nw	0.689 [0.37–1.29]		nw	
Religion of participant. (ref: protestant)							
Catholic	1.35 [0.28–6.42]		nw	1.416 [0.57–3.90]		nw	
Muslim	0.078** [0.02–0.38]		nw	1.171 [0.42–3.26]		nw	
Origin of participant							
rural - outside Kenya (ref: urban)	0.49 [0.15–1.62]		nw	0.546 [0.21–1.42]		0.48* [0.23–0.99]	0.53* [0.29–0.97]
Ever heard of cervical cancer? (at baseline)							
Yes (ref: No-don't know)	0.43 [0.17–1.11]		0.46 [0.17–1.30]	1.610* [1.09–2.38]		1.84* [1.04–3.26]	2.07* [1.18–3.63]
BARRIERS AT BASELINE							
Need for more information		1.21 [0.86–1.71]	nw		0.99 [0.83–1.18]	nw	

Table 3. Cont.

	ACCEPTANCE - AOR [95% CI]		UPTAKE - AOR [95% CI]				
	Model 1 n = 270	Model 2 n = 278	Model 3 n = 280	Model 1 n = 239	Model 2 n = 246	Model 3 n = 247	Model 4 n = 227
Barriers inherent to vaccination ^a	0.86	[0.56–1.33]	nw		1.06		
	0.94	[0.57–1.53]	nw		[0.66–1.03]	nw	
It might encourage unsafe sex	0.72	[0.48–1.10]	nw		0.82		
	0.67*	[0.45–0.99]	nw		[0.49–1.37]	nw	
Daughter is too young for vaccine against an STI?	0.50**	[0.33–0.74]	[0.45–0.99]		0.99		
	0.47***	[0.32–0.71]	[0.45–0.99]		[0.57–1.09]	nw	
Partner won't approve?	0.68	[0.33–0.74]	[0.32–0.71]		0.89		
					[0.68–1.16]	0.83	
Barriers related to time constraints ^a					1.00		
					[0.27–1.69]	nw	
Cons	9.86	103.60**	138.38***	0.20	0.68	1.07	0.06*
F-statistic (p)	410.3 (0.04)	14.15 (0.01)	13.93 (0.00)	2.661 (0.44)	0.304 (0.91)	5.916 (0.02)	4.443 (0.06)

Model 1: including baseline characteristics; model 2: including barriers perceived at baseline; model 3: including baseline characteristics and barriers obtained by stepwise backward regression – model 4: model 3 + acceptance and being well-informed about the HPV vaccination program.

AOR: adjusted odds ratio – CI: confidence interval.

^a average of: doubt the vaccine works; fear of side effects and interference with fertility; and afraid of unsafe administration; alpha = 0.90.

nw: not withheld in backward stepwise regression.

* p<0.05, ** p<0.01, *** p<0.001.

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Table 4. Baseline acceptance and subsequent decisions regarding uptake of the HPV vaccine.

BASELINE ACCEPTANCE (would you vaccinate your daughter?)	Follow-up:	Follow-up:	Follow-up:	TOTAL
	Decided not to vaccinate (n(%))	Wanted to vaccinate but missed out (n(%))	Vaccinated (1–3 doses) (n(%))	
(very) unlikely	7 (77.8)	2 (22.2)	0 (0.0)	9 (100.0)
neutral	6 (28.6)	10 (47.6)	5 (23.8)	21 (100.0)
(very) likely	32 (14.3)	118 (52.7)	74 (33.0)	224 (100.0)
TOTAL	45 (17.7)	130 (51.2)	79 (31.1)	254 (100.0)

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cervical cancer before the study increased the odds of having a vaccinated daughter, and women who grew up in urban areas reported more uptake than those with a rural background. The third factor, disapproval by the partner, was negatively associated at the 0.1 level ($p=0.09$). Adding acceptance and being well-informed to this model caused this last correlation to disappear while being well-informed became the strongest correlate. Acceptance was positively associated with uptake at the 0.1 level ($p=0.09$) (model 4) (Table 3).

Encountered difficulties and reasons for non-uptake of the HPV vaccine

As can be seen in Table 5, not receiving information regarding where and when the vaccination took place was the most important barrier and was reported by 54.6% of those who wanted yet failed to have their daughter vaccinated. The second most important barrier was fear of side effects, mentioned mostly by mothers who either had a vaccinated daughter or refused the vaccine, followed by a lack of time, which was reported by those who had their daughter vaccinated and by those who wanted to but had missed out, but not by refusers. Transport costs were not a

concern among refusers, but were mainly mentioned by mothers whose daughter had received the vaccine. Other problems raised were a lack of information about the vaccine and other people opposing the vaccine, among whom the partner and the daughter herself. 'Not being in town' or simply 'forgetting the vaccination' were never mentioned by refusers and hardly by women with vaccinated daughters, but were quite frequently reported by participants who had failed to have their daughter vaccinated. Finally, nine refusers claimed that they had never considered vaccinating their daughter against cervical cancer.

Discussion

This longitudinal study measured HPV vaccine acceptance and subsequent uptake in Eldoret, Kenya. At baseline, 88.1% of the participants accepted the vaccine, but only 31.1% reported initiation of vaccination at follow-up. While similar acceptance rates have been found in other studies [9,10,16,18–28], the proportion of vaccinated girls was below expectations: most demonstration projects show a coverage of over 75% and Rwanda's national program even reached 93.2%. [38,40–42,47] However, uptake could have been much higher considering that

Table 5. Encountered difficulties and reasons for non-uptake of the HPV vaccine.

FOLLOW-UP SURVEY	Decided not to vaccinate (n = 45)	Wanted to vaccinate but missed out (n = 130)	Vaccinated (1–3 doses) (n = 79)	TOTAL (n = 254)
	Reasons for non-uptake* (n (%))	Reasons for non-uptake** (n (%))	Encountered difficulties** (n (%))	
Not knowing/finding out where & when to go	0 (0.0)	71 (54.6)	2 (2.5)	73 (29.8)
Fear of side effects	15 (41.7)	12 (9.2)	39 (49.4)	66 (26.9)
Lack of time	0 (0.0)	34 (26.1)	29 (36.7)	63 (25.7)
Lack of vaccine information	5 (13.9)	22 (16.9)	11 (13.9)	38 (15.5)
Partner opposed	11 (30.6)	8 (6.1)	12 (15.2)	31 (12.6)
Transport cost	0 (0.0)	6 (4.6)	20 (25.3)	26 (10.6)
Not in town (travelling)	0 (0.0)	24 (18.5)	0 (0.0)	24 (9.8)
Daughter opposed	3 (8.3)	7 (5.4)	13 (16.5)	23 (9.4)
Family/friends opposed	1 (2.8)	4 (3.1)	13 (16.5)	18 (7.3)
Forgot	0 (0.0)	10 (7.7)	0 (0.0)	10 (4.1)
Never considered it	9 (20.0)	0 (0.0)	0 (0.0)	9 (3.5)

Percentages may add up to over 100% due to multiple answer options.

* open question.

**open and closed question.

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51.2% of the women stated that their daughter did not receive the vaccine even though they had wanted to have her vaccinated. This may have been caused by poor promotion since the main reason for not vaccinating was a lack of invitation (i.e. not knowing where and when they were expected (29.8%)), and 15.5% requested more information on the vaccination. Interestingly, other longitudinal studies have also reported a low coverage due to the absence of doctors' recommendations, [45,46,48] and many have pointed out the importance of outreach by health staff to inform and encourage HPV vaccination. [14,49] Other reasons for non-uptake include time constraints and forgetting or simply not considering the option of vaccinating. Thus the participants indicated that cervical cancer vaccination was not considered a priority, which reaffirms the need for HPV vaccine promotion. School-based vaccination, which has proven to be more efficient, could further facilitate vaccination as it solves practical problems for the family. [14,50]

A remarkable result from this study is that, besides refusers, participants with vaccinated daughters also feared side effects (49.4% and 41.7%, respectively). This was somewhat surprising; Gerend et al. showed that people with a high intention mainly report "practical barriers" and those with a low intention report "global barriers", including side effects. [51] Considering mothers with vaccinated girls as participants with a high intention, side effects were not expected to be their main concern. It is of course possible that the type of health consequences they feared were less severe, and thus more easy to overcome, as opposed to those from refusers. However, we did not determine which health consequences participants exactly referred to, so we cannot demonstrate this. In addition, women whose daughter received the vaccine might have feared side effects at the moment they were actually confronted with the vaccine. This would also explain why those whose daughter did not receive the vaccine even though they had wanted to were hardly bothered by side effects (9.2%): while encountering other, more practical barriers, they were not actually confronted with a final decision or with the vaccine, and hence with the possibility of side effects. Finally, experiencing side effects after receiving a dose might also have caused concerns for the following vaccinations. More detailed information regarding different types of side effects and when these concerns arise would shed light on the translation of intention into real behavior.

With regard to predicting uptake, acceptance was positively related in bivariate analysis; however in multivariate analysis, being well-informed about the program and baseline awareness of cervical cancer were stronger correlates, again confirming the importance of health education. Women who grew up in rural areas were less likely to have their daughter vaccinated. While this may result from less knowledge regarding cervical cancer – a correlation (AOR: 0.52; 95% CI:0.31-0.87), but no interaction was found with baseline awareness – these women might also have less power or means to translate intentions into action. Including socio-psychological factors, such as self-efficacy or perceived control, in future research may provide more in-depth explanations. The importance of such variables is also reflected by the fact that participants whose daughter was vaccinated encountered obstructions from their partner or the daughter but were able to either convince them or to vaccinate without the partner's consent. This further demonstrates that cervical cancer vaccination is discussed among family members. Moreover, opposition of vaccinated girls, perhaps due to becoming weary after one or two doses, is a no Table observation and emphasizes the importance of targeting the sensitization messages to them as well. Cervical cancer prevention

campaigns should thus always address all community members, including men and young girls. [37,52,53]

In addition, the weight of the partner's decision is observed through the strong correlation with baseline acceptance: foreseeing a partner's objection significantly lowered acceptance. Perceiving the daughter as too young was also negatively related, but the daughter's actual age did not influence acceptance or uptake. In general, few demographic variables explained baseline acceptance, which might be due to the small sample size and the homogeneity among participants. Including rural areas and participants of a higher economic status (e.g. with daughters in private schools) could reveal more clear distinctions. Similarly, our results suggest that Muslims accepted the HPV vaccine less (although uptake was not lower among them); however, the number of Islamic participants in our study is limited. Future research should investigate if there are indeed underlying concerns causing non-acceptance. Once clarified, different promotional messages, tailored to the needs of each group, might enhance uptake. [30,54]

Our study contains some limitations. First, 39% of the mothers invited at baseline did not participate in the survey, which can be the result of, amongst others, girls not delivering the invitation or of disinterest in health services and cervical cancer prevention among the women. This might have induced overestimation of baseline acceptability due to the inclusion of women with higher health interests. In addition, social desirability might have moved participants towards accepting the vaccine. Nonetheless, other acceptability studies have found an equally high interest in the HPV vaccine. [9,10,16,18–28] Secondly, the daughter's vaccination status was based on the participant's report only. We are however confident that we collected reliable estimates given that 1) many participants indicated that their daughter did not receive the vaccine, so overestimation of uptake is unlikely, and 2) girls could only receive the HPV vaccine with consent of an adult caregiver, so it is very likely that the mother accompanied them and thus knows the number of doses received. However, future studies might also rely on vaccination cards or on medical records of the vaccination program itself to verify the girls' vaccination status. Finally, our study only presents how women with a daughter in one of the ten initially targeted schools experienced the HPV vaccination program and does not include data from the program itself or from other people in the community.

In conclusion, even if the HPV is accepted, the uptake is largely determined by obtaining appropriate information, including practical information about HPV vaccination opportunities. Given the weight of social influences on decision-making, vaccination messages should target broadly and emphasize the vaccine's safety at all times. Finally, outreach strategies, such as school-based vaccination, might diminish organizational challenges for those willing to vaccinate.

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Author Contributions

Conceived and designed the experiments: HV DVB OD. Performed the experiments: HV DVB VN HM. Analyzed the data: HV KM OD. Wrote the paper: HV VN HM DVB KM OD.

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CORRECTION

Correction: Determinants of Acceptance and Subsequent Uptake of the HPV Vaccine in a Cohort in Eldoret, Kenya

The *PLOS ONE* Staff

There are errors in Tables [1](#), [2](#), and [3](#) of the published article. Please view the corrected tables [here](#).



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Table 1. Baseline characteristics, perceived barriers and acceptance of the HPV vaccine; comparing respondents and non-respondents of the follow-up study.

	TOTAL BASELINE (n = 287)	FOLLOW-UP RESPONDENTS (n = 256)	NON-RESPONDENTS (n = 31)	
BASELINE CHARACTERISTICS				
	Median (IQR)	Median (IQR)	Median (IQR)	p-value
Participant age at baseline	35 (32–40)	35 (32–40)	35 (39–40)	0.43
Range (years)	21–59	21–59	23–56	
Age of daughter at baseline	12 (11–14)	12 (11–14)	12 (11–13)	0.68
Range (years)	8–18	8–18	8–17	
Years of education of participant	8 (7–12)	8 (7–12)	8 (6–11)	0.35
Range (years)*	0–13+	0–13+	0–13+	
Housing characteristics**	5 (4–5)	5 (4–5)	5 (4–6)	0.04
Range	1–7	2–7	3–7	
	n (%)	n (%)	n (%)	p-value
Marital status of participant				
With partner	217 (75.6)	194 (75.8)	23 (74.2)	
Without partner	70 (24.4)	62 (24.2)	8 (25.8)	
Religious affiliation of participant				
Protestant	226 (79.3)	204 (80.3)	22 (71.0)	0.48
Catholic	46 (16.1)	39 (15.3)	7 (22.6)	
Muslim	13 (4.6)	11 (4.3)	2 (6.4)	
Origin of participant***				
urban	171 (60.2)	153 (60.2)	18 (60.0)	0.98
rural—outside Kenya	113 (39.8)	101 (39.8)	12 (40.0)	
Ever heard of cervical cancer?				
No—don't know	117 (40.9)	102 (40.0)	15 (48.4)	0.37
Yes	169 (59.1)	153 (60.0)	16 (51.6)	
BASELINE BARRIERS: if you would decide not to vaccinate, why would that be?				
Need more information?				
(strongly) disagree	98 (34.6)	84 (33.3)	14 (45.2)	0.40
neutral	17 (6.0)	15 (5.9)	2 (6.4)	
(strongly) agree	168 (59.4)	153 (60.7)	15 (48.4)	
Doubt the vaccine works?				
(strongly) disagree	197 (70.1)	174 (69.6)	23 (74.2)	0.36
neutral	24 (8.5)	20 (8.0)	4 (12.9)	
(strongly) agree	60 (21.3)	56 (22.4)	4 (12.9)	
Fear of side effects?				
(strongly) disagree	149 (52.5)	129 (51.0)	20 (64.5)	0.26
neutral	27 (9.5)	26 (10.3)	1 (3.2)	
(strongly) agree	108 (38.0)	98 (38.7)	10 (32.3)	
Fear of interference with fertility?				
(strongly) disagree	171 (60.4)	149 (59.1)	22 (71.0)	0.43
neutral	45 (15.9)	41 (16.3)	4 (12.9)	
(strongly) agree	67 (23.7)	62 (24.6)	5 (16.1)	
Afraid of unsafe administration?				
(strongly) disagree	203 (71.7)	177 (70.2)	26 (83.9)	0.07

(Continued)

Table 1. (Continued)

	TOTAL BASELINE (n = 287)	FOLLOW-UP RESPONDENTS (n = 256)	NON-RESPONDENTS (n = 31)	
neutral	17 (6.0)	14 (5.6)	(9.7)	
(strongly) agree	63 (22.3)	61 (24.2)	2 (6.4)	
It might encourage unsafe sex				0.94
(strongly) disagree	238 (84.7)	212 (84.8)	26 (83.9)	
neutral	23 (8.2)	20 (8.0)	3 (9.7)	
(strongly) agree	20 (7.1)	18 (7.2)	2 (6.4)	
Daughter is too young for vaccine against an STI?				0.91
(strongly) disagree	250 (88.3)	222 (88.1)	28 (90.3)	
neutral	9 (3.2)	8 (3.2)	1 (3.2)	
(strongly) agree	24 (8.5)	22 (8.7)	2 (6.4)	
Partner won't approve?				0.70
(strongly) disagree ****	221 (78.4)	196 (78.1)	25 (80.6)	
neutral	30 (10.6)	28 (11.2)	2 (6.4)	
(strongly) agree	31 (11.0)	27 (10.8)	4 (12.9)	
Vaccination takes a lot of time				0.75
(strongly) disagree	275 (96.8)	245 (96.8)	30 (96.8)	
neutral	6 (2.1)	5 (2.0)	1 (3.2)	
(strongly) agree	3 (1.1)	3 (1.2)	0 (0.00)	
Inconvenience of 3 doses needed				0.08
(strongly) disagree	265 (96.0)	236 (96.3)	29 (93.5)	
neutral	6 (2.2)	6 (2.4)	0 (0.0)	
(strongly) agree	5 (1.8)	3 (1.2)	2 (6.4)	
BASELINE ACCEPTANCE				
Would you vaccinate your daughter against cervical cancer?				0.69
very unlikely	6 (2.1)	6 (2.3)	0 (0.0)	
unlikely	3 (1.0)	3 (1.2)	0 (0.0)	
neutral	25 (8.7)	21 (8.2)	4 (12.9)	
likely	80 (27.9)	73 (28.5)	7 (22.6)	
very likely	173 (60.3)	153 (59.8)	20 (64.5)	

IQR = interquartile range

*13+: those who studied in higher education i.e. college (middle level) and/or university

**housing: continuous variable constructed by scoring aspects of the living place: material of the roof, walls and floors, and toilet and water facilities

*** women were asked where they had lived for most of the time up to 12 years of age

**** includes participants without a relationship

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Table 2. Bivariate logistic regression with acceptance and uptake of the HPV vaccine as outcomes.

VARIABLE	BASELINE ACCEPTANCE			UPTAKE				
	n	Acceptance (%)	AOR	[95% CI]	n	Uptake (%)	AOR	[95% CI]
BASELINE CHARACTERISTICS								
Participant age at baseline	286		1.05*	[1.01–1.08]	254		1.01	[0.97–1.04]
Age of daughter at baseline	285		1.14	[0.85–1.54]	253		1.03	[0.86–1.23]
Years of education of participant	279		0.10	[0.88–1.23]	247		1.05	[0.99–1.11]
Housing	287		0.81	[0.61–1.08]	255		1.12	[0.74–1.70]
Marital status of participant	287				255			
With partner		188/217 (86.6)				57/193 (29.5)		
Without partner		65/70 (92.9)	0.53	[0.15–1.84]		22/62 (35.5)	0.75	[0.43–1.32]
Religion of participant	285				253			
Protestant		202/226 (89.4)				58/203 (28.6)		
Catholic		41/46 (89.1)	1.07	[0.23–4.88]		17/39 (43.6)	1.92*	[1.19–3.09]
Muslim		8/13 (61.5)	0.20	[0.04–1.09]		4/11 (36.4)	1.42	[0.48–4.18]
Origin of participant	284				253			
Urban		155/171 (90.6)				56/153 (36.6)		
Rural—outside Kenya		96/113 (85.0)	0.61	[0.19–1.94]		22/100 (22.0)	0.48	[0.21–1.10]
Ever heard of cervical cancer?	286				254			
No—don't know		107/117 (91.4)				24/102 (23.5)		
Yes		145/169 (85.8)	0.55	[0.22–1.37]		55/152 (36.2)	1.93*	[1.16–3.19]
BASELINE BARRIERS: if you would decide not to vaccinate, why would that be?								
Need for more information?	283		1.00	[0.84–1.20]	251		1.02	[0.89–1.17]
Doubt the vaccine works?	281		0.75*	[0.59–0.97]	249		0.98	[0.76–1.26]
Fear of side effect?	284		0.69*	[0.52–0.91]	252		1.00	[1.76–1.31]
Fear of interference with fertility?	283		0.71*	[0.53–0.96]	251		0.94	[0.71–1.25]
Afraid of unsafe administration (i.e. using unclean needles)	283		0.76**	[0.64–0.91]	251		1.04	[0.78–1.40]
It might encourage unsafe sex	282		0.80	[0.53–1.20]	250		0.81	[0.52–1.26]
Daughter is too young for vaccine against an STI?	283		0.54**	[0.38–0.76]	251		0.94	[0.61–1.43]
Partner won't approve? ^o	282		0.44***	[0.31–0.61]	250		0.87	[0.68–1.09]
Vaccination takes a lot of time	284		0.51	[0.24–1.12]	252		0.86	[0.60–1.21]
Inconvenience: 3 doses needed	276		0.67	[0.36–1.24]	244		0.94	[0.57–1.55]
ACCEPTANCE—WELL-INFORMED								
Would you vaccinate your daughter? (Baseline)					255			
neutral—(very) unlikely						5/30 (16.7)	-	
(very) likely						74/225 (32.9)	2.57*	[1.11–5.94]
Were you well-informed about the cervical cancer vaccination program? (at follow-up)					235			
No						10/88 (11.4)	-	
Yes						68/147 (46.3)	6.37**	[2.21–18.36]

AOR: adjusted odds ratio—CI: confidence interval

^o participants without a relationship are included in category 'strongly disagree'

* p<0.05

** p<0.01

*** p<0.001

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Table 3. Multivariate logistic regression with acceptance and uptake of the HPV vaccine as outcomes.

	ACCEPTANCE—AOR [95% CI]			UPTAKE—AOR [95% CI]			
	Model 1 n = 270	Model 2 n = 278	Model 3 n = 280	Model 1 n = 239	Model 2 n = 246	Model 3 n = 247	Model 4 n = 227
ACCEPTANCE—WELL-INFORMED							
Would you vaccinate your daughter? (at baseline)							3.36
(very) likely (ref. <i>neutr.—(very) unlikely</i>)							[0.80–14.1]
Were you well-informed about the vaccination program? (at follow-up)							6.37**
Yes (ref. <i>No</i>)							[2.24–18.1]
BASELINE CHARACTERISTICS							
Age of participant at baseline	1.06*			1.003			
	[1.00–1.12]		nw	[0.96–1.04]		nw	
Age of daughter at baseline	1.05			1.088			
	[0.77–1.44]		nw	[0.86–1.37]		nw	
Years of education of participant	0.98			1.051			
	[0.89–1.08]		nw	[0.97–1.14]		nw	
Housing	0.90			0.972			
	[0.64–1.26]			[0.60–1.56]		nw	
Marital status of participant							
Without partner (ref. <i>with partner</i>)	0.56			0.689			
	[0.15–2.00]		nw	[0.37–1.29]		nw	
Religion of participant. (ref: <i>protestant.</i>)							
Catholic	1.35		1.416				
	[0.28–6.42]			[0.57–3.50]			
Muslim	0.078**			1.171			
	[0.02–0.38]		nw	[0.42–3.26]		nw	
Origin of participant							
rural—outside Kenya (ref. <i>urban</i>)	0.49			0.546		0.48*	0.53*
	[0.15–1.62]		nw	[0.21–1.42]		[0.23–0.99]	[0.29–0.97]
Ever heard of cervical cancer? (at baseline)	0.43		0.46	1.610*		1.84*	2.07*
Yes (ref. <i>No—don't know</i>)	[0.17–1.11]		[0.17–1.30]	[1.09–2.38]		[1.04–3.26]	[1.18–3.63]
BARRIERS AT BASELINE							
Need for more information		1.21			0.99		
		[0.86–1.71]	nw		[0.83–1.18]	nw	
Barriers inherent to vaccination ^o		0.86			1.06		
		[0.56–1.33]	nw		[0.68–1.63]	nw	
It might encourage unsafe sex		0.94			0.82		
		[0.57–1.53]	nw		[0.49–1.37]	nw	
Daughter is too young for vaccine against an STI?		0.72		0.67*	0.99		
		[0.48–1.10]	[0.45–0.99]		[0.57–1.69]	nw	
Partner won't approve?		0.50**	0.47***		0.89	0.83	0.99
		[0.33–0.74]	[0.32–0.71]		[0.68–1.16]	[0.67–1.03]	[0.74–1.32]
Barriers related to time constraints ^{oo}		0.68			1.00		
		[0.27–1.69]	nw		[0.57–1.74]	nw	
Cons	9.86	103.60**	138.38***	0.20	0.68	1.07	0.06*

(Continued)

Table 3. (Continued)

	ACCEPTANCE—AOR [95% CI]			UPTAKE—AOR [95% CI]			
	Model 1 n = 270	Model 2 n = 278	Model 3 n = 280	Model 1 n = 239	Model 2 n = 246	Model 3 n = 247	Model 4 n = 227
F-statistic (p)	410.3 (0.04)	14.15 (0.01)	13.93 (0.00)	2.661 (0.44)	0.304 (0.91)	5.916 (0.02)	4.443 (0.06)

Model 1: including baseline characteristics; model 2: including barriers perceived at baseline; model 3: including baseline characteristics and barriers obtained by stepwise backward regression—model 4: model 3 + acceptance and being well-informed about the HPV vaccination program

AOR: adjusted odds ratio—CI: confidence interval

°average of: doubt the vaccine works, fear of side effects and interference with fertility, and afraid of unsafe administration; alpha = 0.90

°° average of: vaccination takes a lot of time and 3 doses are inconvenient; alpha = 0.79

nw: not withheld in backward stepwise regression

* p<0.05

** p<0.01

*** p<0.00

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Chapter 7

Uptake of the Human Papillomavirus Vaccine in Kenya: testing the Health Belief Model through structural equation modeling on Cohort Data

Paper 2: Testing the Health Belief Model In this second paper, again determinants of HPV vaccine acceptability and uptake, and the association between these two constructs, were identified. This time this was done using the HBM as theoretical framework: the model and various adapted versions were tested through structural equation modelling. More particularly, the predictive value of the models was evaluated.

Given the result of the first paper, i.e. that adequate promotion of the HPV vaccination programme was crucial for HPV vaccine uptake, we added the variable to verify its impact on the predictability of the model. The variable, which was collected at follow-up and defined as 'feeling well-informed about the programme', allowed us to estimate the influence of the quality of the programme's promotion perceived by the participants. As such, a factor reflecting not only personal characteristics but also implementational issues was incorporated. In next steps, also the added value of a precursor of behaviour was tested as well as of various socio-demographic variables.

Structural Equation Modeling SEM is a statistical method to test and refine theoretical models attempting to explain or predict social or behavioural phenomena. It is mostly used as a confirmatory analysis rather than an exploratory and can be implemented with cross-sectional as well as with longitudinal data. The two main advantages are 1) the possibility to include latent, unobservable variables, and 2) the inclusion of several multiple regressions simultaneously. In fields such as health behaviour research or psychology, where many outcomes have several determinants and many determinants lead to more than one outcome, SEM offers the possibility to investigate how variables behave in each other's company enabling us to test more complex models.

The techniques behind SEM are factor analysis and general linear regression: In a first step, a measurement model is build, allowing to identify unobserved, latent, variables by confirmatory factor analysis. In other words, different items of a questionnaire are loaded into new constructs with factor loadings reflecting the degree of association between the items and the latent variable (between -1 and 1). Based on a theoretical or empirical model, the researcher decides which items tap into which constructs (factors); most loadings will be fixed to zero indicating that certain items do not reproduce a certain construct. The measurement model is then established by estimating the parameters and can be modified or fine-tuned if the estimated covariance or correlation matrix does not reproduce the matrix of the sampled data. Finally, several goodness-of-fit indices can indicate whether the model is supported by the data.

In the second step, the structural model (or path model) is created, examining the relationships between constructs (both observed and unobserved). Through path analysis, multiple regression models can be combined and estimated simultaneously. As such, variables can take up the position of both exogenous (cfr. independent variable) and endogenous variable (cfr. dependent variable). More specifically, SEM allows to verify more complex relations between variables such as indirect effects, mediation chains, i.e. variables influencing an outcome variable through another variable ($X \rightarrow M \rightarrow Y$), and moderating variables, i.e. variables affecting the direction and/or strength of the relation between 2 other variables (cfr. interaction). Consequently, pathway analysis is more parsimonious, has a reduced type I error rate and will yield more precise estimates (smaller standard errors) compared with for example 2 sequential regressions $X \rightarrow M$ and $M \rightarrow Y$ [246]–[248].

For this second paper, SEM was chosen due to the technique's flexibility in terms of identifying different types of associations. The first step was however not implemented, i.e. the measurement model, since the goal of the research was not measuring the cohesion between several items but testing the Health Belief Model. We did check for internal consistency by applying Cronbach's alpha. Other possible techniques such as multilevel analysis were considered but an inter-class correlation coefficient for clustering of vaccine uptake at school level was calculated and was not considered high enough. Moreover, all of the other included variables are at personal level, while for the variable 'adequate promotion', which can be considered a personal validation of the promotion activities, a variable at school level, was created in order to include the fact that vaccine promotion was done at school level (i.e. the average of 'adequate promotion' per school was calculated).

Full title

Uptake of the Human Papillomavirus Vaccine in Kenya: testing the Health Belief Model through structural equation modeling on Cohort Data

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ABSTRACT

Background: Many studies investigate HPV vaccine acceptability, applying health behavior theories to identify determinants; few include real uptake, the final variable of interest. This study investigated the utility of the Health Belief Model (HBM) in predicting HPV vaccine uptake in Kenya, focusing on the importance of promotion, probing willingness to vaccinate as precursor of uptake and exploring the added value of personal characteristics.

Methods: Longitudinal data were collected before and after a pilot HPV vaccination program in Eldoret among mothers of eligible girls (N=255). Through Structural Equation Modeling, associations between vaccine uptake and the HBM constructs, willingness to vaccinate and adequate promotion were examined. Adequate promotion was defined as a personal evaluation of promotional information received. Finally, baseline cervical cancer awareness and socio-demographic variables were added to the model verifying their direct, mediating or moderating effects on the predictive value of the HBM.

Results: Perceiving yourself as adequately informed at follow-up was the strongest determinant of vaccine uptake. HBM constructs (susceptibility, self-efficacy and foreseeing father's refusal as barrier) only influenced willingness to vaccinate, which was not correlated with vaccination. Baseline awareness of cervical cancer predicted uptake.

Conclusions: The association between adequate promotion and vaccination reveals the importance of triggers beyond personal control. Adoption of new health behaviors might be more determined by organizational variables, such as promotion, than by prior personal beliefs. Assessing users' and non-users' perspectives during and after implementing a vaccination program can help identifying stronger determinants of vaccination behavior.

Key words:

HPV vaccination - Health Belief Model – Cohort – Kenya - Structural equation modeling

BACKGROUND

Cervical cancer poses a high burden on women's health in Kenya due to its high incidence and the poor prognosis of most patients. This elevated incidence rate is related to the high prevalence of HIV, the low screening coverage in Kenya (only 3.2% of all women are screened every 3 years), and the absence of the Human Papillomavirus (HPV) vaccine in the national vaccination program. [1] If the HPV vaccine becomes available in Kenya, it would provide women on-going protection against several high-risk HPV types. [2-4]

However, before adding the HPV vaccine to a national vaccination program, a situation analysis is valuable to prepare the introduction of the vaccine in terms of costs and infrastructure but also to assess readiness among the population. [5, 6] Worldwide, many studies have investigated girls' caregivers' willingness to vaccinate, often before the vaccine was introduced. While acceptability is usually high, doubts about the safety and efficacy of the vaccine are common. [7-11] In certain subpopulations, there is also the belief that the vaccines might promote promiscuity although past research does not support these claims. [12, 13]

Frequently, these acceptability studies apply (health) behavior theories that include a variety of factors (e.g. attitudes, beliefs, perceived barriers) which are believed to influence the likelihood of a certain action. [14, 15] By investigating these theories' constructs, researchers aim to identify determinants of vaccine uptake and refusal to incorporate them in vaccination strategies. An example of such theory is the 'Health Belief Model' (HBM), an established model often used to identify determinants of vaccination behavior. [14, 16] The original HBM indicates that in order for an individual to take action (e.g. to vaccinate your daughter), this person would have to (1) perceive the disease at least as 'moderately severe'; (2) perceive a susceptibility or vulnerability to the disease; (3) believe that there are benefits in taking the preventive action; and (4) not perceive major barriers obstructing the action. [17] Additionally, the HBM is often extended with two more constructs: (5) self-efficacy, indicating the '*expectancies about one's own competence to perform the behavior*' and (6) cues to action (CTA), i.e. '*the specific stimuli necessary to trigger the decision-making process*'. [18-20] Through a review of HPV vaccine acceptability studies in the USA, Brewer et al. showed that the abovementioned constructs influence people's willingness to vaccinate against cervical cancer. However, they do caution for overreliance on the results: since almost all studies included were cross-sectional no causal relations could be identified. [14]

It is generally agreed upon that there is a need to further test health behavior theories as to justify their use in promotion and vaccination interventions and to verify their applicability in different settings. It is known that the utility of the HBM varies according to the type of behavior that is predicted (preventive versus curative) and the health condition to be tackled (prevalence, morbidity and mortality of the disease in the study setting). Furthermore, cultural or socio-demographic variables might affect the predictive value of the model. [21, 22, 19] According to Janz and Becker, socio-demographic characteristics can have both direct and modifying effects on the (associations between) HBM constructs. [19] With regard to HPV vaccination, characteristics such as cervical cancer knowledge, age of the daughter or conservative thinking often affect acceptability. [14, 15] However, there is no clear description on which are most important and there is no agreement on how such personal characteristics fit the HBM (e.g. directly, mediated, or moderating effects).

Similarly, CTA are poorly studied. In theory, two types are distinguished: internal cues, such as symptoms, and external cues, such as advice from others or a promotional campaign. While these conventional definitions seem straightforward, measuring CTA remains a challenge given that “*a cue can be as fleeting as a sneeze or the barely conscious perception of a poster*”. [20] In addition, to truly be a factor that influences behavior, the trigger does not only have to reach the person, it also needs to prompt adoption of the behavior. [23] So depending on an individual’s perception, a certain cue might be interpreted as a trigger or not. Therefore, we propose to include a personal assessment of a cue such as promotion, expanding CTA to receiving and personally evaluating the motivator, e.g. ‘did you receive an invitation and was this appealing to you?’.

Finally, another point of discussion about the operationalization of the HBM is the outcome measure. While the original HBM had actual behavior as outcome (e.g. ‘vaccine uptake’), many studies apply the HBM to identify factors influencing acceptability or intention, considering these intervening variables as a precursor of behavior. [15, 14, 21] However, attitudes and intentions do not always translate into health behavior. [24] Research should therefore not only include antecedents but also the actual behavior as to distinguish factors that influence willingness versus those that inhibit or drive true behavior. Moreover, theories should be tested through longitudinal studies in which the influence of past behavior – often the biggest predictors of future behavior – is, if possible, excluded. [22, 21] Given that HPV vaccination in Kenya is not yet widespread, a pilot vaccination program offered the opportunity to measure the predictive value of the HBM constructs in this context and to explore the additional value of innovative variables.

The purpose of the present longitudinal study was to examine the applicability of the HBM to predict HPV vaccine uptake in Kenya. This general aim is specified into three underlying research objectives. First, we examined whether the HBM constructs predicted vaccine uptake, including a subjective evaluation of promotion. Second, we evaluated the validity of adding willingness to vaccinate to the HBM as mediator of uptake. Lastly, a hypotheses generating component was added, examining the direct- and modifying effects of personal characteristics on the (associations between the) HBM constructs.

METHODS

Pilot HPV vaccination program

Through the Gardasil Access Program (GAP), Moi Teaching and Referral Hospital (MTRH – Eldoret) received 9000 doses of the HPV vaccine. Ten out of forty-two public primary schools in Eldoret Municipality were randomly selected to participate in this pilot vaccination program. All girls in classes 4 to 8 of these schools (i.e. around 4000 pupils, approximately 9-13 years old), were eligible to receive three free doses of the quadrivalent vaccine. The vaccination was provided in MTRH, located in the center of Eldoret, while promotion was organized at school: health care providers informed the teachers who then passed on the information to students and parents. Implementation of such promotional activities differed from school to school, from parents meetings at school to teachers asking their pupils to notify their parents about the vaccination opportunity. The baseline and follow-up study took place in March 2012 and May 2013 respectively, i.e. right before and after the pilot program, which ran from May 2012 till March 2013. [25, 26]

Participants and Procedures

For this study, a random selection of girls eligible for vaccination were given an invitation letter for the face-to-face baseline interview, addressed to their mother. The number of girls per school was in proportion to the size of the school. Contact information requested at baseline was used to make an appointment for the follow-up interview: participants were contacted by phone, or the interviewers went looking for them at the description of the living-place or at school. If those contacted by phone were not able to participate in the complete, face-to-face follow-up interview, they were invited to answer by phone whether or not their daughter had received the HPV vaccine. (Figure 1) The women were interviewed in Swahili or English, depending on their preference.

During the baseline interview, mothers were given basic information and had the opportunity to ask questions regarding cervical cancer, HPV vaccination and the upcoming program in order to enable them to make an informed decision. More detailed information about the planned vaccination effort was meant to be provided to all parents of all eligible girls by promotional activities at school. To achieve consistency in the interviews, standard guidelines for introductions, interviews, and informed consent requests were practiced. [25, 26].

-- Figure 1. Flow diagram of the recruitment and response of study participants.--

Measures

Outcome variable uptake: The main outcome of the study was the actual behavior, i.e. HPV vaccine uptake, reported by the participants during the follow-up survey (i.e. when the pilot HPV vaccination program had closed). Uptake was reported per dose but assessed as a dichotomous variable (0 = received no HPV vaccine doses, 1 = received one or more doses of the HPV vaccine) given that few vaccinated girls had not completed the required scheme of three doses.

HBM constructs: All constructs were measured at baseline (before the pilot HPV vaccination program started). Perceived severity, susceptibility and three barriers ('foreseeing father's refusal', 'doubting vaccine efficacy' and 'perceiving lack of information') were assessed directly, while other HBM constructs (self-efficacy, trusting the health benefit of the vaccine and the two barriers 'having safety concerns' and 'foreseeing time constraints') were measured through several items (Table 1). All items were derived from the literature, and benefits and barriers were chosen based on previous research in similar contexts [15, 27, 28, 7, 29].

Mediator willingness to vaccinate: This variable was composed of the sum score of 2 baseline items, i.e. 'Would you vaccinate your daughter against cervical cancer?', and, 'Will you let your daughter get vaccinated against cervical cancer through this program?'. (Table 1)

Adequate promotion: During the follow-up interview, people were asked whether they had heard of the HPV vaccination program through school after the baseline interview and if so, whether they felt well-informed regarding the cervical cancer vaccination program. Through this we assessed if promotional activities had reached the women (cfr. CTA) and how the messages were perceived. Adequate promotion was thus a subjective evaluation of outreach messages. Since promotion differed among schools, we created a variable reflecting the level of adequate promotion in each school (i.e. the average of being well-informed at personal level for each school). This variable captured the 'school effect', i.e. the different levels of

promotion among the different schools, while the original variable measured being well-informed at personal level. (Table 1)

Means, standard deviations, and correlations across HBM constructs, willingness to vaccinate, adequate promotion and vaccine uptake are provided in the Supplementary Material (SM Table I).

--Table 1. Complete list of items used to assess Health Belief Model (HBM) constructs. --

Personal characteristics: We included ten personal factors and socio-demographic variables to explore their potential direct and modifying effects on the HBM constructs, willingness and uptake: (1) age of the participant; (2) age of the daughter; (3) class of the daughter; (4) marital status of the participant; (5) number of children (< 18 years) in the household; (6) ever heard of cervical cancer (awareness participant); (7) years of schooling of the participant; (8) origin of the participant: whether the participant grew up in an urban or rural area; (9) religion of the participant; (10) socio-economic status (SES): a scale representing the quality of the building materials used for the house. All these factors were obtained from the baseline survey. [25] For some of the items (marital status, origin, and religion) answer options in the questionnaire were merged based on preliminary analysis and to facilitate interpretations.

Statistical Analyses

To compare participants who completed versus participants who did not complete the follow-up survey, we performed an univariate analysis of variance (ANOVA). Cronbach's alpha was calculated to check for internal consistency of constructs' items (>0.75 was considered acceptable). [30] Personal characteristics with less than 5% missing data were imputed using the expectation maximization method (EM), after establishing that the data were missing completely at-random (Little's MCAR $\chi^2(259) = 257.583, p = .513$). If a background characteristic had more than 5% missing values, only data from participants without missing values was used to build models including that variable. Structural equation modeling (SEM) was applied to investigate the three specific research objectives.

The first research objective, evaluating whether the HBM predicts HPV vaccine uptake in a Kenyan context, was examined with two models: Model 1, containing the HBM constructs measured at baseline (perceived severity, susceptibility, benefits, barriers, and self-efficacy) and Model 2, adding adequate promotion, measured at follow-up, as predictor for uptake.

The second research objective, assessing the validity of adding willingness to vaccinate to the HBM as mediator of uptake, was examined with Model 3. This model contained all the

predictors of Model 2. However, the baseline HBM constructs were specified to predict willingness, and willingness and adequate promotion to predict uptake.

Finally, we examined the direct and modifying effects of all ten personal characteristics on the (associations between the) HBM constructs. To do so, we applied an exploratory modeling procedure. First, all factors were independently added as direct (e.g. heard of cervical cancer → uptake), mediated (e.g. religion → severity → willingness), or moderating effect (e.g. age of the daughter → willingness, with barrier ‘father’s refusal’ moderating the effect) in Model 3 (ESM Table II). Next, Model 4 was fitted containing all significant effects from this exploratory procedure in addition to the predictors specified in Model 3. To correct for multiple testing we applied a more conservative critical p-value of 0.01.

Models were fitted using the weighted least-squares estimator with mean and variance adjustment (WLSMV; because of the dichotomous primary outcome variable (uptake)). [31] To ensure reliable interpretation of the results, the underlying assumptions of SEM were checked for all variables included in the models (multicollinearity, linearity in the logit, missing data, and outliers). Furthermore, the nine baseline HBM constructs were allowed to correlate in all models. In addition, all models were evaluated by assessing the efficacy of each model in predicting willingness and uptake (R^2). Since uptake is a dichotomous variable, R^2 is estimated assuming that the categorical indicator is a coarse categorization of a normally distributed underlying dimension. Furthermore, the fit of the path models (Model 3-Model 4) was assessed with the chi-square overall goodness-of-fit statistic (CHISQ), the comparative fit index (CFI), the root-mean-square error of approximation (RMSEA), and the weighted root mean square residual (WRMR). RMSEA values $<.06$, CFI $>.97$, and WMSR <1.0 indicate close fit. [32, 33]

Sample size

The necessary sample size was calculated for a previous study and data analysis. [25] With 255 observations, the data set is however also adequate for SEM (i.e. minimum 200 observations). [32]

Ethics, consent and permissions

The Institutional Research and Ethics Committee of Moi Teaching and Referral Hospital, and the Ethical Committee of Ghent University Hospital approved this study (approval numbers FAN:IREC 000771 and B670201212980-B670201317007, respectively). Written informed consent was requested before the baseline interview, and this was verbally confirmed before the follow-up interview. Participants received no incentives for participation in the baseline

survey, while a financial compensation of 200 Kenyan Shilling (US \$2.34) was given for the time and effort they invested in a second face-to-face interview. [25]

RESULTS

Participation

A flow diagram of recruitment and response of participants within this longitudinal research design is presented in figure 1. Of the 472 invited participants, only 287 agreed to participate in the baseline survey (61%), while 256 of them (89%) agreed to participate in the follow-up survey. Non-completers ($n = 31$) were similar to completers ($n = 256$) on all HBM constructs and personal characteristics with only one exception. Compared to completers, the non-completers scored slightly lower on self-efficacy ($t(285) = 2.547, p = 0.011$).

Of the 256 participants of the follow-up survey, 8% ($n = 20$) only provided the information about their daughter's vaccination status through the short telephone survey; data on adequate promotion is missing for them. One participant was deleted from analysis because she did not report whether her daughter was vaccinated ($N_{\text{analyses}} = 255$).

The baseline HBM constructs did not have any missing values and Cronbach's alpha was found to be acceptable ($>.75$) for all HBM constructs (table 1). [30]

Descriptive analysis

Of the 255 participants included in the analyses, the average willingness to vaccinate was 4.4 (range 1-5). This positive attitude towards the HPV vaccine was reflected in the baseline measured HBM constructs: the average perceived severity was 3.8 (range 1-5), average perceived susceptibility was 3.7 (range 1-5), average perceived health benefits was 4.6 (range 1-5). Furthermore, proposed barriers were not often agreed on. The average scores on the barriers (range 1-5) were: lack of information 3.5 (range 1-5), doubting vaccine efficacy 2.4, time constraints 1.4, safety concerns 2.6, and father's refusal 1.5. Lastly, the average score of mothers' self-efficacy was 4.3 (range 1-5). (ESM Table I)

In the follow-up survey, 37% of the participants mentioned they had not been well-informed about the program (adequate promotion=0). However, the average percentage of people mentioning this lack of promotion fluctuated per school (18% - 83%). By the end of the program, 31% had their daughter vaccinated against cervical cancer with one dose or more (72% of them had received 3 doses).

Of all personal characteristics, 4 had less than 5% missing values (age of the daughter, age of the participant, cervical_cancer_awareness and origin_of_the_participant) and one had more than 5% (years of schooling of the participant). The characteristics of the participants can be summarized as follows: the average age of the mothers was 36 (range 21-59); the average age of the daughter was 12 (range 8-18); the average class of the daughter was 6 (range 4-8); 76% of the participants had a partner (married or living together) while the remaining 24% was either separated, widowed or never had a partner (i.e. currently single); 4.5 (range: 1-7) was the average number of children in the household; 60 % had at least heard of cervical cancer (awareness); the average years of schooling of the participant was 8.4 (range: 0-16); 60% of the participants grew up in a Kenyan city, 38% were originally from the countryside and 1% was from outside Kenya (the latter 2 were grouped for analysis); 80% of the participants indicated to be Protestant, 15 % Catholic, 4% Muslim, 1% other or no religion (for analyses this was combined into Muslim (4.3%) vs. non-Muslim (95.7%)); and the average score of the quality of the building materials of the house was 4.6 (range 2-7).

The Health Belief Model

Research objective 1: Application of the HBM

First, to examine how the nine HBM constructs measured at baseline predicted uptake, we fitted Model 1 (figure 2.a). The nine predictors only accounted for 8% of the variance in uptake. The only significant predictor of uptake was self-efficacy (standardized path coefficient self-efficacy $\beta = .31$).

In Model 2 (figure 2.b) it was examined whether addition of the two adequate promotion variables increased the explained variance of uptake. The two included adequate promotion variables, adequate promotion at the individual level ($\beta = .33$) and adequate promotion at the school level ($\beta = .49$), increased the explained variance of uptake to 49%. None of the other predictors were significantly related to uptake.

-- Figure 2. Health Belief Model to predict the HPV vaccine uptake without adequate promotion (a. Model 1) and with adequate promotion (b. Model 2) --

Research objective 2: Willingness as a predictor for uptake

Model 3 (Figure 3) assessed the validity of adding willingness to vaccinate to the HBM as mediator of uptake. In Model 3, the nine baseline HBM constructs were specified to predict willingness, and willingness and adequate promotion to predict uptake. Model 3 provided a close fit to the data [CHISQ(11) = 7.276, $p = .776$; RMSEA = .00; CFI = 1; WRMR = 0.51].

Overall, 47% of the variance in uptake and 41% of the variance in willingness was explained by predictors in the model. Willingness was not significantly associated to uptake. In contrast, adequate promotion at the individual level ($\beta = .34$) and at the school level ($\beta = .46$) were significantly related to uptake. Susceptibility ($\beta = .25$), the barrier 'foreseeing father's refusal' ($\beta = -.15$), and self-efficacy ($\beta = .41$) were significantly related to willingness.

-- Figure 3. Health Belief Model to predict the HPV vaccine uptake mediated by willingness (Model 3). –

Research objective 3: Influence of personal characteristics in the HBM

Finally, in Model 4 we examined the direct and modifying effects of personal characteristics on the (associations between the) HBM constructs. A priori, an exploratory modeling procedure was applied examining the effects (1. direct, 2. mediated, 3. moderating) of each personal parameter individually. Of the direct effects of the characteristics, only cervical cancer awareness was found to be significantly ($p < .01$) related to uptake. Next, the effect of religion (i.e. being Muslim) on willingness was found to be significantly mediated ($p < .01$) by: severity, susceptibility, self-efficacy, 'trusting the health benefit', and the barriers 'foreseeing time constraints' and 'foreseeing father's refusal'. Furthermore, the age of the daughter was found to have a significant ($p < .01$) effect on the relation between barrier 'foreseeing father's refusal' and willingness. Lastly, marital status and SES had a significant ($p < .01$) effect on the relation between susceptibility and willingness. (ESM table II)

In Model 4 (figure 4) we added all these significant effects of the personal characteristics to Model 3. To avoid estimation errors, only the strongest of the interactions with susceptibility (i.e. susceptibility*marital status) was incorporated in the model. The predictors in the model explained 48% of the variance in willingness and 52% of the variance in uptake; willingness was not significantly associated with uptake ($p=0.185$). Religion was found to be significantly ($p < .05$) related to severity ($\beta = -.23$), susceptibility ($\beta = -.13$), self-efficacy ($\beta = -.15$), 'trusting the health benefit' ($\beta = -.20$), and the barriers 'foreseeing time constraints' ($\beta = .19$), and 'foreseeing father's refusal' ($\beta = .24$). Next, susceptibility, the barrier 'foreseeing father's refusal', and self-efficacy were related to willingness ($\beta = .46$, $\beta = -.63$, $\beta = .39$ respectively). Furthermore, two interactions were significantly related to willingness: marital status*susceptibility ($\beta = -.27$), and age of the daughter*barrier 'foreseeing father's refusal' ($\beta = .40$). Lastly, in addition to adequate promotion at individual level ($\beta = .30$) and at school level ($\beta = .51$), baseline cervical cancer awareness was significantly related to uptake ($\beta =$

.20). Acceptable goodness of fit was obtained with Model 4 (CHISQ (85), $p=0.0001$, RMSEA = .052; CFI = 0.920; WRMR = 0.910).

-- Figure 4. Health Belief Model to predict the HPV vaccine uptake with modifying personal characteristics (Model 4). --

DISCUSSION

The Health Belief Model is an established health theory often used as framework to develop health interventions. In this model, constructs concerning severity, susceptibility, benefits, barriers and self-efficacy are considered important determinants of the health related behavior. [17-20] This study examined whether the HBM can be applied to predict HPV vaccine uptake in Kenya, a country with little research on HPV vaccine acceptability and uptake.

Research objective 1: Application of the HBM, including adequate promotion

A first remarkable result of this study was the large difference between Model 1 and Model 2: adding adequate promotion, at both personal and school level, increased the predictive value from 8% to 49%. The strong correlation between adequate promotion and HPV vaccination is not surprising since many studies have stressed the importance of triggers such as health provider's recommendation. [34, 35, 16, 36] Our results might, however, overestimate the strength of the association because of two reasons: 1) Unlike the other HBM constructs, adequate promotion is measured at follow-up, i.e. when uptake was also recorded, which means the direction of the correlation is indeterminable, and 2) adequate promotion reflects the quality of the promotion from the perspective of the participant. This means that two participants who received the same information through the same channel, might report adequate promotion differently, most possibly in agreement with the vaccination status of their daughter. Nevertheless, the strong correlation cannot be overlooked: whether or not the daughter received the vaccine was highly associated with obtaining sufficient information. Furthermore, it is important to mention that before adequate promotion was added to the model, self-efficacy was the only HBM construct found to have a positive correlation with vaccine uptake. This clearly shows that besides an external trigger, participants still need to perceive themselves capable in performing the action, i.e. taking their daughter for a vaccination, and therefore justifies addition of this construct to the HBM.

The fact that none of the other HBM constructs predicted uptake is surprising, yet there are several explanations possible. First of all, threat (severity and susceptibility) and 'trusting the health benefit' are very skewed, making it more difficult to identify relations. All participants considered cervical cancer as a very severe disease which their daughter was (very) likely to get, and they all were driven to protect their daughter's health. Given that cancer is perceived severe and deathly worldwide, it is not a startling ascertainment that also in Kenya, where treatment remains inaccessible for many people, cervical cancer is considered a serious disease. Moreover, severity has often been identified as a construct with less predictive value, definitely with regards to preventive behavior. [37-39, 19] With regard to susceptibility, one can wonder how well parents are capable to estimate future (sexual) behavior and well-being of their daughter. Do they overestimate their daughter's vulnerability because of concern and anxiety? Such emotions clearly also influence decision-making yet they are not included in cognitive theories. [20, 40] Finally, the current HIV epidemic, affecting all layers of society, might have increased their sense of vulnerability regarding sexual transmittable infections. Barriers are very often among the strongest predictors of behavior [19, 38], but in our study none were associated with uptake. Again, little variance was found: almost all participants trusted the efficacy and safety of the vaccine and worried little about time boundaries or objection of their partner. Social desirability and poor assessment skills of the participants might be at the base of these highly pro-vaccine statements. On the other hand, other studies found similar results and the worldwide success of childhood vaccination might also encourage Kenyan women to truly trust and welcome the new HPV vaccine, as other studies have also found. [7-9] Future studies can explore this more in-depth e.g. by applying more multiple item measures, since they have better predicting power, or by assessing users' and non-users' perspectives during and after program implementation. While this latter approach would not contribute to identifying causal relations it could help to explore and identify other determinants than the HBM constructs given that in this study we found little or no support for the HBM in the current context of cervical cancer vaccination in Kenya.

Research objective 2: Willingness as a predictor for uptake

Adding willingness to vaccinate as mediator of uptake lowered the predictive value of the HBM from 49% to 47%. Moreover, willingness had no effect on vaccine uptake, while adequate promotion remains highly associated. These results raise the issue of control, i.e. to what extent are people truly in control of vaccination behavior if they are depending on providers' motivation and initiation? As stated by Sheeran P. (2011), the gap between

intention and behavior is caused by those with high intention who don't act (inclined abstainers) and those with low intentions who do act (disinclined actors). [24] In the case of this HPV vaccination pilot program, it seems that many participants are inclined abstainers as a result of poor promotion, i.e. they wished to vaccinate their daughter against cervical cancer but were not well enough informed to do so. On the other hand, we need to ask ourselves the question how well people can express their wish and predict their behavior in this context. Again, socially desirable answers may have caused overestimation of willingness, but there are many other *factors* [24] that may have led to expression of high interest and/or low uptake. Most participants had never heard of the HPV vaccine and 40% had never heard of cervical cancer. For them to process all information received during the baseline interview and immediately report acceptability and intention to vaccinate might have been difficult or unreliable (*cognitive variables*). [24, 40] In addition, the time-lapse between the first interview and the start of the pilot program, might have given participants time to overthink (*temporal stability*) and discuss cervical cancer vaccination with friends and family (*subjective norms*). As a result, some participants might have changed their opinion and preferred not to act. [35, 41, 24] Finally, other important activities (*competing intentions*) might have inhibited participants from taking the time to let their daughter get vaccinated against cervical cancer. [24] Given the harsh living circumstances of many of our participants, other priorities are not unlikely.

The nine baseline HBM constructs, which only explained 8% of the variance of uptake (Model 1a), explained 41% of the variance of willingness. Given that willingness to vaccinate was also measured at baseline (as opposed to uptake at follow-up), it was expected to detect more correlations among the cross-sectional data. Self-efficacy was the strongest correlate, but also susceptibility was positively associated. Perceived vulnerability has been previously related with acceptability [10, 34] and uptake of (preventive) behavior [19, 20, 18, 16], yet as described above, we did not find the latter correlation. Finally, participants who thought of their partner as somebody who would oppose to vaccinate their daughter against cervical cancer, were less likely to accept the vaccine. Interventions should target these characteristics and include all decision makers as to increase the willingness to vaccinate.

Research objective 3: Influence of personal characteristics in the HBM

Personal characteristics altered Model 3 and increased the explained variance of willingness from 41% to 48% and of uptake from 47% to 52%. However, given that only acceptable goodness of fit was achieved, we merely consider this as a sketch on how these variables are

related with HBM constructs, willingness and uptake as opposed to an adapted version of the model. For example, awareness had a direct impact on uptake which supports the importance of cognitive variables: participants who had heard of cervical cancer before baseline were more likely to vaccinate their daughter. Whether the effect is a result of knowledge of cervical cancer rather than the ability to process the new information regarding the vaccine more easily, is yet to be determined. Also, religion clearly affected the HBM constructs: Muslims were more likely to agree with the barriers ‘father’s refusal’ and ‘time constraints’, were less likely to perceive cervical cancer as severe, thought their daughter was less susceptible, had lower self-efficacy, and were less driven by the fact that the vaccine would protect their daughter’s health. The underlying reasons, e.g. a more conservative attitude or mistrust in the health system, are to be investigated more in-depth. Finally, the positive effect of susceptibility on willingness was higher for single mothers, and the negative relation of perceiving the father as a barrier for willingness weakened when the daughter was older. While the former interaction might reveal a kind of freedom to express intentions among women without a partner, the latter hints that even though a partner may object, mothers of older girls still intended to vaccinate, maybe without his consent. Our results suggest that personal characteristics influence vaccination differently in different circumstances, demonstrating the complexity of the decision-making process regarding cervical cancer vaccination. Further research is necessary to define whether or not some of these variables would have an added value to the HBM.

CONCLUSIONS

We found little support for the HBM in the context of HPV vaccination in Kenya and neither was willingness a good predictor for uptake. Due to pro-vaccine attitudes at baseline and low vaccination rate (31%) at follow-up, our study may have lacked power to find associations. However, other longitudinal studies have equally showed that attitudes, health beliefs and intentions are not always strong correlates of HPV vaccination. [36, 35, 42] Reiter et al. proclaim that *“beliefs and attitudes may not be important determinants in the early adoption of behaviors that are not well understood by most individuals”*. [35] In the same light and based on the strong correlation between adequate promotion and vaccine uptake, we hypothesize that supportive important others, motivation by health providers and general trust in the health system may be of extreme importance to counteract knowledge gaps and doubts. Therefore, we recommend to further study whether interpersonal variables and variables at the

level of community or health system are important determinants of new (preventive) health actions in addition to personal beliefs, and in which contexts. [43, 40] By monitoring future HPV vaccination programs and by assessing users' and non-users' perspectives these variables could be more explored and if deemed appropriate added to the HBM. Furthermore, such research could help identifying specific components of promotion interventions necessary for the target group to perceive promotion as adequate. Finally, our results also encourage the examination of modifying effects of personal characteristics since they might boost the predictive value of the HBM. Identification of such determinants might then help to increase the efficacy of future promotion campaigns and as such, create awareness, consensus and support for HPV vaccination at the community level.

Authors' contributions

HV participated in the conception and design of the study, carried out data collection and helped with interpretation of the data and drafting of the manuscript. MAVS contributed to the design of the study, carried out data collection and analysis, and helped with interpretation of the data and drafting of the manuscript. VN helped carrying out data collection, assisted with interpretation of the data and critically reviewed the manuscript. KM & OD participated in the conception and design of the study, helped with interpretation of the data and critically reviewed the manuscript. FO contributed to the design of the study and data analysis, assisted with interpretation of the data and critically reviewed the manuscript.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Table 1. Complete list of items used to assess the health belief model (HBM) constructs and willingness.

CONSTRUCTS	baseline/ follow-up ^a	Item wording (response options)	# items	α^b
Severity	baseline	How serious would it be if your daughter would have cervical cancer? (1=not serious at all–5=very serious)	1	n/a
Susceptibility	baseline	How likely is it that your daughter would develop cervical cancer in the future? (1=very unlikely–5=very likely)	1	n/a
Benefit health	baseline	You would vaccinate your daughter because: The vaccine will protect her health. (1=strongly disagree–5=strongly agree)	3	.888
		The vaccine will protect her reproductive health. (1=strongly disagree–5=strongly agree)		
		The vaccine will prevent her from having cervical cancer. (1=strongly disagree–5=strongly agree)		
Barriers	baseline	You would not vaccinate your daughter because: You need more information first (1=strongly disagree–5=strongly agree)	1	n/a
Lack of information		You doubt that the vaccine will truly prevent cervical cancer and genital warts (1=strongly disagree–5=strongly agree)	1	n/a
Doubt vaccine efficacy		You think vaccination always takes a lot of time. (1=strongly disagree–5=strongly agree)	2	.791
Time constraints		You think it's inconvenient that she needs 3 doses. (1=strongly disagree–5=strongly agree)	3	.882
Safety concerns		You think it might have unknown future side effects. (1=strongly disagree–5=strongly agree)		
		You think it might interfere with her fertility. (1=strongly disagree–5=strongly agree)		
		You're afraid the vaccine will not be administered safely (clean needles). (1=strongly disagree–5=strongly agree)		
Father's refusal		You think your partner or her father won't approve it. (1=strongly disagree–5=strongly agree – 0=no current relationship)	1	n/a
Self-efficacy	baseline	Are you confident that you could let your daughter get vaccinated if you wanted? (1=not confident at all–5=very confident)	2	.762
		For you, if you want your daughter to be vaccinated against cervical cancer, that would be. (1=very difficult–5=very easy)		
Adequate promotion^c	follow-up			
Personal level		Did you feel well informed regarding the cervical cancer vaccination program? (0=no, 1=yes)	1	n/a
School level		School average of adequate promotion at personal level	1	n/a
Willingness to vaccinate	baseline	Would you vaccinate your daughter against cervical cancer? (1=very unlikely–5=very likely)	2	.901
		Will you let you daughter get vaccinated against cervical cancer through this program? (1=very unlikely–5=very likely)		

^aMeasure obtained from baseline or follow-up interview.
^bCronbach's alpha (α) indicating the reliability.
^cParticipants were asked if that had heard about the HPV vaccination study at the hospital after being informed during the baseline interview. If yes, they were asked whether or not they had felt well-informed.

Figure 1. Flow diagram of the recruitment and response of study participants.

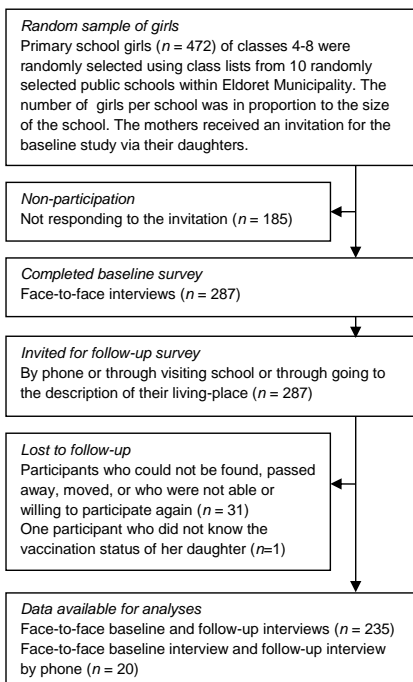


Figure 2. Health Belief Model to predict HPV vaccine uptake without adequate promotion and with adequate promotion.

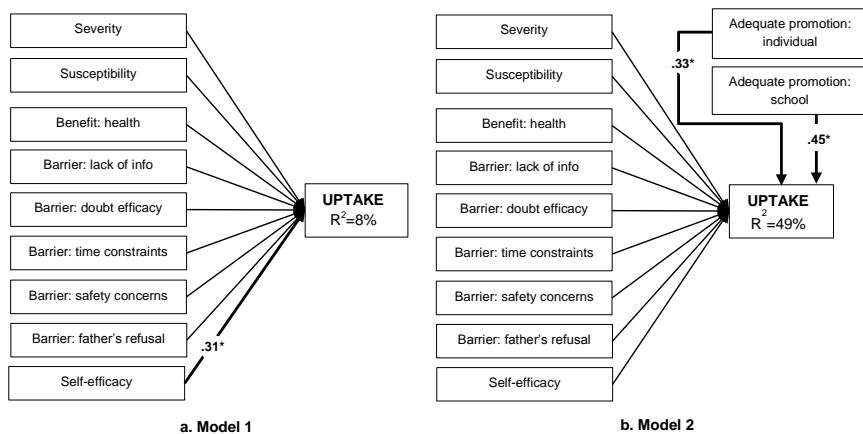


Figure 2. Health Belief Model to predict HPV vaccine uptake without adequate promotion (a. Model 1) and with adequate promotion (b. Model 2). Numbers represent the significant ($p < .05$) standardized parameters (β). Thin lines without numbers represent non-significant parameters in the model. R^2 represents the explained variance of the dependent variable. ($N = 255$)

Figure 3. Health Belief Model to predict HPV vaccine uptake fully mediated by willingness to vaccinate.

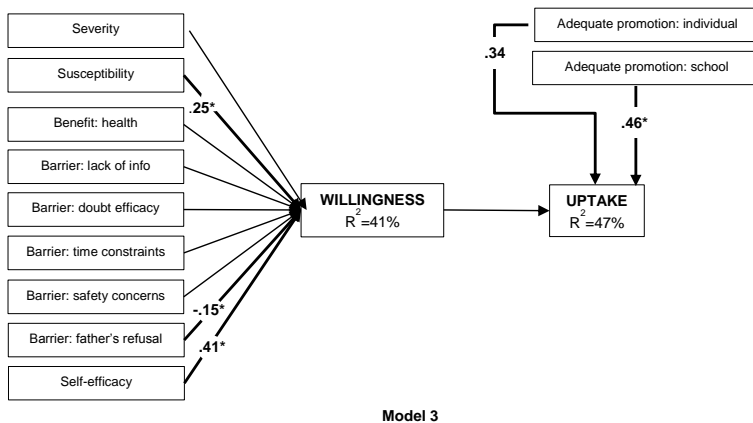
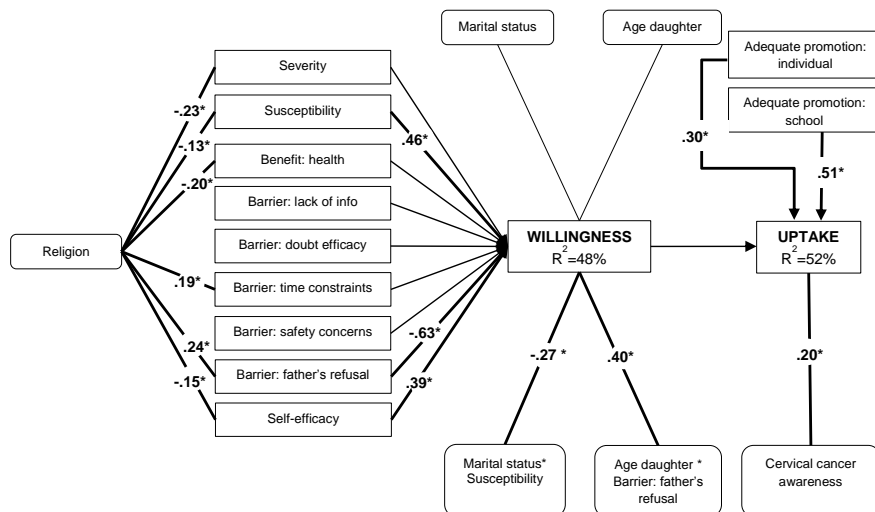


Figure 3. Health Belief Model to predict HPV vaccine uptake fully mediated by willingness to vaccinate (Model 3). Numbers represent the significant ($p < .05$) standardized parameters (β). Thin lines without numbers represent non-significant parameters in the model. R^2 represents the explained variance of the dependent variable. ($N = 255$)

Figure 4. Health Belief Model to predict HPV vaccine uptake including personal characteristics and mediated by willingness.



Model 4

Figure 4. Health Belief Model to predict HPV vaccine uptake including personal characteristics and fully mediated by willingness to vaccinate (Model 4). Numbers represent the significant ($p < .05$) standardized parameters (β). Thin lines without numbers represent non-significant parameters in the model. R^2 represents the explained variance of the dependent variable. ($N = 255$)

Supplementary Material

Table i. Correlations, means, standard deviations, and ranges of Health Belief Model constructs.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
Correlation coefficients:													
1. vaccine uptake	1.00												
2. Willingness to vaccinate	.13*	1.00											
3. Severity	.00	.25*	1.00										
4. Susceptibility	.02	.38*	.21*	1.00									
5. Benefit health	.08	.34*	.31*	.06	1.00								
6. Barrier lack of information	.02	.02	.06	-.09	.22*	1.00							
7. Barrier doubt vaccine efficacy	-.01	-.15*	.03	-.14*	-.07	.38*	1.00						
8. Barrier time constraints	-.03	-.21*	-.18*	-.08	-.29*	-.02	.10	1.00					
9. Barrier safety concerns	.00	-.15*	.03	-.17*	.02	.37*	.79*	.10	1.00				
10. Barrier father's refusal	-.08	-.39*	-.09	-.28*	-.13*	.09	.26*	.19*	.29*	1.00			
11. Self-efficacy	.18	.54*	.27*	.15*	.56*	.11	-.03	-.32*	-.02	-.32*	1.00		
12. Adequate promotion: individual	.36*	.14*	.03	.05	.04	-.07	.06	-.05	.05	-.17*	.11	1.00	
13. Adequate promotion: school	.36*	.16*	.07	.07	.09	.02	.09	-.07	.10	-.08	.15*	.42*	1.00
Mean ^a	31%	4.43	4.82	3.79	4.60	3.51	2.37	1.38	2.55	1.54	4.33	62%	.62
SD	.46	.86	.59	1.03	.58	1.47	1.35	.56	1.29	1.43	.81	.47	.20
Range	0/1	1-5	1-5	1-5	1-5	1-5	1-5	1-4	1-5	0-5	1-5	0/1	.18-.83

N = 255.

^a Means of dichotomous variables are replaced by proportions of ones observed.

Table ii. Direct, mediated, and moderating effects of socio-demographic variables (X_{adv}) on Health Belief Model constructs (X_{hbmc}), willingness and vaccine uptake: unstandardized path coefficients (β).

	Socio-demographic variable (X_{adv})	N^a	Direct effect of X_{adv} on Uptake^b	By X_{hbmc}-mediated effect of X_{adv}^c	Moderating effect of X_{adv} on the relations in Model 3^d	Direct effects of interaction terms^e
1.	Age of participant	255	--	--	--	--
2.	Age of daughter	255	--	--	Age daughter * Barrier father's refusal- Willingness 0.049 (0.015)*	Age daughter – Willingness - 0.047 (0.039)* Barrier father's refusal -0.689 (0.179)*
3.	Class of daughter	255	--	--	--	--
4.	Marital_status of participant (single vs. with partner)	255	--	--	Marital_status * Susceptibility- Willingness -0.267 (0.086)*	Marital_status- Willingness 1.543 (0.321)* Susceptibility- Willingness 0.385 (0.072)*
5.	Number of children in household	255	--	--	--	--
6.	Heard of cervical cancer	255	0.664 (0.213)*	--	--	--
7.	Schooling of participant	236	--	--	--	--
8.	Origin of participant (urban vs. rural)	255	--	--	--	--
9.	Religion of participant (non-Muslim vs. Muslim)	255	--	Severity -0.661 (0.086)* Susceptibility - 0.628 (0.239)* Benefit health - 0.558 (0.113)* Barrier time constraints 0.505 (0.104)* Barrier father's refusal 1.036 (0.275)* Self-efficacy -0.523 (0.153)*	--	--
10.	Socio-economic status (SES) ^f	255	--	--	SES*Susceptibility-Willingness- 0.116 (0.038)*	SES-Willingness 0.419 (0.130)* Susceptibility- Willingness 0.716 (0.157)*

* $p < .01$; -- = indicating that no significant (direct/moderated/mediating) effects were found for the socio-demographic variable; standard errors are in parentheses.

^a If a background characteristics had more than 5% missing values, models, verifying the direct, mediated or moderated effect of the variable, were compared using only data from participants who had no missing values.

^b Direct effects were examined through specifying a direct effect of the personal characteristic on vaccine uptake within Model 3.

^c Mediated effects were examined through specifying direct effects from the personal characteristic to the ten predictors in Model 3.

^d Moderating effects on the relations in Model 4 were examined for all personal characteristics separately.

^e Direct effects of the variables in the moderation on dependent X_{hbmc} .

^f A score representing the quality of the building materials of the house.

Chapter 8

Implementation of an HPV vaccination program in Eldoret, Kenya: results from a qualitative assessment by key stakeholders

Paper 3: Evaluating the HPV vaccination programme The last paper reflects on the HPV vaccination programme from a different angle: qualitative data is presented (versus the quantitative results in the first two papers), collected among several stakeholders (as opposed to the mothers of girls). By assessing the perspectives of fathers, teachers and vaccinators, we complemented the previous results with insights at family as well as community and organizational level. Since the FGD were organized after the HPV vaccination programme had taken place, we were able to capture users' perspectives as opposed to hypothetical attitudes towards the HPV vaccine. Furthermore, barriers identified in the longitudinal study could be explored more in-depth.

RESEARCH ARTICLE

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Implementation of an HPV vaccination program in Eldoret, Kenya: results from a qualitative assessment by key stakeholders

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Abstract

Background: Cervical cancer strikes hard in low-resource regions yet primary prevention is still rare. Pilot projects have however showed that Human Papillomavirus (HPV) vaccination programs can attain high uptake. Nevertheless, a study accompanying a vaccination demonstration project in Eldoret, Kenya, revealed less encouraging outcomes: uptake during an initial phase targeting ten schools (i.e., 4000 eligible girls), was low and more schools had to be included to reach the proposed number of 3000 vaccinated girls. The previously conducted study also revealed that many mothers had not received promotional information which had to reach them through schools: teachers were sensitized by health staff and asked to invite students and parents for HPV vaccination in the referral hospital. In this qualitative study, we investigate factors that hampered promotion and vaccine uptake.

Methods: Focus group discussions (FGD) with teachers (4) and fathers (3) were organized to assess awareness and attitudes towards the vaccination program, cervical cancer and the HPV vaccine, as well as a FGD with the vaccinators (1) to discuss the course of the program and potential improvements. Discussions were recorded, transcribed, translated, and analyzed using thematic analysis. In addition, a meeting with the program coordinator was set up to reflect upon the program and the results of the FGD, and to formulate recommendations for future programs.

Results: Cervical cancer was poorly understood by fathers and teachers and mainly linked with nonconforming sexual behavior and modern lifestyle. Few had heard about the vaccination opportunity: feeling uncomfortable to discuss cervical cancer and not considering it as important had hampered information flow. Teachers requested more support from health staff to address unexpected questions from parents. Non-uptake was also the result of distrust towards new vaccines. Schools entering the program in the second phase reacted faster: they were better organized, e.g., in terms of transport, while the community was already more familiarized with the vaccine.

Conclusions: Close collaboration between teachers and health staff is crucial to obtain high HPV vaccine uptake among schoolgirls. Promotional messages should, besides providing correct information, tackle misbeliefs, address stigma and stress the priority to vaccinate all, regardless of lifestyle. Monitoring activities and continuous communication could allow for detection of rumors and unequal uptake in the community.

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Background

In Kenya, cervical cancer has the highest incidence and is the most lethal cancer among women, after breast and esophagus cancer. Yearly, almost 5000 women are diagnosed while close to 2500 die. East Africa is indeed one of the most affected regions of the world, with age standardized incidence and mortality four times as high as in more developed regions [1]. This health inequality gap is not only the result of limited screening and treatment options, also awareness of the disease and its symptoms is insufficient [2, 3]. If uptake of preventive measures remains inadequate, and taking into consideration the present population growth, the burden of cervical cancer could exponentially increase with over 50 % more new cases and deaths over the coming years [4].

Primary prevention through HPV vaccination has the potential to significantly reduce the incidence of cervical cancer and to eliminate cervical cancer disparity. The vaccines currently on the market are likely to prevent up to 70 % of cervical cancers, i.e., those caused by HPV 16 or 18 [5–7]. National vaccination programs are already rolled out in over 39 - mostly high-income - countries. In less wealthy regions, where the vaccines can have most impact, large scale vaccination efforts are still scarce [3, 4, 8]. Through demonstration projects, many low- and middle income countries have however gained experience regarding the introduction of the HPV vaccines. Results are very promising: high uptake is achieved (>70 %) and drop-out rates for second and third doses are low [9–14].

A longitudinal study linked with a demonstration program in Eldoret, Kenya, revealed however a different outcome: although the majority of mothers of eligible girls had expressed a wish to vaccinate their daughter before the start of the program (88 %; 253/287), only 31 % (79/254) of those who entered the follow-up study reported to have eventually done so. The main reason for non-uptake was lack of information on where and when the vaccination took place [15]. Poor promotion might thus have hampered the program. Other pilot programs already showed that thorough formative research followed by sensitization, especially through community influencers, is indeed key for success [11, 16, 17]. But as Kane et al. pointed out, one cannot expect similar results without investing a considerable amount of time and money to promotional activities [4]. Another reason for the noted difference in coverage might be a variation in the definition of uptake, and more particularly the targeted population (i.e., the denominator). Ladner et al. presented uptake rates of 21 demonstration projects; all achieved over 75 %. However, these figures might be overestimations for two reasons, as reported by the authors: 1) it is not clear what data was used in each study to calculate the target population which means the

denominator might have been unreliable, and 2) programs might have targeted and recruited more girls than originally planned [10]. Post-vaccination studies could provide clarification. In the case of the program in Eldoret, it remains important to further investigate why coverage was insufficient and why people were ill-informed. By interviewing several stakeholders, further insight can be obtained and findings of the abovementioned study, in which women's perspectives were assessed, can be triangulated. Including the male guardian, for example, helps clarifying whether women discuss cervical cancer prevention with their partner and whether they involve them in the decision (given that male partners often have decisive power [15, 18]). Also teachers are deemed important since they had an important task in this program, i.e., promotion of the vaccine, which was not well perceived by the women in the longitudinal study. Giving the teachers a voice enables us to understand how they experienced the program. Finally, the vaccinators themselves as well as the program coordinator can give insights regarding the organization and can reflect on the course of the program. The latter was in charge of promoting the HPV vaccination program among the teachers.

Many studies have already provided important insights from pilot vaccination projects. Through monitoring and evaluation, barriers are recognized, underserved populations are detected and effective sensitization and delivery strategies are identified [9, 11, 17, 19–25]. In general, internationally more attention is going to implementation research and process evaluations in order to improve and understand effectiveness of programs. Additionally, there is a call for a close follow-up of vaccination strategies: "Introducing new vaccines and ensuring they reach all people for whom they are intended is a challenging task, and the science related to implementing interventions effectively, efficiently, and with equity and high fidelity has received inadequate attention, particularly in African and Asian countries where overall research capacities are limited" [26].

In light of this, the aim of this study was to evaluate the implementation of the HPV vaccination demonstration program in Eldoret. In order to do so, three specific objectives were identified: 1) to verify whether fathers and teachers were aware about the program and had supported it, 2) to assess barriers in promotion, such as the level of understanding of cervical cancer and attitudes towards HPV vaccination, and 3) to gather recommendations, among fathers, teachers, vaccinators and the program coordinator, to contribute to the improvement of future HPV vaccination programs in Kenya.

Methods

The study context

The pilot HPV vaccination program - From May 2012 till March 2013, an HPV vaccination program was rolled

out in Eldoret, Kenya. With support from the GARDA-SIL Access Program (GAP), Moi Referral and Teaching Hospital (MTRH) was able to vaccinate 3000 girls against cervical cancer. The vaccines were administered for free in the hospital on Wednesdays and Saturdays. Promotion took place in a pool of ten randomly selected schools as to avoid over-demand in the community. Through this, 4000 eligible girls, i.e., girls from class 4 to 8 (9–14 years old), were targeted. Health care providers went to the schools to inform the teachers who were then asked to promote the vaccine among the students and their parents. Each time, two pieces of information had to be passed: 1) basic information on cervical cancer and the HPV vaccine, and 2) practical information on the whereabouts of the vaccination program. However, due to poor response after three months, the program opened up to all other schools in the community, public and private.

Acceptance and uptake of the HPV vaccine – We assessed HPV vaccine acceptance among a randomly selected sample of women with eligible daughters in the ten initially included schools using a structured questionnaire (March 2012). During the interview, all women received basic information about cervical cancer and the upcoming HPV vaccination program. Once the program was completed, a follow-up survey was conducted to collect data regarding vaccine uptake (May 2013). Despite high baseline acceptance, reported uptake at follow-up was low. Main reasons for not receiving the vaccine were not feeling well-informed, fear of side effects and lack of time. In addition, women also reported that they had been confronted with opposition from people around them, among others their partner. More details about the program and the longitudinal study are described elsewhere [15].

Recruitment of participants

The organization of the focus group discussion (FGD) was a stepwise process during which schools were randomly selected, asking the head teacher permission to set up a FGD in the school with either teachers or fathers. Each time a school was selected for a discussion, it was excluded from the pool (i.e., the ten schools that were targeted during the first wave of the vaccination program) to avoid two FGD in one school which could otherwise result in receiving the same information from both teachers and fathers regarding the organization of the program at school. Schools were invited until saturation was reached.

Once a school agreed to participate, the team set up the ideal date and time with a teacher, appointed by the head teacher, and participants were invited: 1) Fathers - Partners of the women who participated in the above-mentioned longitudinal study were invited, hence they

had a daughter who went to one of the targeted schools and had been eligible for vaccination. They were contacted by phone since contact information of the households had already been gathered during the cohort study [15]. 2) Teachers – The team invited all teachers present the day when permission to organize a FGD was asked. In addition, information letters were left behind inviting also other teachers to participate.

Recruitment of the vaccinators was done by contacting the head nurse responsible for the team, who then invited the other nurses for a FGD in the hospital. All FGD took place in May 2013. Finally, the program co-ordinator was directly invited by phone to meet in a place selected by him (October 2014).

Procedures

All interviews were audio-recorded; FGD with fathers and teachers were moderated by researchers of the local team, who have considerable experience in conducting qualitative interviews regarding medical topics in the community. The discussion with the vaccinators and the validation meeting with the program coordinator were led by the first author of this paper. Before the start of the discussion, respondents were explained that participation was voluntary, that they could choose not to answer or leave the discussion at any point. Also signed consent forms were requested from all participants.

Interview guidelines for teachers and fathers were very similar and addressed awareness of the HPV vaccination program and whether or not they had participated in it. In addition, knowledge regarding cervical cancer and prevention was assessed, followed by a short, standardized informative session to provide correct information. The discussion ended by asking for recommendations on how future programs should be organized. During the FGD with teachers, extra attention was paid to their role as promoters and to their willingness to discuss cervical cancer prevention with their students.

The vaccinators were interviewed about two topics: their tasks during the program and whether they felt prepared, and how they thought the program could have been improved. Finally, a validation meeting with the program coordinator was organized to reflect on the vaccination program and the results of the FGD.

Analysis

The interviews with the teachers and the vaccinators were in English, while the interviews with the fathers were in Swahili. English discussions were transcribed *verbatim* while Swahili sessions were translated and transcribed simultaneously, providing final transcripts in English. Transcription was done by local team members who at all-time could discuss interpretation of Swahili among each other. The transcripts were coded by two

independent researchers, initially based on a list of codes deducted from the interview guidelines, focusing on awareness and perception of the HPV vaccination program, cervical cancer knowledge and attitudes towards the HPV vaccine. These codes were then gradually adapted and grouped into emerging themes [27]. Finally, results and conclusions of this analysis were discussed with the program coordinator to place them in the specific context of the HPV vaccination program and to formulate recommendations for future programs.

Ethics statement

The study protocol was approved by the ethical boards of Moi University and Ghent University. All participants of FGD received a small compensation (200 KES, i.e., approximately 1.5€) to cover their time and transport cost. Written informed consent was obtained from all respondents.

Results

Characteristics of the participants

Seven schools were included given that saturation was reached after four FGD with teachers and three with fathers. In total, 67 teachers and fathers participated. FGD with teachers consisted of more female than male respondents and always included a mix of teachers of class 4 to 8, i.e., the classes targeted by the HPV vaccination program, and teachers of younger students. As there were no male vaccinators, the FGD with the nurses only included women (Table 1).

The HPV vaccination program

Knowledge about the program

Few fathers had heard about the past HPV vaccination program and when they had, it was mostly through their children and wives. When asked if they had discussed it

with others, they explained that it was difficult given that it is taboo to openly discuss such topics. In addition, even if cervical cancer was brought up in conversations participants considered it a far-flung event, far removed from their own personal lives.

Father (FGD 7): I heard of it from my children, that they are supposed to go and get checked.

Father (FGD 7): I only talked to my wife, not to other people. When talking about private parts to other people, they start drawing away from you.

Father (FGD 6): This is a new thing so we haven't talked about it so much. Even if we hear about it, we don't take it seriously....We've famous people like [name 1] being affected by cancer and went for treatment abroad....[name 2]....But to us it is a new thing.

Similarly, not all teachers had received information about the HPV vaccination program or if the promotion had reached them, they “took it lightly” or “didn't pay so much attention”. It was clear from all FGD with teachers that the health care providers had never sensitized the entire teacher corps but rather a subset of teachers, appointed by the head teacher or those responsible for classes 4 to 8. As a result, in none of the schools an overall campaign or program was set up which led to misunderstandings and distrust.

Teacher (FGD 4): They [the health care providers] met just some of the teachers, only those who were concerned with the... or those who had been given the duty of taking the children, because us we didn't hear.

Table 1 Characteristics of participants of FGD

FGD #	Participants	Number of participants			Teachers' class		
		Men	Women	Total	Class 1-3	Class 4-8 ^a	Missing
1	Teachers of school 1	2	6	8	1	4	3
2	Teachers of school 2	2	10	12	-	9	3
3	Teachers of school 3	3	9	12	1	5	6
4	Teachers of school 4	4	7	11	1	3	6
5	Fathers of school 5	6	-	6	NA	NA	NA
6	Fathers of school 6	7	-	7	NA	NA	NA
7	Fathers of school 7	6	-	6	NA	NA	NA
8	Vaccinators (nurses of MTRH)	-	5	5	NA	NA	NA
	TOTAL	30	37	67			

^agirls targeted for vaccination, approximately 9–14 years old

In total, 10 schools were enrolled in the first phase of the vaccination program. Later the program opened up to the entire community due to low uptake in the initial phase

FGD: focus group discussion; MTRH: Moi Teaching and Referral Hospital; NA: not applicable

A last reason why the program had not been discussed among participants was that cervical cancer, and health in general, concerns only women. Therefore, male teachers and fathers had not felt part of the vaccination activities.

Teacher (male) (FGD 2): I think the name should be changed. You know, when I pass and I find a poster talking of cervical cancer. It bothers me less, I feel that I'm not of that part.

Teacher (female): To draw the attention of men.

Teacher (male): Men look at it and they see women's issues.

Participation in the program

Simply not being aware of the program or lack of information were the main reasons why not all teachers had cooperated in the program. Those teachers who had been involved, explained that they had just quickly passed practical information or invitation forms to their students, as opposed to also inform them about HPV and cervical cancer and encourage them to get vaccinated. Some teachers also remembered that parent meetings had been organized during which HPV vaccination was discussed.

Teacher (FGD 2): I think that time we only mentioned. We were told [by health care providers] 'you tell these children to take their forms to the parents, those who are interested can go to MTRH for this'... It was just as simple as that. We didn't think much about it.

Teacher (FGD 4): They [health care providers] came but there was a room which was organized for just the mothers, the parents of the girls who had accepted, so they talked to them and they went away.

In terms of vaccination, some fathers and teachers reported having their girls vaccinated but most had not done so.

Father (FGD 7): I took my children to all the three vaccinations.

Teacher (FGD 1): Yeah, I have heard about it, I even took my daughter.

Father (FGD 6): We didn't take them.

Father (FGD 6): We didn't know the importance of the vaccine but now we know.

Barriers of promotion: knowledge of cervical cancer and attitudes towards HPV vaccination

Given that the program was poorly known, we searched for reasons why promotion had failed and found two

major reasons. First of all, due to a limited understanding of cervical cancer, prevention had not been considered a priority and many participants had not felt comfortable enough to discuss it. By providing correct information, participants did however welcome the HPV vaccine. Secondly, the new vaccine had instilled safety doubts which made people feel insecure to promote it.

Cervical cancer knowledge

Cervical cancer was poorly understood by fathers and teachers. For some of them, it was the first time they heard about it while other participants had problems with differentiating several types of cancer or distinguishing cervical cancer from other reproductive health conditions, such as fibroids or pelvic inflammatory disease.

Father (FGD 7): I had heard about cancer but I didn't know that there is cervical cancer. I always knew cancer is that which is caused by smoking. That's what I knew.

Teacher (FGD 4): I think also when one is not clean maybe it can result into pelvic inflammatory disease, which can also lead to cancer, of the cervix.

When asked about the causes of cervical cancer, many possibilities arose, yet HPV was rarely mentioned as a primary cause. Moreover, 'cancer' was interpreted in various ways: depending on the participants' perception of causality, cervical cancer could be a wound, a rupture, an abnormal growth or swelling, a combination of diseases, an inflammation or an inherited condition. In turn, the 'cancerous wound' had many causal pathways, such as early sexual intercourse, coils (IUD), infectious diseases, (in)consistent use of contraceptives (pills or injection), unsafe abortion, accumulated dirt, rough sex and the use of sex toys.

Father (FGD 5): I think when a girl engages in sex when young, if she develops a wound in the reproductive system and the wound takes long to heal, it might be the onset of cancer.

Father (FGD 5): Ok, I think a child is born while 'fresh' but when one becomes sexually active...in the process of coming into contact with several diseases especially the STIs...If the diseases are not treated, they block the reproductive organ which leads to something like cancer because I think cancer is nothing but a combination of several diseases.

Teacher (FGD 1): I think there might be, [a relation with bad hygiene] because if there is some dirt, let us say the accumulation, if it accumulates and

accumulates and there is no attention taken to it or there is no cleanliness, that accumulation may stay there for long and it may cause, maybe, a wound and then from there a problem can develop.

In general, participants either brought up risk factors related with sexual practices or with lifestyle. Sexual activities different from a monogamous, heterosexual relationship were mostly linked to cervical cancer. Examples of such practices are starting to be sexually active at young age, having sex during menstruation, having sex but not conceiving, masturbating (with dirty hands or objects), using and sharing sex toys, having multiple partners and having intercourse too soon after giving birth.

Teacher (FGD 3): Also, when a mother is giving birth and then she gets an injury (pauses) and she goes for sexual intercourse before healing.

Teacher (FGD 2): We also have these habits that have cropped up nowadays. Eh, there is a practice of lesbianism and even sometimes they use sex toys. I don't know what standard of hygiene they reach to keep those things clean for them to share.

*Teacher (FGD 3): Yes, I had a point... it is not only the machines they use. When you go to these children in boarding schools most of them use bananas and carrots. Teacher: and the fingers
Teacher: and their fingers ...They might be infected, they might be dirty.*

The majority of the fathers and teachers, yet not all, also thought 'bad hygiene' was potentially harmful, but this could be defined as either a lack of personal care, using dirty toilets or again engaging in certain sexual actions, such as masturbation or sex during menstruation.

Teacher (FGD 1): When you have different sexual partners and you don't pay attention to hygiene, you can get it.

Teacher (FGD 1): I think there might not be [a relation with bad hygiene] because I understand there are areas in Kenya where access to water is an issue and these people do not suffer from these diseases. But in urban areas, like here in Eldoret, in town so many people have such disease while these are the people who know how to wash, who know how to use even the vaginal soaps and still they are getting it.

Furthermore, participants had different opinions whether or not cervical cancer was sexually transmitted. Similarly, heredity was also questioned by both fathers and teachers.

Father (FGD 6): According to what my friend said that it is sexually transmitted, I don't think it is true.... I had an aunt who was suffering from cervical cancer and died. The husband is still alive and he doesn't seem to be having any problem.

Teacher (FGD 2): It is [inherited] because a new-born has directly inhaled everything from the parents. So even the blood of the parents who are cancerous, at least that kid would take some blood, which is cancerous.

With regard to lifestyle, taking up 'new or modern' habits, whether it concerned smoking, food, cosmetics, medicines, contraceptives, using microwaves or exposure to X-rays, these behaviors were very often mentioned as 'cancerogenic'. Especially contraceptives and food were of major concern, more particularly canned, packed or processed food or food exposed to fertilizers and chemicals. This resulted mostly out of the impression that cervical cancer, and cancer in general, is a disease of the rich, urban population. However, some teachers countered this and started to reflect on lack of diagnoses in remote areas. Likewise, one teacher questioned the relationship with contraceptives given that older women, who have never used such methods, are also affected.

Father (FGD 6): A woman could plan with the man when to get a child but nowadays they use pills and injections. As days pass by they forget to go for the injection or to take the pills consistently. When this happens, they might cause a growth in the womb or they become toxic and cause cervical cancer.

Teacher (FGD 1): There are some older women who have suffered from cancer who have never used contraceptives, but their story is that they have had multiple partners, sexual partners earlier on when they were young, but they didn't use contraceptives those days, it might not be, in my opinion it might not be a real reason.

Teacher (FGD 2): I'm just on the side of the food eaten by different people. People should ...use indigenous food. Some of this food ... The food colours, the chemicals they mix with this food. They facilitate different types of cancers. So people should turn to the indigenous food, the original African food.

Teacher (FGD 2): If you go in town, you'll find that this is very common in town. As compared to the village and the remote areas. Why? Because, while in town, people eat different foods. Because of the living standards of the people, the living standard is high. People eat different food. Somebody can eat meat for

six days in a week and a poor person can have meat maybe twice in a year.

Teacher (FGD 4): Many Africans are poor so most of us are dying, because of these things, so we are dying because of cervical cancer without knowing. Whenever we hear of it, it's from those people who are able, maybe they go to London for checkups so you hear, 'she was sick with cervical cancer', and that is why we relate it to the rich. Otherwise we are dying without knowing it is the disease which is killing us.

Finally, cervical cancer was perceived severe, affecting one's fertility, and deadly; treatment was just too expensive. Preventive methods suggested by the participants were mostly abstinence of all aforementioned activities or products that could cause cancer. However, awareness was specified as the best prevention of all. One teacher even went further and mentioned that "ignorance itself causes cancer".

Father (FGD 6): When one hears the term cervical cancer especially when your child has it, you get scared. You then ask yourself whether she will ever give birth...Because when she has cervical cancer, she might not give birth and will finally die, so a parent loses hope.

Teacher (FGD 1): I have seen someone who suffers from it and was in a lot of pain and bleeding from the inside - where exactly, I don't know, but somewhere in the uterus; it was very painful and was not curable.

Teacher (FGD 3): Ignorance of the ways of preventing cancer itself can produce cancer.

Moderator: can you give an example?

Teacher: When you use the gels [lubricants] for example, suppose they cause cancer...You see what has caused cancer is not the gel but ignorance.

Attitudes towards HPV vaccination: drivers and barriers

Once participants were fully informed about cervical cancer and HPV vaccination, they were all accepting the vaccine. "Prevention is better than cure" was frequently brought up as main driver, together with the fact that the disease is deadly and cures are either unavailable or unaffordable. Fathers were especially in favor since it would protect their daughters' fertility and therefore her future life as a mother. In general, foreseeing the girls' future task such as providing grandchildren or taking care of the parents were reasons to consider HPV vaccination.

Teacher (FGD 1): Now that you have taught us about it I think it's good.

Father (FGD 6): If the father refuses to take his daughter - yet we are being told the disease can be prevented - he will be ruining his daughter's life...she will not have children and may be unhappy in her marriage.

Some teachers also pointed out a certain necessity for their pupils to be protected against cervical cancer. More particularly, they considered the students' home situation or sexual activities as unsafe hence the need for prevention.

Teacher (FGD 4): I can add, it is okay because we are living in a slum where the trend of prostitution is very high, and children are seeing those things going on and some of them are involved because of the status of their home, so I think it is ok.

Teacher (FGD 1): And I think it's okay, and what should be done is that even our children should be taught, they should be sensitized, so if they are aware even this matter of having sex at an early age is not good because it gives rise to other diseases.

Respondents also reported reasons why the vaccines could have been refused or why they themselves had not supported them. Several barriers concealed a certain level of distrust, towards vaccines in general or towards the HPV vaccine specifically. Bad experiences or rumors about other vaccines (polio and asthma especially) were brought up as to indicate the possible danger of vaccines, and the fact that this vaccine was new implied a potentially hidden experiment. Surprisingly, while protecting a girl's fertility was a driver for accepting the vaccine, the same vaccine generated fear in terms of harming the girl's fertility. In addition, several teachers thought that parents might have feared that vaccination would enhance sexual activity among the children.

Father (FGD 6): There are parents who still have traditional beliefs and don't believe in complementary medicine.

Teacher (FGD 4): Others think it is the disease of the rich (laughter); you know these chronic diseases, they think they are for the rich [after the moderator asked reasons to refuse the vaccine].

Teacher (FGD 1): We have not heard about people who have been vaccinated so we think they are starting with our children, they are used as guinea pigs or something, people try to see if it can work.

Father (FGD 6): There was a time we were told that when one is vaccinated, she might be unconscious for

half an hour....I heard it somewhere and it prevented me from taking my daughter...

Father: Yes, I heard it somewhere. It scared me because I thought that was very dangerous.

Teacher (FGD 4): She [a mother of a student] was telling me that it is going to make our girls infertile, or maybe they will become sexually active, she said 'me I refused my child to go for it', but I didn't ask anything more about it, so I left it at that. I was also of the belief that it has negative effects but now, I am for it.

Finally, certain religious groups were known for rejecting all vaccines so participants mentioned them as refusers.

Father (FGD 5): Religion is a very important factor. There are some religions which do not agree to treatment or vaccine.

Moderator: Which religion? Please give me examples.

Father: There is this church at our place with a red cross, Holy Spirit Church

Moderator: Yeah Holy Spirit Church

Father: Legion Maria and Wakorino

During the short informative session and in the course of the remaining discussion, moderators often had to re-explain cancer-related issues or answer questions of participants. It was clear that once they had received the basic information, they started to interpret the obtained knowledge, each according to his or her capacity and according to his or her understanding of health and disease. For example, the fact that cervical cancer is sexually transmitted led to additional questions. Particularly male participants started wondering why boys were not targeted, given that they are "carriers of the virus".

Teacher (male) (FGD 4): Excuse me, somebody has talked about it being transferred from one woman to another by men, so men are carriers, I think also men should be vaccinated.

Also eligibility was a topic of discussion. The moderator had to explain carefully that targeting young girls, in this case from class 4 to 8, was just a strategy to obtain girls who are not yet sexually active. Especially teachers were concerned about what would happen if a sexually active girl would receive the vaccine and whether or not they truly had to know which girls were already sexually active.

Recommendations for future programs

Clearly, more information was requested by all participants, combined with facilitating HPV vaccination for parents, e.g. through school based vaccination. Furthermore,

a stronger collaboration between health workers and teachers seemed essential for successful HPV vaccination.

Fathers and teachers

A first and very clear request from all participants was more sensitization, and any place or any channel would do: at churches, market places, schools, through radio, through community elders, etc. Everybody was welcome to help and spread information about cervical cancer vaccination but surprisingly, while churches were considered good venues, religious leaders themselves were not always seen as the correct source given that they have no medical background. Furthermore, fathers expressed the wish to be more included in health programs given that they considered themselves, often together with their spouse, the main decision taker regarding vaccination.

Teacher (FGD 3): If people or ladies or girls or communities, if all people in general are taught about this cancer; let people know first about cancer and what brings cancer...Once they have the understanding of it, then they are going to take caution in the right way. But so many people don't know about cancer. So let people learn about cancer, teach people about cancer! In schools, villages or where, wherever they can get the information....

Moderator (FGD 6): What about religious leaders, do they talk about it?

Father: Whenever they try we tell them they are not doctors.

Secondly, the participants recommended to vaccinate at schools, as it would be more convenient for many parents. Moreover, some distrust towards hospitals or the health system in general was revealed which could be diminished by bringing the vaccines to the schools.

Father (FGD 5): I heard about it [the vaccination program] but I lacked transport to take my daughter for the vaccination.

Teacher (FGD 3): Also going to the hospital will encourage bribing so we want to avoid that by taking it to school..because somebody tells you, bring something small so that I attend to you faster.

Teacher: And you might not even get the right vaccine even after giving out your bribes.

Teachers were - "now that we are informed" - very keen to provide help and to promote the vaccines. They suggested themselves that they indeed should be the ones providing information given that they have day to day contact with the children. When asked, they

claimed to feel comfortable to discuss such a topic in class, although some teachers showed some reluctance. For example, some of them would remind the others that in order to talk about it in class, it should be part of the curriculum, while others mentioned that it would be easier to discuss it with girls only. The latter statement was often rejected and led to discussions among participants regarding the importance to also inform boys. In the end, teachers did acknowledge that they wanted support by health workers to tackle difficult questions.

Teacher (FGD 2): Teachers spent almost all their time with the children and children really listen to the teachers. Whatever teachers say, a child does not doubt. They can go home and convince the parent 'this is what the teacher said'.

Teacher (FGD 4): I think what happens in a class, I think it should go hand in hand with the curriculum. I don't see how this cervical cancer information can come, not unless it is also included in the curriculum.

Teacher (FGD 1): I have a different opinion. I think both the sexes should be told because nowadays they teach sciences about delivery, how the baby is formed and all that. I think they should teach in the same manner. So I think it is beneficial because they are growing. One time they will be parents and they need to have this knowledge.

Teacher (FGD 4): Or you can call a health worker to come and tell the parents.

Moderator: So you think it should be the health workers' tasks?

Teacher: yes! Because I don't have much experience. They might shoot questions that I don't know how to answer; I may not be able to answer the questions.

Thirdly, support from local authorities and the government was deemed essential, both in terms of assuring the safety and effectiveness of the preventive method as financially. Especially fathers were worried about the cost and thought the vaccines should be subsidized.

Father (FGD 5): It shows I care about my daughters... and as I care, the government should do the same. It should be a national thing in schools and whatever. The vaccine should be taken to schools, to the ground.

Father (FGD 6): I agree with my colleagues because that amount is too high...the government should intervene because these children are our future

leaders...He has talked of Kshs 2000 I would suggest Kshs 100 [referring to how much the vaccine should cost now that it was no longer available for free through the vaccination program] . With the current cost of living and if one has five children, it is a lot of money...One can try to get the 100 but 2000 [Kshs] is a lot of money.

Teacher (FGD 4): It is a good idea but I suggest, I think the government should do a bit of educating the masses because, if we teachers do not know what cervical cancer is, then how about that mother in the village, she will not accept; so education is very important.

Finally, in all FGD people wanted to know when a next vaccination program would be organized, or where they could go to vaccinate their daughters given that now they were better informed, they did not want to wait any longer. Cervical cancer vaccination was now considered a priority.

Program coordinator and vaccinators

Similar to the teachers and fathers, the nurses stressed the need for information. More particularly, they stated that before the onset of the program they were unaware that cervical cancer is caused by a sexually transmittable virus. A short training before the start of the program, provided by the program coordinator, had informed them about HPV.

Moderator (FGD 8): Before you were vaccinating the girls, were you aware that it was a sexually transmitted disease?

Nurse: Before that I didn't know, until I was sensitized about that.

In addition, the nurses also reported that they doubted their communication skills with the girls as to inform them about the vaccination, as well as how to address parents' questions, e.g., why boys were not eligible. How to face these difficulties was not addressed in the training.

Nurse (FGD 8): With the guardians, we were comfortable [discussing cervical cancer]. It is only that we thought with the children, of course they also have to know, but you could be wondering whether they understand, because someone who is like 9 years may not, in fact may not have started with reproductive or other health subjects. I was wondering if they understood, what we were talking about.

While the program coordinator was surprised to hear that there were many teachers and parents unaware of the HPV vaccination program that had taken place, he

offered some possible explanations based on his experiences. First of all, he had noticed that the attitude of the head teacher was crucial: during the program he saw that more pupils got vaccinated from schools with an enthusiastic and supportive head teacher. The nurses had perceived a similar effect. In addition, the coordinator confirmed that the health care providers visiting schools never spoke to the entire teacher corps leaving it up to a few to further inform and involve their colleagues.

Nurse (FGD 8): I think that it depended with how the authority of the school took this message. Did they take it with some weight, or did they just take it lightly.... So if they didn't, then the girls would not appear. I think it depended on the authority of the school and how they received the message.

Secondly, in one school teachers foresaw distance and thus transport time and cost as a major barrier for the parents, which made them doubt the feasibility of the program from the start. Lastly, during his contact moments with the schools he observed that two types of promotion were implemented: while in some schools the teachers informed the students who on their turn had to inform their parents, other schools organized contact moments with the parents to inform them directly. Likewise, some schools organized transport for the girls and a teacher accompanied them to the hospital to receive the vaccine. This was confirmed by the nurses.

Nurse (FGD 8): Mostly they were brought by teachers, in groups.

Especially schools that were not included in the first selection of 10 schools, tended to respond faster and more organized. These were often, yet not exclusively, private schools. The coordinator provided some possible explanations as to why these schools handled more swiftly: Private school teachers are considered more accountable for the well-being of their pupils, making it their responsibility to respond to vaccination efforts. Furthermore, both parents and teachers often have a higher socio-economic status compared with public school settings, making it easier for them to pick up and understand public health messages as well as to spend time and money for preventive medicine. Regarding the decision to open up the program to more schools, as opposed to, for example, revisiting the original selection, the coordinator explained that they called the ten schools to ask them to reinforce their promotional activities. However, teachers reported that parents were aware of the vaccination opportunity and were maybe simply refusing to vaccinate their daughters. As a result, the team decided to include more schools.

Finally, both the program coordinator and the nurses pointed out that the program knew a slow start but once it took off, demand increased exponentially. Particularly when the program opened up to more schools, the schools themselves started to inform neighboring schools inducing a type of snowball-effect.

Nurse (FGD 8): At first, the message was not received kindly. Many people had questions, everyone had questions about this vaccine. So in the first place, I think it was considered like testing. Like someone wanted to know, 'are others taking their children?', but after that...most of them came and I think it was because they saw that almost everybody else was doing it.

Nurse (FGD 8): Yeah, in the beginning of the program, people were not willing, but towards the end, you see most of them are now coming and ask for the vaccine.

Discussion

The results clearly show that promotional activities were suboptimal: not all teachers were informed by health care providers, only some schools invited the parents for informative sessions (others relied entirely on students passing the invitation), and there were hardly any contact moments between health care providers and parents. Consequently, several bottlenecks were induced, blocking the flow of information from the health promoters, through the teachers and students, to the parents.

As stated before, target groups need to receive two pieces of information in order for them to undertake action to receive the HPV vaccine. First of all, they need to be aware of cervical cancer and they need to understand the importance of HPV vaccination. In order to achieve this, the information provided should correspond with the needs of the community. Secondly, potential participants need to know how they can receive the vaccine: where and when are vaccination activities rolled out?

Many women who participated in the longitudinal study, stated that none of this information had reached them [15], which was confirmed by the fathers in this study. However, the majority of the men also reported that their wife had informed them neither, meaning that many women had not shared the basic information they had received during the baseline interview. In addition, men are in general less informed given that they don't feel addressed by public health campaigns regarding cervical cancer and that they find it particularly difficult to discuss it with others. Nevertheless, in case of an HPV vaccination opportunity they do want to discuss this with their wife and they do feel responsible for the final decision. Their lack of understanding might however result in vaccine refusal: opposition against the HPV vaccine by men was indeed reported as an important

barrier by the women in the previous study [15]. Including men in cervical cancer prevention strategies and encouraging couples to discuss this might be challenging but seems crucial for success.

Following discussion will reflect first on the condition of awareness and understanding in the context of this demonstration project. Subsequently, the role of the teachers in public health programs will be discussed, more particularly to what extent teachers might take up certain types of promotional messages regarding HPV vaccination. Finally, the introduction of new vaccines will be assessed, i.e., how some people might need more time to gain confidence or to respond for them to adopt the new behavior, regardless of the information they received.

Appropriate promotional messages

Besides the fact that many participants had not heard of the program, an equally important conclusion is that those who had received information had not given it thought and had not shared it with others. Fathers found it inappropriate to talk about cervical cancer with others while teachers stressed the need for more information for them to feel confident. However, there might have been other reasons. First of all, just like the fathers, some teachers felt equally uncomfortable to share this type of information with their colleagues or students. While they all wish to have a better understanding of cervical cancer, the topic causes them discomfort and anxiety.

Secondly, one might ask how participants, including the teachers, process and interpret the received information. How do they define viruses and transmission, what do they consider cancerogenic and who is at risk? During the discussions, it became clear that some had a very limited understanding of the human body and diseases. So even if the correct information was passed on, the question remains whether this newly gathered knowledge fitted into their vision of health and diseases and what they perceive as important to remember. For example, participants who knew about the cervical cancer vaccination program, still did not mention HPV as the main cause. Also in Vietnam and Italy, participants still had limited knowledge about cervical cancer after the implementation of an HPV vaccination program, even though they themselves considered them well-informed or had received the vaccine [20, 28].

Finally, and related with the previous argument, both teachers and fathers might not have perceived a cervical cancer prevention program as important: the strong conviction that cancer in general is a disease that affects rich people, or people with a "modern lifestyle", provokes a certain indifference. Compared with a 2001 study from Gatune et al. (2005) in a rural area close to Nairobi, participants now stressed much more the causal

relation with processed food or chemicals, rather than only sexual behavior and the use of contraception [29]. Given that participants did not feel part of this modern society exposed to those external, modern, risks, there was a strong overall feeling that cancer strikes others. Not observing cervical cancer among the general population is probably a result of lack of diagnoses and not discussing the sickness out of shame. The fact that participants did not perceive themselves or their environment susceptible for cervical cancer is however contradictive with previous findings where mothers reported that it was very likely that their daughter would have cervical cancer in the future [15]. The latter was of course a more direct and quantitative question concerning ones daughter which may have induced a socially desirable expression of concern while the FGD were more generally speaking.

Overall, we can conclude that translation of received information into action remains very challenging. Because of lack of understanding or not feeling addressed by promotional messages, people remain vulnerable for cervical cancer since they won't feel urged to undertake actions to prevent it. Health messages should therefore go beyond providing essential information and should also address misunderstandings and rumors (e.g., *cervical cancer is not heritable and is not linked with the use of cosmetics*), assure that the target group is properly reached (e.g., *cervical cancer occurs both in urban and rural areas*), and actively fight stigma (e.g., *condom use can protect against cervical cancer instead of having multiple partners increases the risk of cervical cancer or cervical cancer is not caused by bad hygiene*). In order to identify the needs and worries of the target population, formative research should be carried out not only before the start of the program, but monitoring activities should continuously screen for new or evolving rumors [30]. Also, both men and women should be approached and empowered to discuss such a sensitive topic among each other. Moreover, support from the government and local authorities will increase the credibility of the program [25].

Teachers as public health promoters

Besides receiving and sharing information, there were clearly other factors that influenced the HPV vaccination program. The program might have over-relied on teachers without considering their motivation or availability. Early involvement and clear communication with teachers regarding the design of the program was skipped, whereby taking up promotion could be more perceived as a favor towards the health staff instead of an agreement or responsibility.

However, even teachers who were addressed by health staff and had agreed on cooperation had not informed all their colleagues nor had they set up large-scale

promotional activities. This failure to perform, may be caused by various factors. As in many low-income countries, Kenyan teachers might be poorly motivated due to little job satisfaction, few material tools, low salary, etc. [31]. Extra tasks might not be received well. Teachers requesting to include HPV and cervical cancer in the curriculum for them to discuss it in class, hints to the need for approval of the ministry of education as well as to delimiting work load. In addition, some teachers described their pupils' background and behavior in a rather negative way, pointing out the worrying situation some students find themselves in. While this might be a driver for some teachers to help and protect the children, it might also pull some of them down.

Finally, talking about sexual health has always been a challenging task for teachers. Besides feeling uncomfortable to discuss such topics in class, some teachers might not agree with the type of information that should be shared or with what to promote (e.g., condom use vs. abstinence) [32]. Indeed, teachers often discussed whether or not boys should be informed as well, in which type of class cervical cancer could be discussed (is it the responsibility of the science teacher?), which age groups should be included, etc. Others even saw it as an opportunity to preach morality and discourage sexual freedom (i.e., masturbation or early sexual onset), using HPV and cervical cancer as a potential threat. Promoting it as a cancer vaccine and not mentioning the STI-aspect of cervical cancer was however never mentioned as an option. Teachers expected questions from both the students and the parents and therefore stressed the necessity to be well informed. It is also in this light that it becomes clear why teachers had only given their students the message to go to the hospital for vaccination as opposed to explaining them about HPV and cervical cancer: they opted to share logistical information rather than discussing prevention of a sexually transmittable disease.

So while school based vaccination was perceived as a good approach by all of the participants and while various studies have showed good results of such programs [33, 34], teachers should not stand alone when it comes to promotion. Health systems will have to support the schools, clearly describing and differentiating the responsibilities and messages that both parties will take up. As showed in a study by Brabin et al., close collaboration and good relationships between the schools and the health system are important predictors of vaccine uptake [35]. In addition, the schools might serve as a bridge between the health care providers and parents, whose contact is also crucial to achieve good coverage [34, 36]. Finally, the HPV vaccine might be seen as an opportunity to roll-out school health programs, including e.g., sexuality education, addressing the large but

underserved group that are adolescents in low-income countries [37–39].

Introducing new vaccines

New vaccines always provoke some hesitance and doubts, which diminish after a while but might linger for a very long time. These worries emerge from the fact that people have not yet seen the effects of the vaccine – or rather have not yet confirmed the absence of side-effects - but these concerns are also fed by persistent memories of bad experiences or rumors about other vaccines. Kennedy et al. showed that the combined MMR vaccine still causes worries in Scotland, after a controversy of more than 10 years ago, and even influenced decisions regarding new vaccines [40]. Likewise, participants in this study recalled stories of the polio vaccine and even an asthma vaccine, indicating previous failures of vaccine efforts and health communication. However, as reported by the vaccinators and the coordinator, the HPV vaccination program did eventually become successful, after a first period of habituation and trust gaining. Just like other new techniques, adoption of a vaccine might follow a Gaussian bell-curve of a normal distribution, representing diffusion throughout the community with early adopters setting the example while others lag behind (Diffusion of innovations, Everett Rogers). Indeed, people have reported a 'wait and see' approach when it comes to uptake of the HPV vaccine as to evade unknown side-effects [9, 41]. However, it will be important 1) to minimize the time span between adoption by innovators and laggards, and 2) to ensure that usage is not delayed among already underserved subpopulations, out-of-school youth or groups who refuse the vaccines for religious purpose. The high response noted during the second wave of this demonstration program may thus follow from late adopters coming round but might also reflect a difference between the ten selected schools and the newly included. Private vs. public schools was one of the aspects noted by the coordinator, indicating a potential threat for reaching health equity. Studies have indeed showed that ongoing HPV vaccination programs do not always eliminate cervical cancer disparity: girls from more deprived origins tend to have less chance to be fully vaccinated and non-school approaches may even induce more inequality [42–46]. Similar, parents with lower socio-economic background often have less cervical cancer knowledge and HPV vaccine awareness, which remains a first condition for uptake, while also financial restrictions impede vaccination [47–49].

In order to enhance acceptance and to speed up vaccine uptake, we need not only to spread information but we need to enter into dialogue with community members, addressing context specific concerns. What used to be predominantly a top-down approach, should become

a continuous and open dialogue between all stakeholders [30]. In addition, surveillance programs should be put in place to assure that the HPV vaccines actually reach everybody – timely - and that they fulfill their potential to reduce the health inequality gap regarding cervical cancer.

Limitations

The study has some limitations. First of all, selection of the vaccinators was not random, given that the nurses were invited by the head nurse. Although this might have induced selection bias, having duty around the time of the FGD was the major criteria for them to participate. In the end, five nurses participated in the FGD representing almost 50 % of the entire vaccinators team (i.e., twelve nurses).

Secondly, not all teachers who participated in the FGD gave classes to girls in class 4 to 8, i.e., the target group of the vaccination program. This means that these teachers were not asked to promote the vaccine among their students. Still, proper school based promotion would imply inclusion of the whole teacher corps (maybe not in terms of active responsibilities but at least everybody should be informed). Moreover, their participation in the study revealed clearly that the vaccination opportunity was not discussed widely.

Thirdly, FGD with fathers were not transcribed *verbatim* in Swahili but were simultaneously translated into English. This may have led to the loss of some nuances or cultural specific concepts. In order to limit this type of error, researchers experienced in qualitative research in public health were given the task, while other local team members were always available to assist.

Finally, our study was conducted 14 months after the onset of the program which might have induced a recall bias. Participants had sometimes troubles remembering clearly what they had heard about the vaccination effort and from whom, or which promotional activities were organized. Especially the lack of insight in how promotion was implemented in each school limits the understanding on which channels were more successful than others. However, this also is a reflection of a lack of structural organization of, and exposure to sensitization.

Conclusions

Although an HPV vaccination program had been implemented, people still had poor knowledge regarding cervical cancer. In general, cervical cancer prevention was not truly prioritized given that the disease is stigmatized through associations with non-accepted sexual activities and highly linked with usage of modern products such as cosmetics, contraception or processed food. Therefore many participants did not feel addressed by the promotion effort and had found it uncomfortable discussing the topic. Teachers pointed out that support from health

staff would be essential in order for them to feel confident to promote the vaccine among students and parents. A closer collaboration with health care providers and schools would help to address questions of parents as well as teachers' own doubts. Finally, distrust towards (new) vaccines had also hampered uptake: small-scale vaccination projects are often confused with trials, but also bad experiences during previous vaccination programs had reduced faith. Suspicion did however fade away after a couple of months, once the community was convinced about the safety of the vaccine. Also the inclusion of schools with higher capacities to respond to the vaccination invitation had boosted uptake.

Health care promoters of future programs will need to enter in dialogue with the community, as opposed to just provide information, to increase awareness and actively tackle misbeliefs and rumors. In addition, rolling-out HPV vaccination programs should go hand in hand with careful monitoring to assure that cervical cancer disparities are not further induced by differences in HPV vaccine coverage.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

HV conceived of the design of the study, carried out the field work and data analysis, and drafted the manuscript. VN participated in the coordination of the field work and helped drafting the manuscript. OD assisted in designing the study and helped drafting the manuscript. KM assisted in designing the study and helped drafting the manuscript. All authors read and approved the final manuscript.

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Part VII

DISCUSSION

Chapter 9

Acceptability and uptake: how to bridge the gap?

Conclusion 1: HPV vaccine acceptability is rather a reflection of a desire to prevent cancer than a predictor of uptake.

The longitudinal study found a positive relation between HPV vaccine acceptability and uptake, yet only significant in bivariate logistic regression. Also in the mediation analysis, willingness to vaccinate was not a predictor of vaccination. As hypothesized, none of the non-acceptors reported to have a vaccinated daughter while half of the acceptors had not lived up to their own expectations. Lack of information (regarding both the vaccine and the programme) and being afraid of side-effects were reported as main barriers during baseline and follow-up, as well as having a partner who opposed.

Other prospective studies regarding HPV vaccination found similar results, i.e. relative high willingness to vaccinate compared to the final uptake, and a positive association between the two outcomes [210], [211], [215], [217]–[219], [249]. Among these studies, some were also unable to detect a significant association when controlling for other variables [217], [218] and one other study did not

find any relation at all [216]. These mixed results reflect that while HPV vaccination is considered the right thing to do by many people, intentions diverge from actual actions and several factors might influence the final behaviour. Also previous reviews studying the correlation between intention and other health-related behaviours demonstrated that there is a reliable, but no perfect association between reported intention and behaviour [250]–[253].

9.1 What causes the intention-behaviour gap?

According to Sheeran (2011), there are several properties of intention that strongly determine the relation with behaviour [254]:

- **Degree of intention formation:** The extent to which participants have thought through the action and the related consequences.
- **Temporal stability of intention:** Intentions may change over time and can therefore lose their predictive value for behaviour.
- **Attitudinally versus normatively controlled intentions:** Whether the expressed intention is the result of one’s own attitudes or rather determined by subjective norms.

These and other factors that might have influenced the correlation between HPV vaccine acceptability and uptake are further discussed below.

9.1.1 Overestimation of acceptability

Socially desirable answers versus heuristic decision-making

At baseline, women reported a high willingness to vaccinate which is similar to the findings of many other HPV vaccine acceptability studies [158], [183]. Given however the short time between receiving cervical cancer information during the baseline interviews and expressing acceptability towards the vaccine, the *degree of intention formation*, can be brought into question. As specified by Sheeran (2003), not taking the time to think things through might result in poor estimation of one’s own intention and thus hampers the

intention-behaviour association. Also, as mentioned before, gauging willingness to vaccinate in a hypothetical situation where the vaccine is not yet available, or with limited understanding about the disease can lead to socially desirable answers [213]. Considering that vaccine decisions can be seen as risk decisions - evaluating the risk of harm due to the vaccine against the potential risk of the disease - it is indeed remarkable that a new vaccine is so well accepted without any previous experience with it: given that such decisions involve more information than can easily be processed (or for which basic knowledge is lacking), we would expect that people tend to rely on heuristics or 'cognitive short-cuts' which result more easily in a negative opinion towards the vaccine as opposed to the measured positive one. An example of a heuristic that is applicable in the context of HPV vaccination is *omission bias*, i.e. preferring not to vaccinate given that one would feel more responsible for sickness as a result of vaccination than for illness of a vaccine-preventable disease. Also *protected values* (zero tolerance towards risk) and *ambiguity aversion* (opting for the familiar risk instead of new or ambiguous risk) are heuristics which people may use during the decision-making process regarding the uptake of the HPV vaccine [255]–[257]. So while people might have reported high acceptability, given that this is the socially desirable answer, their true opinion might have been the opposite, having relied on the above-mentioned heuristics.

Intention versus desire Another reason for the discrepancy between acceptability or willingness to vaccinate and uptake, might be that women have expressed their desire instead of an estimation of their intentions. In the analyses presented here, acceptability was defined as 'would you vaccinate your daughter against cervical cancer', and willingness to vaccinate - used in the mediation analysis - was a combination of acceptability and intention, i.e. 'will you vaccinate your daughter in the upcoming programme'. It is possible that these variables have not measured direct precursors of behaviour but actually the antecedents of intention: according to Perugini and Bagozzi (2004), "*desire is a state of mind whereby an agent has a personal motivation to perform an action or to achieve a goal, which is typically followed by an intention to do so. Therefore, desire should be distinguished from concepts such as intentions, attitudes and goals.*" [258] The concept of desire is however not present

in the leading theories of health behaviour and also in the literature regarding HPV vaccination there is no differentiation between desire and acceptability or intention. However, it seems quite likely that in some studies stated acceptability comes closer to desire as opposed to intention, or that participants report a wish to vaccinate rather than their true intention. When this is the case, a correlation with vaccine uptake is rather unlikely given that reported desire might be independent of the intention to actually perform the behaviour [258].

Perugini and Bagozzi (2004) propose three criteria to distinguish between intention and desire: *perceived performability*, *temporal framing* and *action-connectedness* [258]. The first criteria refers to the fact that desires can stand alone, i.e. they don't need to be feasible, while intention contains inherently an evaluation in terms of *performability*. This can be interpreted as either a form of self-efficacy and confidence in carrying out the action or it can be linked to the belief that the behaviour will lead to the underlying goal. With regard to HPV vaccination, this means that one has to be capable to go for vaccination and one has to belief in the protection offered by the vaccine. The fact that self-reported efficacy was high in this study and correlated with both willingness and vaccine uptake, indicates that participants have truly expressed an intention and not a desire. On the other hand, the poor uptake and the many participants who reported fear of side-effects as major barrier, indeed suggest that women reported a wish to protect their daughter from cervical cancer without relying on the vaccine to actually provide this protection.

Also the second indicator, *temporal framing*, can partially explain the failure of finding a strong significant correlation between HPV vaccine acceptability and uptake: temporal framing implies that while desires are often time indefinite, intentions are to be translated into action in the short run. The wait-and-see attitude, reported in the qualitative component of this study, might therefore also be considered a reflection of poor intention in the community - instead of just distrust towards the HPV vaccine - and might be a more correct assessment than the quantitatively reported intention by the mothers in the longitudinal study.

Finally, the last criterion, *action-connectedness*, supports the idea that participants have expressed a desire given that it simply states that intention has a stronger connection with behaviour than desire. This is based on the idea that intention implies a certain readiness and commitment, whereas desire does not.

9.1.2 Underestimation of external factors

Changing opinion towards HPV vaccination While people might indeed have reported an overestimation of their acceptability, felt unable to answer truthfully on the spot, or expressed a desire rather than an intention, it is also possible that they changed opinion afterwards: the results show indeed that some acceptors became refusers in follow-up. *Temporal stability* is another characteristics of intention that affects the link with behaviour according to Sheeran (2003-2011) [252], [254] and there are various reasons to assume that this might be applicable in the context of HPV vaccine decision taking. In the aftermath of the baseline interview, participants' feelings towards the vaccine or the programme can change due to many external factors. In the same light, while a lot of participants still wanted to vaccinate their daughter at follow-up they had been unable to do so: various factors had blocked the translation of their acceptability into behaviour.

Volitional control: blocked by others Looking at the determinants reported by the women, both for acceptability and uptake, it becomes clear that they are more related to actions or attitudes of others than to the participants' own characteristics and feelings towards the HPV vaccine. The main barrier, lack of information is primarily the responsibility of the organizers of the programme rather than of the target group and even fear of side effects can be partly seen as a result of poor promotion. Similarly, the objection of the father to vaccinate his daughter indicates that the participants of the cohort study were not in control of the action to vaccinate, meaning that in these cases not their wish but the partner's wish to (not) vaccinate is translated into the corresponding behaviour. As such, one can wonder to what extent HPV vaccination is the result of each of the most important players, i.e. the parents of the girls

and the organizers of the vaccination programme. It is known indeed that perceived behavioural control (PBC), a main construct of the TPB, has an important impact on the relation intention-behaviour: intention tends to be a weaker predictor for actions lacking volitional control [251]. This also resembles the fact that intentions can either be *attitudinally or normatively controlled*, as stipulated by Sheeran (2011), with the latter having a negative effect on the predictive value of intention.

Volitional control: a variety of barriers Finally, behaviour is often blocked by community norms, hit up against inadequate or low quality health services, or obstructed by a range of barriers such as access to promotion, time restrictions and cost. As a result, these factors might be stronger determinants compared with acceptability reported among the target population.

9.1.3 Overestimation of uptake in other demonstration projects

Scale of promotion: creating demand Another remarkable result in this study is the low uptake (31 percent received at least one dose) compared with other demonstration projects (over 70 percent received all three doses) [122]. Given these high coverage rates in other settings, and the high acceptability measured in these places where formative research has been conducted, no such discrepancy between HPV vaccine acceptability and uptake was detected [121], [146]. Of course, the large-scale promotional activities - going from media attention to door-to-door sensitization - will have boosted uptake in these programmes as opposed to the limited sensitization activities of the Eldoret pilot programme [134]. While the latter might have hampered the credibility of the programme, the wide-reaching promotion of other demonstration programmes might have led to over-demand (which can raise ethical questions). Also, whether such wide-reaching sensitization strategies will remain possible when scaling up to national roll-out, and thus whether uptake will continue to reflect high acceptability in these settings is yet to be seen.

Scale of promotion: estimating the denominator In addition, the scale of the promotion programmes implemented during these demonstration projects is not only questionable in terms of feasibility in future programmes, it might also have influenced coverage determination. As shown by Ladner et al. (2014), some of these pilots report over 100 percent uptake, indicating that the denominator was poorly determined. This is indeed mentioned as a limitation in the review: each programme calculated the denominator based on different sources (census or population data or school enrolment lists, among others) of which the quality is unknown [122]. However, besides poor demographic data, certain outreach activities, such as radio spots, also make it difficult to estimate the coverage area and thus the denominator, which clearly leads to unreliable coverage rates.

Defining the denominator A final explanation for the difference in uptake lies again in the definition of the denominator and can be clearly illustrated with the example of the demonstration project in Kenya, as presented in the review of Ladner et al. (2014). They define the denominator as "the number of girls targeted determined prior to implementation based on data from available sources" (cfr. the demographic data mentioned above). However, the denominator they report and use in the review, i.e. 3000 girls, was the goal established by the programme organizers in Eldoret, rather than the girls they planned to reach through promotion - initially the 4000 eligible girls in the ten schools - or approached in the end (girls from other schools and reached through the radio spot). It is possible that staff of other demonstration projects has also interpreted and reported 'targeted' differently. So besides the challenge of precisely defining the catchment area and the eligible population in it (due to poor demographic data), misinterpretation of 'targeted group' might also have led to an underestimation of the denominator. The resulting high coverage, on its turn, then creates the false impression of a strong, positive relation between acceptability and uptake.

9.2 When is measuring acceptability as precursor for uptake acceptable?

It is clear that, in order to detect a correlation between a precursor of behaviour and the actual behaviour, certain conditions need to be fulfilled. Whether or not acceptability, for example, leads to HPV vaccine uptake is a complex issue which may vary across time, place, type of participants, etc. As such, it is possible that in certain contexts not acceptability but other (organizational) variables are more defining for the behaviour. Before implementing formative research, researchers should thus more carefully reflect on which and how variables need to be measured, when and among who. Below we outline some of the steps that can help justifying measuring precursors and their association with an action, as well as other important determinants of behaviour.

Defining precursors A first condition to further understand the predictive value of HPV vaccine acceptability is good determination and the use of validated measures: currently, concepts such as acceptability, intention and willingness to vaccinate are not standardized resulting in non-accurate labels and thus confusing results [143]. Also the difference between desire and other precursors needs to be highlighted. In a next step, the relationship between these precursors and vaccine uptake, i.e. the only true outcome variable of interest, can be defined as well as how they relate to each other. As such, mediation effects and thus the pathway of decision-making will be better understood.

Repeated measurements However, even with well defined and validated measures, other methodological challenges still remain when determining a valid proxy of behaviour, e.g. social desirability, temporal stability of constructs or limited knowledge leading to poorly-informed decisions and heuristics. Repeated measurements of precursors and self-reported behaviours, after providing basic information, might help in identifying and diminishing the effect of these biases.

Identify moderators at personal level Given that the correlation determined in this study was mainly driven by non-acceptors who did not vaccinate their daughter, future studies should further focus on distinguishing acceptors who vaccinate from those who do not as to identify moderating factors of the association with uptake. Who fulfils his own prediction and who does not? It is possible that personal characteristics define whether or not somebody is more likely to translate desires and intention into behaviour. In this study, baseline cervical cancer awareness was however a direct predictor of vaccine uptake rather than a mediating or moderating factor of willingness and vaccination. Other socio-demographics were not related to uptake but should be further investigated. Educational level or socio-economic status can clearly influence a participant's capacities to resist socially desirable answers, to process new information rapidly or to foresee logistics barriers. Hence, in some subgroups the relation acceptability-uptake might be stronger than in others. More heterogeneous sampling, including a more diverse population, can help identifying such factors. In addition, volitional control over the action should be considered as this strongly defines the possibility to translate intentions into behaviour: only the one who is truly in control of the behaviour can make valuable prediction [251].

Identify moderators at community or organizational level

Also the impact of external factors on the relation precursor-behaviour should be taken into account. Different delivery platforms, such as school-based or hospital-based vaccination obviously induce several types of barriers and include different stakeholders who can affect the vaccine's credibility and uptake. In addition, the roll-out should be monitored since design and final implementation might differ or change over time due to unforeseen circumstances. These deviations from the original planning can affect vaccination and thus the link between predicted and actual uptake.

Intention versus behaviour among health care providers

Finally, besides investigating the correlation between e.g. intention and vaccination behaviour among the target group, also the health care providers' intention to promote and offer the HPV vaccine should be investigated. In the case of the pilot programme in Eldoret, teachers' promises to support the project turned out to be

unreliable or their final effort was minimum. Moreover, during the FGD they expressed again a high willingness to cooperate in future cervical cancer prevention programmes yet also they might bump (again) into various barriers while trying to fulfil their promises. A review by Eccles et al. (2006) found indeed that the variance in behaviour explained by intention among health providers was of the same magnitude as among non-health professionals. Given that clinical behaviour is a form of human behaviour, the same theories and thus the same mediating and moderating variables might cause the intention-behaviour gap regarding promotional activities of providers [259].

Chapter 10

Health behaviour theories

Conclusion 2: Health behaviour theories at personal level have poor predictive value in the context of HPV vaccination - programmatic characteristics influence uptake more.

The HBM was for the first time tested in an African context through structural equation modelling. The relation of the constructs with HPV vaccine uptake was examined, as well as with willingness to vaccinate. Overall, the HBM had low predictive value: only self-efficacy was associated with uptake while willingness to vaccinate was predicted by self-efficacy, susceptibility and father's refusal. Also other longitudinal studies, in HIC, have found limited support for the HBM in the context of HPV vaccination [210], [215]–[219], [249].

The added variable of adequate promotion, i.e. the perception of having received sufficient information, was a strong predictor of HPV vaccine uptake and increased the predictive value of the model. Also socio-demographic variables such as cervical cancer awareness at baseline influenced vaccination behaviour directly.

These results hint to two main reasons as to why the HBM did not prove to be very predictive: 1) the constructs are either not taken into account when the decision regarding HPV vaccination is taken, and 2) other factors weigh more in the decision taking process. In any way, the usefulness of the HBM in the context of HPV vaccination seems doubtful.

10.1 An evaluation of the constructs of the Health Belief Model

10.1.1 Perceived severity

When is cancer not severe? The HBM assumes that the more serious a disease is perceived, the more likely preventive methods are performed. A review by Janz and Becker (1984) showed however that for preventive behaviours, the association was limited [207]. A meta-analysis by Brewer et al. (2005) also found a limited effect for severity, which was even diminished in case of skewed risk response distribution [260]. Given that cancer is a serious health threat all over the world, skewed results are very likely which jeopardizes the relevance of the construct. On the other hand, being unfamiliar with cervical cancer might make it difficult to estimate the impact of the disease. Similarly, the seriousness of an HPV infection, which could also be used to measure severity, might be too abstract. In conclusion, it is unlikely that perceived severity can distinguish compliers from non-compliers in the context of HPV vaccination.

10.1.2 Perceived susceptibility

Cervical cancer: in general a far-flung event but what if we discuss a daughter's risk? Generally, susceptibility is defined as the likelihood that one becomes ill. In this study, women perceived their daughters at high risk for contracting cervical cancer in the future, which positively influenced willingness to vaccinate but not vaccine uptake. However, besides the likelihood of harm, i.e. the chance to become infected, susceptibility can also be defined as an individual's constitutional vulnerability to an illness. The first version is represented by questions like 'How likely is it that you will

get cervical cancer?', the second by questions like 'Are you more likely than other people to get cervical cancer?'. [260]. So while the general likelihood, i.e. the probability of getting infected, might be small, your own constitution might increase the chances of becoming ill. The other way around is of course also possible: while objectively the likelihood of developing cervical cancer is large, your own chances can be lower if you do not engage in risk behaviour. As such, women might have answered, socially desirable, that given the high incidence of cervical cancer - which was communicated to them during the baseline interview - their daughters too were exposed to high risks, while in fact, they more subjectively believed that this would not happen to their daughter. This was also more reflected in the qualitative component of the study when participants described the disease as something that happens to other, rich people or individuals with a more modern lifestyle. Finally, also other studies showed that people rate their daughter's risk higher than their own which means that susceptibility might relate differently with behaviour depending on who's risk is estimated [183]. As such, this construct can be interpreted differently and thorough validation seems necessary as to define its impact on preventive behaviour designated to protect different persons.

10.1.3 Perceived benefits

Estimating the unknown The main benefit investigated in relation to HPV vaccination is of course prevention of cervical cancer, i.e. the efficacy of the vaccine. In this study context, given the novelty of the vaccine, participants had no previous experience with the vaccine and thus had to hypothesize whether or not the HPV vaccination would work. Although prospective studies investigating new behaviours are least likely to be influenced by past HPV vaccination, which helps identifying causal relations [214], they do induce a certain 'guesswork'. Obviously, people will rely on similar experiences to judge, for example childhood vaccines, but in the end it will also be a matter of 'blind trust'. This was also illustrated in a longitudinal study from Brewer et al. (2011) in which both HPV vaccine effectiveness and uncertainty about the vaccine were questioned. While effectiveness was not correlated with uptake, uncertainty was [215]. Given that trust was also a major factor brought

up during the FGD, both towards the vaccine and the health system in general, it might be interesting to measure specifically trust related variables when identifying predictors of new behaviours.

10.1.4 Perceived barriers

Estimating the unknown With regard to barriers, several types are often investigated, such as cost or time, lack of information, fear of side effects, doubting efficacy and opposition of important people [143], [158]. Of course, the diversity makes it more difficult to compare results but generally, barriers are among the strongest predictors of the HBM [207], [208]. The absence of significant associations in this study is therefore rather surprising. However, similarly to benefits, participants needed to anticipate problems regarding an unknown preventive action.

Volitional control Just like described above regarding the 'underestimation of external factors' when discussing the intention-behaviour gap, control can be an issue: individuals have to predict barriers (cfr. express their intention) while they are not in control of for example organizational aspects, which may induce time or cost constraints, promotional activities, which may lead to information shortage or the will of others, who may stop them from doing what they think is best. As such, their predictions are unrelated to their subsequent behaviour. Two main constructs of the TPB could be very valuable here, i.e. subjective norms and perceived behavioural control (PBC), and raise the predictive value of the HBM [251]. Also including some personal characteristics, for example socio-economic status as moderator for perceived financial constraints or community embeddedness to counteract promotional failure, might improve the predictive value of the model. However, adding factors beyond the personal level, for example characteristics of the vaccination programme will have an even greater impact.

Different types of barriers distinguish different types of intention Besides vaccine uptake, the association between the barriers and willingness to vaccinate was also investigated: except for father's refusal, none of the measured barriers was related. According to Gerend's multidimensional nature of barriers (2013), global

barriers, inherent to the vaccine (for example fear of encouraging sexual risk behaviour), are negatively linked with intention, and practical barriers, such as financial constraints, positively. This is based on the assumption that people who are interested in the vaccine will already look for possibilities to achieve their goal and as such identify practical barriers while those who have no interest at all will mainly mention their concerns regarding the practice that is discussed [261]. Given that fathers' refusal lowered willingness to vaccinate classifies the variable as a global barrier, inherent to the vaccine. This indicates that some women expressed their interest in the vaccine in function of their partner's wish (normatively intention) and not their own attitudinal intention [254].

10.1.5 Perceived self-efficacy

Being able as precursor for intention Perceived self-efficacy, the ability to perform a behaviour, was found to be positively related to both willingness and actual vaccination behaviour. This is similar to what was found in a meta-analysis of the TPB, which included self-efficacy along with perceived behavioural control ([251]). While self-efficacy resembles behavioural control, it distinguishes itself in that it covers the ability to perform a certain action from a cognitive perspective, based on internal factors, whereas perceived behavioural control rather evaluates external factors. Therefore, self-efficacy is often a strong predictor of intention (and subsequently behaviour) given that positive intentions are especially formed for behaviours one believes he/she can enact on. However, if unexpected, external events change this ability, self-efficacy will lose its predictive power.

10.1.6 Cues to action

Causality issues Generally, cues to action (CTA) can be extrinsic, for example receiving an invitation, or intrinsic, for example the anxiety to become ill. CTA is however one of the less developed constructs of the HBM and is therefore left out of meta-analyses [207], [208]. A first problem to investigate the causal relationship between CTA and behaviour is the fact that, especially for extrinsic CTA, people cannot predict what cues they will receive, they can merely say what or from whom they would like to get advice, which

does not imply this will actually happen. This is however how most studies assess CTA (with a physician's recommendation as main trigger) [95], [100], [101], [145]. On the other hand, if measured retrospectively, it becomes more difficult to argue that one investigates a causal pathway, yet it might be the closest thing to do so. A second problem is related to the value each of us gives to different CTA: while one person might find a poster very convincing, the other can think the opposite. In this case, a dichotomous variable of having received the cue, i.e. having seen the poster, will not be able to predict correctly the uptake of a certain action.

Evaluating cues versus predicting them In this study, it was opted to ask not only whether the participants had received information but also if they found it sufficient. By doing so, the second problem was avoided but of course, the estimated correlation cannot be considered purely causal. However, the strong association with HPV vaccination and feeling well-informed should stimulate future research to not only ask users and non-users which cues were received but also how they were perceived. This might give more insight in how to trigger people, rather than asking this prospectively and thus hypothetically ('what would encourage you to?'), even though it would complicate measuring its predictive value in the HBM.

10.2 When to use the Health Belief Model?

As outlined above, each of the constructs of the HBM has its own strengths and limitations, or is more or less applicable in different situations. Consequently, the predictive value of the HBM depends on many factors and might vary greatly. When foreseeing to apply the model as a framework to identify predictors of behaviour, following considerations, based on own reflections, should be taken into account:

- **Interaction between threat and control** - Risk perception is an important driver to look for medical care. The predictive value of perceived threat differs however greatly according to who is in control of the behaviour, who is the decision taker and who will benefit from it.

- **Hypothetical estimations versus users' perspective** - What is the value of trying to predict new, unfamiliar behaviour versus assessing and understanding real life experiences of users and non-users?
- **The outcome variable of interest** - Do we want to identify determinants of precursors such as desire or intention, or of actual behaviour? And what is the impact of time on the predictive value of these precursors.

Threat-control interaction Cognitive models, such as the HBM, share the vision that the desire to prevent a medical condition originates from the perception of a threat that needs to be avoided (while at the same time balancing the advantages and disadvantages of that preventive action). Risk perception is however more important when the preventive behaviour is truly an individual choice (for example the use of sun screen) instead of vaccination or screening, which depend heavily on providers [260]. The predictive value of the model depends thus heavily on the type of behaviour and the volitional control associated with it. Given that controllability may vary along diverse settings - for example through different levels of access to information or to high quality care - the model's strength may differ greatly across the world. Estimating the impact of structural factors might help in the decision whether or not the HBM is a suitable model to rely on.

A second problem with threat as one of the main drivers of preventive behaviour is, as described above, the ability to correctly assess severity and susceptibility. As such, the type of disease (e.g. cancer versus the flu) and the person who needs protection will highly influence the applicability of the HBM. For instance, in the case of child vaccination, the beneficiary is not the one in charge of the decision while the decision makers, the parents, might overestimate the risk as a consequence of overprotection. These factors should thus be taken into account when the HBM is taken into consideration.

Users' perspectives Besides the level of control and the ability to estimate threat, also the type of behaviour in terms of 'novelty' will define the functionality of the constructs of the HBM. Ideally, predictors of behaviour are defined without the influence of past actions [214]. However, this induces a catch-22: without having performed the action one can only guess, while through carrying out the behaviour, perspectives are formed based on that experience. In this case, the question is whether identifying causality is of major interest as opposed to distinguishing users' perspectives. Ravindran et al. (1997) advocated already in 1997 for investigating users' perspectives of contraceptives rather than hypothetical acceptability, arguing that such information would not only help improving health services but also assist potential users in assessing the appropriateness of the method [213]. Constructs such as benefits, barriers and cues to action might thus serve better in the context of evaluating past behaviour than supposed to predicting new actions. For example, in the longitudinal study, women who had vaccinated their daughter did bring up fear of side effects as a difficulty they had to overcome. Since HPV vaccination requires more than one dose, reinforcing the safety of the vaccine might be equally important to ensure completion of the scheme than to stimulate uptake of the first dose among 'new users'.

Defining and timing of precursors and outcome variable

Furthermore, the HBM is supposed to predict behaviour but, as stated by Armitage (2001) in the context of the TPB, constructs are often closer related to desire than with intention or actual behaviour [251]. As such, the outcome variable of the HBM could be evaluated and if deemed appropriate replaced by desire. If of course the objective is to truly identify the predictive value of precursors, time should be taken into account: given that time has a moderating effect on the association between precursors of behaviour, such as desire and intention [208], the constructs and behaviour should be measured in a relatively short timespan and, if included, the precursor should be assessed with a time limit ('I intend to vaccinate within one month'), to improve the predictive value of the model.

Exploration of the HBM Finally, while carefully evaluating whether or not the HBM is the optimum model in each context, the model itself can of course also be improved in order to increase its usefulness for predicting a diverse set of health behaviours in a diverse set of contexts. Adding variables, such as trust or personal and structural determinants might be one possibility, but might also complicate measurement and analysis. Therefore, focussing on the original constructs itself is also a useful step. Although the HBM is a widely used theory, there are still surprisingly many knowledge gaps: the relationship between the variables has never been spelled out and the definitions of the constructs are ambiguous [143], [213]. Barriers and benefits can cover somehow everything and cues-to-action has never been properly defined, as such there is a need to specify each construct if we want to compare research results. Additionally, the simple four-variable additive model should be re-evaluated and possible mediation and moderator effects among the constructs should be tested.

Chapter 11

Introduction of cervical cancer vaccination: the importance of tailored promotion and strategic service delivery

Conclusion 3: Wide-spread tailored promotion can diminish the importance of delivery strategies that guarantee easy access, and vice-versa. Vaccine uptake is the result of personal conviction and effort combined with health system investments and outreach. Focussing on one can take away the need of the other, yet a balance between both is more desirable.

The need for more information was continuously expressed by all participants during all phases of this study. Information on cervical cancer and the vaccine, as well as information regarding the vaccination programme was requested. Also indirectly it became clear

that people were ill-informed: participants were still unaware about the link between HPV and cervical cancer and missed the sense of urgency to undertake action against HPV infections. The importance of awareness and knowledge became however clear in the strong correlations found of vaccine uptake with both baseline cervical cancer awareness and a self-reported feeling of being well-informed at follow-up. Participants thus required some basic information and a sense of conviction of the need for prevention, yet detailed knowledge did not seem crucial for vaccine uptake. Also other post-vaccination studies, in Vietnam and Italy, reported that participants who had vaccinated against HPV could still have suboptimal knowledge, even though they considered themselves well-informed [133], [262]. A certain level of knowledge is thus required yet it remains unclear what type of messages are necessary and in which contexts to guarantee successful HPV vaccination. The information people request might also be related to the level of trust in and accessibility of the health system, with high levels of trust and access minimizing the need for (vaccine specific) information.

Lack of information obviously hampered vaccine uptake, but also the choice of the vaccination venue has influenced parents' decision. Especially during the FGD it became clear that school-based programmes were preferred over the current hospital-based programme and also the quantitative study revealed that time constraints had hindered women in vaccinating their daughter. Bringing the vaccine to the community was considered the right approach. In general, schools are promoted as an effective place to reach the target group and several demonstration projects have achieved good coverage with this approach. However, as with outreach vaccination, school-based programmes require movement of health staff and vaccines, which brings extra costs along. So while this strategy might be more attractive for potential participants, eliminating practical barriers, it does ask for more investments from the health care system and, in addition, the schools [113], [138].

11.1 Determinants of successful health promotion

During the FGD, participants were asked what they understood by cervical cancer and how they thought it was caused. Surprisingly, HPV was hardly mentioned even though some of the fathers reported having discussed cervical cancer with their wife - who had received direct information during the baseline interview and a leaflet to take home afterwards - and some of the teachers had been involved in the vaccination programme that had taken place in their school. As a result, one can doubt the adequacy of the information that was passed (basic concepts about cervical cancer and HPV transmission were communicated). On the one hand, the messages might not have been adapted to the audience so more attention to health literacy could resolve this problem. On the other hand, providers' skills to communicate appropriately with the community, i.e. teachers and parents, might have been sub-optimal. In that case, improving (cultural) competency of providers should be the focus.

11.1.1 Health literacy

Evaluating the four competences of health literacy - to access, understand, appraise and apply health information (table 3.1 [191] - in the context of the HPV vaccination programme in Eldoret, implies that potential participants had to have access to information on determinants and risk factors of cervical cancer in the first place. Additionally, given the role that teachers were given in the promotional strategy, they too had to receive adequate information: not only to convince them to support HPV vaccination but also to enable them to pass the information to the students and parents. Given that mothers and fathers who participated in the study reported to have received insufficient information, it is clear that health care promoters from the vaccination team should have put more effort in spreading information, among teachers and directly among parents (and students). However, one can also question whether the parents themselves also had a responsibility in obtaining information. Given that women knew, from the baseline interview, that a vaccination effort would take place in the hospital, they could also have actively searched for information regarding HPV vaccination.

Secondly, even though information is spread, receivers need to understand and process the information. Were people capable to comprehend and evaluate messages regarding cervical cancer and HPV vaccination? And finally, was the provided information applicable to their vision of health and disease? Reactions of participants during the FGD suggest that they did not always use the information as expected or that the given information was not compatible with their idea of cancer.

Applying Stuart Hall's theory of encoding and decoding (1980) might help here to clarify the hampered flow of communication [263]. Encoding, defined as the process to transfer ideas and feelings into messages, could have gone wrong if providers were not capable of passing the information in a clear, culturally acceptable way (cfr. cultural competence below). Additionally, there is little or no research done regarding how the HPV vaccine promotional messages are decoded, i.e. how they are interpreted and which ideas and feelings they evoke among the target group. Studies that have started addressing this issue, tested for example whether focussing on either cancer, warts, or STI prevention influenced people's acceptability towards HPV preventive measures: Cancer prevention seems to be more appealing yet more research is needed before results can be generalized [264]–[266]. Other studies have investigated different communication styles, such as attribute and goal framing. The former compares positive messages regarding the vaccine's effectiveness (able to prevent HPV types causing 70 percent of cervical cancers) versus negative ones (the vaccine is ineffective against 30 percent of cervical cancer causing HPV types) [267], while the latter refers to either stressing gain (benefits of the vaccine) or loss (costs of not receiving the vaccine) [268]–[270]. Current results are not conclusive but tend to favour positive goal framed messages (gain-framed), just like a meta-analysis of Gallagher et al. (2012), evaluating the effect of messages on attitudes towards preventive behaviour, concluded [271]. More research is necessary to better understand why different promotion styles evoke different reactions and to distinguish the effect of personal and cultural characteristics on interpretation of preventive health promotion. A study in the USA, for example, found that goal framing had a different impact on African-Americans and Hispanics compared to non-Hispanic whites [270]. It

is quite likely that people with different cultural backgrounds and frameworks of illness and disease prevention respond differently to health messages. Definitely in Sub-Saharan Africa, where health beliefs might substantially differ from the Western view, the effect of health information and how it is integrated in the existing model of cancer needs to be unravelled. More qualitative research regarding people's perspectives on the functioning of the body and on illness would be a first step to do so, combined with in-depth investigation on how messages derived from Western medicine are interpreted. Such studies would benefit from a phenomenological approach since this would help describing and interpreting people's experiences with disease and preventive medicine [272]. Furthermore, these studies are extremely timely now medical information becomes more easily available through all sorts of media.

11.1.2 Cultural competence

In order for the general public to understand health related messages, the information needs to be tailored to the audience. But also the health staff, who are the messengers, needs to be capable to reach and convince the clients. In a Kenyan setting, physician-patient communication might be hampered by socio-economic barriers but also by cultural ones. First of all, Kenya is a multi-cultural society, including many tribes (accompanied by different languages) and religions, each with their own perspective on health and medicine. Secondly, adoption of Western views by medical staff during their training might move them away from their own and their patients' cultural background. As such, sharing the same nationality might not be sufficient to cover the discordance between providers and clients.

Miscommunication might especially occur when providers only use the Western biomedical template of disease and illness rather than applying other cultural patterns. Following Habermas' theory of Communicative Action, Mishler (1984) identified two voices in doctor-patient interviews: the voice of the lifeworld and the voice of medicine. The former refers to the patient's subjective experience of illness and prevention, while the latter is the objective, scientific account of the biological manifestations of a disease or in this case the

efficacy of a preventive method. Barry and colleagues (2001) then further classified several communication styles: 1) strictly medicine, when provider and patient both use the voice of medicine, 2) mutual lifeworld, when the physician acknowledges how the patient experiences health and illness, 3) lifeworld ignored, when the physician holds on to the voice of medicine while the patient expresses him or herself through the voice of lifeworld, and finally, 4) when the physician does not react to lifeworld expressions [273], [274]. This study did not determine the presence of these different voices in promotional activities carried out during the HPV vaccination programme. Future projects might need to focus on the communication styles of providers to gauge their impact on effective vaccine promotion. In addition, just like it is important to understand the perspective of the patient, also the experience of the providers can learn us more regarding vaccine counselling sessions. As such, phenomenological studies should not only be carried out to understand the patients' view, as mentioned above, they can also help to explore providers' experiences with regard to vaccine promotion [272].

With this in mind, providers should also be sufficiently trained to acquire good communication skills and to enable them to recognize the cultural mix they are confronted with on daily basis and the socio-cultural barriers that might impede them to transfer messages efficiently: conscious or unconscious stereotyping shapes their behaviour and decisions during consultations and health promotion activities. Knowledge about particular cultural beliefs, values and practices is important to hypothesise about an individual's perspective, as well as the capacity to assess the degree to which the individual adheres to the cultural background. As such, cross-cultural expertise can significantly improve providers' persuasiveness. A first step towards a cross-cultural competent health system is however acknowledgement of the importance of culture and disentangling social factors (economic and educational status) from cultural ones [275]–[277]. Only then, models of prevention interventions can be culturally adapted, i.e. can become responsive to the cultural needs of the community by addressing core values, beliefs and norms of the target group's views and lifestyles. Finally, this approach also contributes to health equality as it diminishes discrimination of subgroups [278].

11.2 The role of the service delivery platform

Communication strategies addressing all members of society are crucial to establish an accessible health system for all. Yet, choosing the right service delivery platform might be equally important. As witnessed during the demonstration programme in Eldoret, which used a hospital based approach, a certain wait-and-see approach was adopted justified by awaiting potential side effects among the vaccinated. However, discussions with the vaccination team (vaccinators and programme coordinator) revealed that after the vaccination opportunity was opened up to the whole community - as opposed to targeting only ten public primary schools initially - some schools were capable in reacting promptly and organized transport for their pupils to go for vaccination. This raises the hypothesis whether school-based vaccination might be able to totally eliminate health inequality: schools with better capacity to organize and follow-up a vaccination programme - often private schools - will easily obtain better results in terms of coverage and completion of the vaccination schedule.

In general, school-based vaccination is however considered a delivery method through which the target group can be easily reached (conditional on sufficiently high enrolment and attendance) [113], [142]. But besides the above-mentioned risk of unequal uptake among schools, there is also the question on how to reach non-school going girls. Or, for example in South-Africa, the national programme only includes government schools, assuming that families with daughters in private schools can organize and pay for HPV vaccination themselves [279]. School programmes should be combined with community-based or health centre-based vaccination efforts in order not to miss out the opportunity to improve health equity regarding cervical cancer.

Finally, HPV vaccination might be considered as a momentum to introduce or fortify school health or more in general, adolescent health. Adding other important health services to HPV vaccination could help establishing routine HPV vaccination. Several options are possible, going from sexuality education, to de-worming or eye check-

ups [280]. MacPhail et al. (2013) also recommended to evaluate the local context when considering additional health services to take into account not only local priorities but also regional resources available [281].

11.3 Vaccine confidence, complacency and convenience

It is clear that the synergy between communication, i.e. promotional activities, and service delivery is crucial in order to obtain high vaccine uptake. Both components need to convince the target group of the need, the safety and efficacy of the vaccine, while limiting potential barriers. Taking in mind the three C's as crucial factors for vaccination, we can reflect on the HPV vaccination programme in Eldoret and how the promotion strategy and service delivery influenced these three crucial variables.

Vaccine confidence: lack of trust in vaccine or provider.

There are various reasons related to confidence why participants did not vaccinate their daughter against cervical cancer. As mentioned before, fear of side effects was among many participants. This is partially due to the newness of the vaccine but also the promotion activities, i.e. teachers informing parents and students, might have affected trust: are teachers considered a reliable source of information? While schools might be a good venue, participants of FGD did express the wish to be informed by health professionals. A bit contradictory to this, is the request of participants to vaccinate in schools, instead of health facilities, because of the low quality of services offered in the hospital. Improving quality of care, including communication skills of health staff, seems necessary to boost the confidence towards the health facilities in general (definitely when school vaccination is not an option). However, vaccine confidence went beyond trust in medical science and health systems, as expressed by worrying about possible experiments of the pharmacy or potential infertility. Unfortunately, these concerns derive from a general distrust towards the West due to (past) domination and exploitation, as well as from internal tribal conflicts where fertility is considered necessary to maintain power. Support by important

influencers, e.g. (local) politicians, can take away this fear yet they also need to gain confidence in new vaccines.

Vaccine complacency: not perceiving the need, not valuing the vaccine. Results regarding perceived risks were contradictory: quantitatively, mothers reported that is very likely for their daughter to develop cervical cancer while qualitatively, teachers and fathers reported that cancer is not a disease that strikes them (as opposed to people with a 'modern lifestyle'). Given the low uptake, the susceptibility mentioned by the women might have been an overestimation (due to social desirability) or the risk of the vaccine out-reached the risk of the disease. Again, better communication can tackle vaccine complacency but also good cancer registration and provider-patient communication can help combating the belief that cervical cancer is not common among the general population in Kenya. Finally, certain service delivery operations might also affect complacency, more particularly defining the target group. While the quantitative study did not identify age of the daughter as a determinant for HPV vaccine acceptability or uptake, including slightly older girls in the target group might facilitate vaccination: given the difficulty to discuss cervical cancer, older girls might eliminate this discomfort.

Vaccine convenience: access. Participants of the qualitative component called for 'bringing the vaccine to the community' instead of parents taking their daughters to health facilities for HPV vaccination. School-based vaccination was one of the preferred options, but other venues (church, markets, etc.) would do as well. From this we can conclude that indeed the convenience for the parents - as long as the health system reaches out to them and not the other way around - is priority. However, when vaccine confidence is high and complacency is minimized, people might be willing to invest more in HPV vaccination, i.e. take on a more active attitude and responsibility towards cervical cancer prevention. In this light, the question remains to what extent sensitization, which provides understanding, is important, and to what extent the type of delivery, which might induce or lift up barriers, influences people's vaccination behaviour.

11.4 Vaccine hesitancy

Given the wait-and-see approach reported by participants of this study, it seems appropriate to consider the possibility that vaccine hesitancy influenced the HPV vaccination programme in Eldoret. Another observed sign of vaccine hesitancy is the measured intention-behaviour gap: many participants were probably still in the decision making process, hence the discordance between (over-)expressed intention and uptake. The large group of participants reporting at follow-up that they had wanted to vaccinate their daughter but had not managed to do so is however worrisome, as is the poor support of the teachers. These results hint that there are many hesitant people in the community with little interest in vaccination or maybe in cancer prevention in general. If they remain indifferent towards sensitization, their reported intention might never be converted in vaccine uptake. Wegwarth et al. (2014) looked into the effect of balanced versus unbalanced messages, defining balanced as correct (evidence-based), transparent (risk presented in absolute numbers, providing a reference class) and complete information (i.e. pointing out both harms and benefits of the vaccine). They found that stated intention to vaccinate was more reliable among the participants who received the balanced information, i.e. the information helped them translating their intention into behaviour [282]. Communication is thus a tool to eliminate vaccine hesitancy and to push people towards action. On the other hand, if service delivery operations limit the effort of the parents, for example through free school-based vaccination requesting active opt-out, also more children could receive the vaccine, with or without parents' conscious decision.

Chapter 12

Conclusions and recommendations

12.1 Principal findings

Measured HPV vaccine acceptability is often high but does not always reflect behavioural intentions or does not always translate into uptake. While it is a precursor of behaviour, i.e. an essential step in the pathway of decision-making towards vaccination, its predictive value depends on certain conditions. Indeed, many factors moderate the relation between acceptability and uptake, or influence uptake directly. A first important determinant is awareness and knowledge of cervical cancer and HPV vaccination. People's reported acceptability will miss out stability and truthfulness if they are not familiar with the disease or the concept of vaccination. As such, socially desirable answers, desires or even guesses will occur more frequently, hampering the link with vaccine uptake. Secondly, volitional control is crucial as it determines who will be responsible for the final decision. Assessing acceptability among those without a certain level of freedom to act will thus also lead to a poor association with behaviour. Finally, many factors beyond personal control, especially organizational factors, can interrupt the intentional behaviour if they were not taken into account or changed since the moment of formulating the willingness to vaccinate.

Besides the acceptability-behaviour gap, also other attitudinal factors loose predictive power due to the above-mentioned factors. For example, estimating the threat of an unknown disease or the cue that would trigger an new action is challenging. And also the outcome variable itself plays a role in the strength of the correlation: new actions are more difficult to evaluate and rely on trust or past experiences of similar behaviour. This should be taken into account when health behaviour theories are chosen as to help identifying determinants of acceptability and/or behaviour.

The failure to find strong associations between several constructs of the pathway of decision making, and more particularly between an antecedent and the behaviour, is mainly driven by non-compliance, i.e. people do not fulfil their own expectations. While non-believers primarily need information in order to be persuaded by the importance and benefits of HPV vaccination, non-compliers need both (practical) information and an accessible vaccine. Therefore, emphasis on promotion only versus rolling out an accessible vaccination strategy will lead to vaccine uptake among people with different points of view and different levels of willingness to invest in vaccination: the first approach will lead to vaccination among those who rely on information and who, once convinced, are willing to invest in it. The latter strategy will stimulate vaccine uptake among people who might be less interested but are willing to vaccinate given the small effort it takes them. Ideally, vaccination programmes focus on both components as to reach as many people as possible.

12.2 Future steps

Formative research, as has been done, has helped identifying knowledge gaps or gauging expected barriers, but has however mainly focussed on vaccine acceptability. As discussed above, this construct might not cover all aspects of the decision-making process and might not always lead to vaccine uptake. Measuring **vaccine hesitancy**, and its determinants confidence, complacency and convenience, might offer a better insight in the 'state of preparedness' and willingness of people to vaccinate against HPV. Similarly, in addition to investigating the constructs of the HBM in particular and of health behaviour theories at personal level more generally,

factors at higher levels should get more attention as to better understand vaccine uptake. Combining constructs of different theories such as the HBM, the TPB or the socio-ecological model might lead to stronger predictions [210].

Furthermore, implementation studies, assessing **users' perspectives**, can contribute a lot to the understanding of uptake of preventive behaviour by identifying true benefits, barriers or cues, as opposed to those mentioned in hypothetical situations [213]. As such, besides preparing the introduction of a vaccine by formative research, implementation itself needs to be carefully monitored, continuously assessing attitudes and uptake:

- Attitudes, through open communication with the community, as to timely detect vaccination hesitance, rumours and doubts and to tackle them with tailored sensitization.
- Uptake, through vaccine registration, as to verify if the delivery platform is reaching the entire, previously identified target group.

In order to address specific concerns timely, **surveillance systems** should be put into place to measure uptake and to monitor vaccine acceptability [230], [283] and more broadly vaccine hesitancy. Therefore, validated and standardized tools are needed to gauge vaccine hesitancy and its determinants in different settings. A first survey measuring vaccine hesitancy has been developed by the SAGE Working group (2015) yet it still needs to be validated and tested [226], [284].

Finally, strategies need to be developed to, once identified, address vaccine hesitancy. Given the complexity, there is however no single intervention to address all types and aspects of hesitancy: **tailored interventions** are necessary to cover the specific concerns of each group. Of course, lessons learned should still be shared; a review of interventions found that uptake was most likely to increase if strategies either

1. directly targeted under-vaccinated populations,
2. aimed to increase knowledge and awareness,
3. improved access to vaccination,

4. targeted specific subgroups,
5. mandatory vaccinations or sanctioned non-vaccination, and/or
6. engaged religious or other influential leaders to promote vaccination.

Regarding the tools that can be used, interventions can be dialogue-based or apply incentives or reminder-recall systems. In general, evidence for successfully increasing vaccine uptake is often still relying on traditional tools, such as passive information sharing (leaflets or mass media campaigns), and do not fully address vaccine hesitancy. Especially in LMIC, carefully planned interventions with strong evaluation components are needed to better understand and counteract vaccine hesitancy [234], [285].

12.3 Limitations

This research study was set up around an HPV vaccination programme which was an independent effort from health care providers of the referral hospital of Eldoret, Kenya. While this is also definitely a strength - research results are not biased by conflicts of interest - it also brings along some limitations.

First of all, the decision of the programme makers to open up the vaccination opportunity to more than the ten initially selected public schools, resulted in the fact that the entire target group, the denominator, of the programme was no longer identifiable. As such, we could only report coverage among our study participants which is independent from the actual coverage reached by the programme. Furthermore, by not including people who were included in the second wave, we could not verify whether they differed from the first group in socio-demographics or attitudes towards cervical cancer vaccination.

Secondly, promotional activities among the different schools were poorly recorded. The idea to track them down during the FGD with the teachers and parents resulted also to be difficult given that so few people had heard of the programme or remembered how it was announced. While this is of course also an important result, it did hamper the analysis in terms of clearly identifying which activities and which types of messages had persuaded people to vaccinate their daughter.

Finally, because of the fixed vaccination strategy - which was in the context of Eldoret and the financial situation of the programme makers definitely a justified choice - no comparison between different delivery strategies or promotional campaigns could be made. In order to identify the most cost-effective programme different variations should be implemented and evaluated.

Another shortcoming of this study is that while we critique the misuse of health behaviour theories and the lack of clear definitions of constructs, we also have mixed the use of several antecedents of behaviour, such as acceptability, intention and willingness to vaccin-

ate. However, it was not our intention to propose new definitions or differentiate one of the other. Rather, we aimed at showing as to why these constructs need to be questioned and better defined.

Part VIII

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