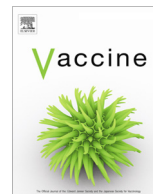




Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Integrating HPV vaccination programs with enhanced cervical cancer screening and treatment, a systematic review [☆]



Charlotte Wirtz ^{a,b}, Yasmin Mohamed ^b, Danielle Engel ^c, Anissa Sidibe ^d, Megan Holloway ^d, Paul Bloem ^e, Somesh Kumar ^f, Julia Brotherton ^{a,g}, Veronica Reis ^f, Christopher Morgan ^{a,b,f,*}

^a School of Population and Global Health, University of Melbourne, Victoria 3010, Australia

^b Burnet Institute, 85 Commercial Road, Melbourne, Victoria 2004, Australia

^c Sexual and Reproductive Health Branch, Technical Division, United Nations Population Fund, 220 E 42nd Street, NY 10017, USA

^d Vaccine Programmes, Gavi, the Vaccine Alliance, Chemin du Pommier 40, 1218 Grand-Saconnex Geneva, Switzerland

^e Life Course and Integration/EPI, Department of Immunization, Vaccines and Biologicals, World Health Organization, Avenue Appia 20, CH-1211 Geneva 27, Switzerland

^f Jhpiego, a Johns Hopkins University affiliate, 1615 Thames St, Baltimore, MD 21231, USA

^g VCS Foundation, 265 Faraday Street, Carlton, Victoria 3053, Australia

ARTICLE INFO

Article history:

Available online 1 December 2021

Keywords:

Human papillomavirus

Cervical cancer

Immunization

Screening

Integration and integrated health services

Low-income countries or lower-middle-income countries LMIC

ABSTRACT

A WHO global strategy launched in November 2020 sets out an ambitious pathway towards the world-wide elimination of cervical cancer as a public health problem within the next 100 years. Achieving this goal will require investment in innovative approaches. This review aims to describe integrated approaches that combine human papillomavirus (HPV) vaccination and cervical cancer screening in low- and middle-income countries (LMIC), and their efficacy in increasing uptake of services.

A systematic review was conducted analyzing relevant papers from Embase, Medline, CINAHL and CAB Global Health databases, as well as grey literature. Narrative synthesis was performed on the included studies. Meta-analysis was not appropriate due to the heterogeneity and nature of included studies.

From 5,278 titles screened, 11 uncontrolled intervention studies from four countries (from Africa and east Asia) were included, all from the past 12 years. Four distinct typologies of integration emerged that either increased awareness of HPV and/or cervical cancer screening, and/or coupled the delivery of HPV vaccination and cervical cancer screening programs. The synthesis of findings suggests that existing HPV vaccination programs can be a useful pathway for educating mothers and other female caregivers about cervical cancer screening; through in person conversations with care providers (preferred) or take-home communications products. Integrated service delivery through outreach and mobile clinics may overcome geographic and economic barriers to access for both HPV vaccination and cervical cancer screening, however these require significant program and system resources. One study promoted HPV vaccination as part of integrated service delivery, but there were no other examples found that examined use of cervical cancer screening platforms to promote or educate on HPV vaccination.

This review has demonstrated gaps in published literature on attempts to integrate HPV vaccination and cervical cancer screening. The most promising practices to date seem to relate to integrated health communications for cervical cancer prevention. Future research should further explore the opportunities for integrated health communications to support the efforts towards the new global cervical cancer elimination agenda, and costs and feasibility of integrated service delivery for underserved populations.

© 2021 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HPV, Human papillomavirus.

[☆] This article was published as part of a supplement supported by Centers for Disease Control and Prevention Global Immunization Division. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or World Health Organization. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors.

* Corresponding author.

E-mail addresses: charlotte.wirtz12@gmail.com (C. Wirtz), yasmin.mohamed@burnet.edu.au (Y. Mohamed), engel@unfpa.org (D. Engel), asidibe@gavi.org (A. Sidibe), mholloway@gavi.org (M. Holloway), bloemp@who.int (P. Bloem), somesh.kumar@jhpigo.org (S. Kumar), jbrother@vcs.org.au (J. Brotherton), veronica.reis@jhpigo.org (V. Reis), christopher.morgan@jhpigo.org (C. Morgan).

<https://doi.org/10.1016/j.vaccine.2021.11.013>

0264-410X/© 2021 Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Background	A117
2. Methods	A119
3. Results	A119
3.1. Description of included studies	A119
3.2. Demography	A119
3.3. Quality assessment	A119
3.4. Integration typologies	A119
3.5. Feasibility and acceptability of various typologies of integration	A119
3.6. HPV vaccination uptake	A120
3.7. Cervical cancer screening uptake	A121
4. Discussion	A121
4.1. Integrated health services delivery	A121
4.2. Integrated health communications	A121
4.3. Future research priorities	A122
5. Conclusion	A122
Funding source	A122
CRediT authorship contribution statement	A122
Declaration of Competing Interest	A122
Appendix A. Supplementary material	A122
References	A122

1. Background

An estimated 311,000 women die each year from cervical cancer, with nearly 90% of these deaths occurring in low- and middle-income countries (LMICs) [1]. The vast majority of cervical cancer cases are caused by persistent infection with oncogenic types of sexually acquired human papillomavirus (HPV) [2,3]. Cervical cancer is largely preventable mainly through primary prevention with HPV vaccination of girls, secondary prevention through cervical screening and treatment of precancerous lesions, and tertiary prevention through early diagnosis and treatment of cancer [1]. However, in many resource-constrained settings access to these effective prevention strategies remains suboptimal.

In August 2020, the World Health Assembly of the World Health Organization (WHO) ratified a global strategy to reach an elimination target of < 4 cases per 100,000 women [4,5]. This global strategy outlines three key goals for scale up by 2030 in order to eliminate cervical cancer as a public health problem within the next 100 years in all countries: 90% of girls being vaccinated by the age of 15; 70% of women aged 30–49 to be screened at least once for cervical cancer using a high-performance test (i.e. HPV DNA testing or equivalent); and 90% of women who have been identified with pre-cancerous lesions or cervical cancer receiving the required treatment. That these goals are ambitious, especially for LMIC settings, is exemplified by the global HPV vaccination coverage rate which stood only at 15% in 2019; and it is now clear that some assumptions regarding vaccination progress that underpin the global strategy may need revisiting, in particular noting the slower than hoped expansion of vaccine coverage, including effects of the COVID-19 pandemic [5].

Achieving the goals outlined by WHO demands some radical rethinking on how the uptake of HPV vaccination and cervical cancer screening and treatment can be accelerated, and make best use of the resources available. WHO promotes integrating health services including vaccination as one means to promote client-centered and effective health care [6]. In relation to HPV vaccination, a number of reviews and implementation studies have explored the feasibility and benefits of integrating HPV vaccination with adolescent health interventions [7–10], however less has been documented [7] on efforts to integrate HPV vaccination with cervical cancer screening and treatment programs. This systematic review aims

to understand how integration of HPV vaccination with cervical cancer screening has been implemented in LMICs, determine whether and how integration may be effective and ascertain any gaps or missed opportunities that could be explored in future efforts to find innovative service delivery platforms in pursuit of global elimination.

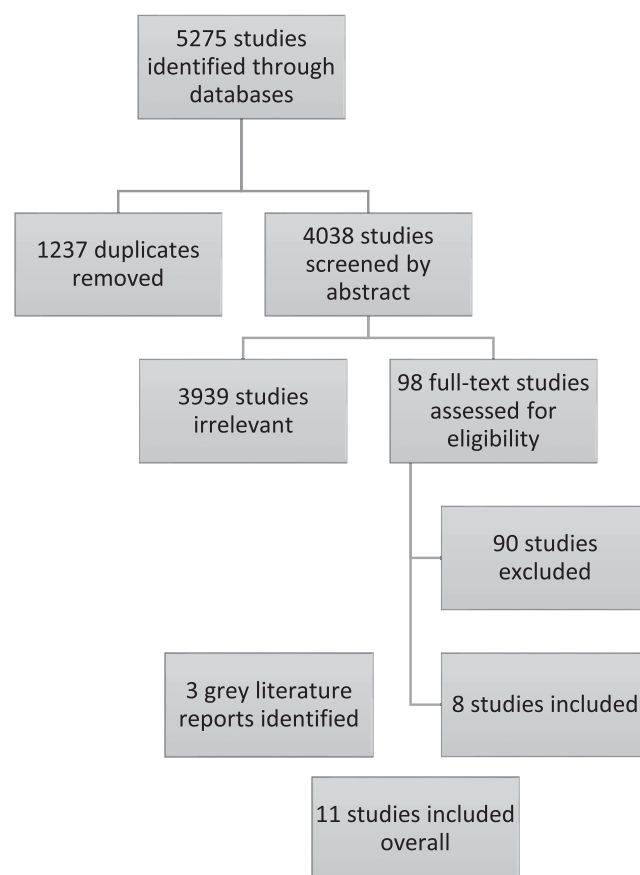


Fig. 1. PRISMA chart for identifying included papers.

Table 1

Description of included papers from the systematic review of the integration of HPV vaccination and cervical screening in LMICs.

Setting and first author	Intervention	Integration typology	Study type	Population and Sample	Outcomes
Cameroon (Yaoundé, North West, South West) Ogembo et al. [14]	Three vaccination delivery platforms (clinics, schools, community spaces) combined both vaccination and cervical screening	2, 4	Uncontrolled intervention Study	No description of population 6851 Girls 3452 Female caregivers	6851 girls received first dose VCR ¹ = 84.6% 3452 women screened
Cameroon (North West Region) Wamai et al. [15]	A sensitization program educating the population about HPV vaccination for adolescent females and cervical screening for older women.	4	Cross-sectional survey	67.7% female, 94% male 40.1% 26–35 years 68.2% married 39.2% completed primary school 317 parents and guardians living in the community in study	Knowledge and awareness of cervical cancer and HPV vaccination post program 75.5% familiar with HPV as a sexually transmitted infection 79.9% associated cervical cancer with HPV/genital warts 94.7% understood the value of HPV vaccine 47.1% knew HPV has no symptoms 54% agreed vaccine was safe 21.1% parents strongly agree with HPV vaccination
Cameroon Welty et al. [16]	Information provided to parents about HPV vaccination and cervical cancer screening. Women's Health Program also provided screening and HPV vaccination	2, 4	Demonstration project with before and after evaluation	No description of population 1600 girls aged 9–13 years vaccinated	1536 received the 1st dose of HPV vaccine
Peru (Amazon Jungle) Abuelo et al. [17]	A mother figure and daughter figure are recruited and paired together. Self-screening undertaken by mother figure and girls vaccinated at schools in line with school year.	3	Uncontrolled intervention study	Rural and Urban Populations 318 girls enrolled for vaccination 320 women completed self-screening	318 enrolled for HPV vaccination 300 received first dose 200 3rd dose VCR = 66.6% 100% women returned self-screening sample (320 women)
Peru (Manchay) Levinson et al. [18]	Community Health Workers using door – to – door approach recruited mother/daughter pairs. Self-collected sample was taken from adult and child was vaccinated on the same day.	3	Community based participatory research project	Hard to reach population due to complex geography. 323 Women aged 30 – 35 years registered with 352 daughter/granddaughters aged 10–13 years	331 received 1st dose VCR = 92.9% 323 women registered for screen and treat 312 specimens collected
Philippines (Los Banos, Minglanilla, Pagbilao) Llave et al. [19]	The integration of HPV vaccination for girls aged 9 – 13 years into a successful screening and treatment program for mothers.	2	Acceptability and feasibility study	Areas had existing cervical screening program. HPV vaccination introduced using existing facilities	4000 girls aged 9 – 13 years vaccinated 400 women surveyed about cervical screening VCR = 88.1%
South Africa Botha et al. [20]	Information session held for parents to gain consent for HPV vaccination also used as an opportunity to educate female caregivers about cervical cancer and screening.	4	Uncontrolled intervention study	Primary schools in low socio-economic areas	3465 parents approached to give vaccination consent. 2046 girls vaccinated for HPV with parents consenting 99.2% - received 1st dose VCR = 87.8%
South Africa (Western Cape and Gauteng Province) Dreyer et al. [21]	HPV vaccination in schools used to inform female caregivers about cervical cancer (information session) and give out self-screening kits	1, 4	Uncontrolled Interventional Study	Women – median age 38 years 906 female caregivers (1st questionnaire), 777 (2nd questionnaire)	558 women given self-screening kits 253 returned self-screening kits Before Intervention 31.7% no knowledge about cervical cancer After Intervention 11.9% no knowledge of cervical cancer
South Africa Moodley et al. [22]	Parents of vaccinated girls provided with educational material about cervical cancer screening/prevention and invited to attend local clinic	4	Uncontrolled Interventional Study	Combination of Urban and Rural Settings	960 girls received 1st dose VCR = 97.8%
South Africa	Self-screening kits (leaflets, informed consent	1, 4	Uncontrolled	Primary Schools Low SES	956 girls invited and

Table 1 (continued)

Setting and first author	Intervention	Integration typology	Study type	Population and Sample	Outcomes
Snyman et al. [23]	form, self-screen kit) handed out to vaccinated girls to take home to female caregivers. Samples brought back to school in sealed containers with personal information for results contact.		Interventional Study	1135 self-screening kits were handed out. 956 girls invited for HPV vaccination	519 consented to be part of the study VCR (of those enrolled) = 95.4% 1135 self-screening kits handed out 14.1% returned a sample
South Africa Snyman et al. [24]	School based vaccination including an information session which was used as an opportunity to invite female caregivers to participate in self screening	1, 4	Uncontrolled Interventional Study	Primary Schools Low SES 1645 girls invited for vaccination 569 women invited to screen	1059 girls consented cohort 99.4% uptake of 1st dose by consented group VCR (3 doses over 1 school year) = 86.5% VCR (3 doses over 2 school years) = 73.5%

Notes: VCR = vaccine completion rate (proportion of those who received first dose that then completed subsequent doses). Integration typologies coded as follows 1 = HPV vaccination used to disseminate cervical HPV self-sampling screening; 2 = Co-location of HPV vaccination and cervical cancer screening services; 3 = Co-recruitment with separate service provision; 4 = Integrated Health Communications.

¹ Vaccination completion rate (received all required doses of the HPV vaccine).

2. Methods

A systematic search of four databases was conducted: Medline, Embase (both using OVID software), CABI Global health and CINAHL Ebscohost. An example of the search strategies used is available in [Supplementary Materials Appendix 1](#). Grey literature documents were sourced through the professional networks of the authors. Papers were included if the abstract was in English, the paper described a health program that explicitly linked cervical cancer screening and/or treatment with HPV vaccination, and the integrated program occurred in a LMIC. We aimed for inclusive criteria, aiming to capture for assessment any publications that described an explicit attempt to integrate these two services.

To aid in analysis, an *a priori* conceptual framework was developed to map how cervical cancer screening and HPV vaccination integration might occur and benefit uptake. This is available online as a supplement to this paper. A data extraction template was based on this conceptual framework and standard health system categories. The extracted data were subjected to narrative synthesis [11,12]. Meta-analysis was not appropriate due to the heterogeneity of the study designs, the outcomes measured and the qualitative nature of the indicators. As the majority of included papers were mixed methods, the Mixed Methods Assessment Tool (MMAT) [13] was used to assess quality.

3. Results

3.1. Description of included studies

The initial search found 5,275 papers from four databases (Medline, Embase, CINAHL and Ebscohost). After removal of duplicates and initial screening of abstracts, 98 studies were eligible for full text review. The majority of these papers (90) were rejected for reasons including: absence of an intervention (48), no explicit integration effort (21), no relevant data (13), data from a high-income setting (7), and a protocol paper (1). The screening outcome is outlined in the PRISMA chart in [Fig. 1](#). Eight studies were identified through the database search, and an additional three unpublished grey literature reports were sourced from researcher networks. The details of the included studies are outlined in [Table 1](#).

3.2. Demography

The demographic information on the participants of the included studies was limited. All studies were conducted in LMICs, with a combination of urban and rural participants. The majority of schools and clinics were located in areas of low socioeconomic status. All studies included, at least in part, the aim of servicing hard-to-reach locations for populations that are typically underserved. More structured demographics, including for example: proportions of in-school or out-of-school girls, were not possible to tabulate, due to inconsistency between studies and a lack of such detail in many reports.

3.3. Quality assessment

The MMAT does not use objective scoring of papers. However, through this tool, all studies were determined to be of a homogeneous low quality, primarily due to the lack of comparison or control groups in any of the included papers. All studies were deemed to be of a similar quality and were therefore given similar weighting during the narrative synthesis process.

3.4. Integration typologies

Four distinct integration typologies emerged from the narrative synthesis process (see [Table 2](#)), in which either *service delivery* and/or *health communications* was the object of the integration effort. *Integrated health services delivery* experiences paired the provision of HPV vaccination and cervical cancer screening services through the dissemination of cervical self-collection screening kits as part of the HPV vaccination program (typology 1), co-location of cervical cancer screening and HPV vaccination services (typology 2), or the simultaneous recruitment of women and girls who later received either cervical cancer screening or HPV vaccination respectively in separate locations (typology 3). *Integrated health communications* experiences used either HPV vaccination or cervical cancer screening as an opportunity to share information about the other service (typology 4).

Table 2

Integration typologies identified through a systematic review of integration of HPV vaccination and cervical screening in LMICs.

Typology	Description of Typology	Relevant studies (country)
<i>Integrated Health Services Delivery</i>		
Typology 1	HPV vaccination used to disseminate cervical HPV self-sampling screening HPV vaccination of girls aged 10–13 years is used as an opportunity to disseminate cervical self-collection screening kits to female caregivers. The cervical screening kits may either be given directly to the female caregivers at face-to-face information sessions or provided to female students to take home to their female relatives with leaflets explaining how to perform and return the self-screening kits.	Dreyer et al. [21] (South Africa) Snyman et al. [23] (South Africa) Snyman et al. [24] (South Africa)
Typology 2	Co-location of HPV vaccination and cervical cancer screening services Co-location of services involves a woman requiring cervical cancer screening (typically a mother or grandmother) being paired with a girl requiring HPV vaccination (typically daughter/granddaughter). Both parties would receive the services at approximately the same time and in the same location. In the included studies, the locations were schools, mobile clinics, outreach programs and central clinics. The cervical screening could be either self-screening or provider-led depending on the services available to the program. Self-screening involves the woman collecting the sample, which is then processed by the health worker for testing. Provider-led involves a health worker collecting the sample from the cervix of the woman.	Ogembo et al. [14] (Cameroon) Welty et al. [16] (Cameroon) Llave et al. [19] (Philippines)
Typology 3	Co-recruitment with separate service provision 'Mothers' and 'daughters' are recruited at the same time by the same health or community worker, but cervical cancer screening and HPV vaccination are provided at separate locations at times that suit the respective parties.	Abuelo et al. [17] (Peru) Levinson et al. [18] (Peru)
<i>Integrated Health Communications</i>		
Typology 4	HPV vaccination programs use either face-to-face information sessions or leaflets to disseminate information to parents (in particular female caregivers) about cervical cancer and the importance of cervical screening, usually as part of the consent process for the HPV vaccine. The information sessions and leaflets draw the connection between the HPV vaccination of their daughters and the risk of cervical cancer to female caregivers. The aim of increasing awareness and highlighting the value of cervical screening is to motivate female caregivers to seek cervical screening for themselves.	Ogembo et al. [14] (Cameroon) Wamai et al. [15] (Cameroon) Welty et al. [16] (Cameroon) Botha et al. [20] (South Africa) Dreyer et al. [21] (South Africa) Moodley et al. [22] (South Africa) Snyman et al. [23] (South Africa) Snyman et al. [24] (South Africa)

3.5. Feasibility and acceptability of various typologies of integration

The feasibility of implementing typology 1, where self-screening kits for female caregivers are distributed through school HPV vaccination programs, varied with the dissemination process chosen. The distribution of self-collection kits at face-to-face information sessions was considerably more resource intensive than dissemination by sending self-collection kits and information leaflets home with girls receiving HPV vaccination [23,24].

Similarly, the feasibility of integrated health communications (typology 4) in South Africa depended upon the communication burden placed on the health workers, for example those providing HPV vaccination. The use of in person information sessions with parents, linked to school vaccination programs, were highly effective in increasing awareness and knowledge, with caregivers having the opportunity to ask questions [24]. However, the time and effort required of both caregivers and providers was judged to be difficult to sustain during a large-scale vaccine rollout. A more feasible integrated health communication technique was the provision of information about cervical cancer and screening in leaflets sent home to caregivers; this accompanied consent procedures for a pilot HPV vaccination program. Leaflets were written in local language using information which was appropriate to the maturity and knowledge of participants [22–24]. While feasible, this technique was deemed by the authors as less effective in motivating the return of cervical self-screening samples than face-to-face discussion [23]. Another study in South Africa that distributed leaflets for both vaccination and cervical cancer screening education, found it feasible to incorporate the communication products in the supply chains used to source and distribute the HPV vaccine [20].

The acceptability of the HPV vaccine to parents, and subsequent uptake, was reported to depend on the education or communication process used. Parents who attended face-to-face information sessions led by a trained health worker were more likely to agree to vaccination compared to those receiving information provided through leaflets [25].

Integrated service delivery using of typology 2, which involves the co-location of cervical screening and HPV vaccination services, was judged overall as feasible in delivering services to some women and girls in the target age ranges. It is notable that these were all small-scale implementation and focused on service delivery through health facilities or community locations, rather than the school-based vaccination that is most commonly practiced in LMICs. There were documented difficulties for both population groups; many women receiving cervical screening did not have daughters within the appropriate age range for HPV vaccination and even when they did, these girls were often in school when the clinics were open [14,16]. This type of integration was reported in two studies as being applicable to women and girls who were hard to reach (including girls not in school) through combined outreach services [14,19].

Typology 3, where women and girls were recruited together but services were provided separately, was also reported as a useful strategy, where home visits for recruitment of women and girls was seen as important to overcoming access barriers [18]. However, this strategy was found to be highly resource intensive and thus may be difficult to apply where there are constraints on staff, transport or funding.

3.6. HPV vaccination uptake

No studies included well-defined control groups, and none measured HPV vaccination coverage. Although several measured other aspects of HPV vaccination uptake, including successful recruitment into pilot vaccination programs and vaccine completion rate (VCR, referring to the full uptake of all recommended doses of HPV vaccine) these measures were not sufficiently homogenous to allow formal inter-study comparisons. The VCR varied by setting, and was clearly influenced by many program factors beyond the integration process. For example: in two clinic- and outreach-based programs, the VCR ranged between 62.9% in a study in Peru [17] to 88.1% in the Philippines [19]; and in two integrated health communications experiences, the VCR ranged from 87.8% [20] to 95.4% in the VACC2S Project in South Africa [23].

Many factors that impacted vaccination uptake or VCR were those common to non-integrated experiences. These included, in Peru, clients relocating after recruitment, geographical inaccessibility, refusal to allow vaccination by caregivers, fear of sterilization, beliefs that HPV vaccine is not required as daughters are not perceived to be sexually active, and girls becoming pregnant and temporarily ineligible [17,18]. Factors specific to integration were seen in clinic-based or outreach programs (typology 2), where associating HPV vaccination with cancer screening of female relatives could not always promote uptake of the vaccine because daughters were not in the appropriate age range or were in school when the clinic was being run. Vaccine completion was also decreased in some typology 2 integration experiences, when girls failed to attend for follow-up doses, although the specific reasons for this were not explored [14]. This study did, in contrast, also report successful improvement in vaccine completion by using peer tracking to locate girls for follow up appointments.

3.7. Cervical cancer screening uptake

The two studies which distributed cervical cancer screening self-collection kits through HPV vaccination programs (VACCS1 and VACCS2 in South Africa) measured the rate of samples returned for screening tests. VACCS1 recorded a sample return rate of 44.5% compared with 29.7% in VACCS2, taking into account the percentage of the population in need of cervical screening [23]. VACCS1 directly engaged with female caregivers at an information session which was being used to inform parents about HPV vaccination of their daughters, offering women cervical self-collection kits. VACCS2 used a less direct distribution pathway, with the cervical cancer screening self-collection kits being provided to girls to take home, along with explanatory letters and HPV vaccine consent forms. This less personal distribution pathway resulted in a lower sample return rate in this comparative study. In two integrated service delivery experiences using typology 2 the rates of return were not reported, however these two studies did record successful return of samples alongside HPV vaccination of an age-appropriate girl; 312 samples [18] and 3452 samples [15] respectively. In the one project that used typology 3, all 320 women recruited provided self-collected cervical cancer screening samples [17]. One study in Cameroon measured the coverage of cervical screening following a community sensitization program that included education in schools; the cross-sectional survey conducted post-intervention found that 35.3% of women self-reported undergoing cervical screening [15].

4. Discussion

The eleven experiences synthesized in this review demonstrated four distinct typologies of integration, across both service delivery and health communications. Despite the limited number and range of experiences, some conclusions can be drawn in both these domains.

4.1. Integrated health services delivery

Overall, for integrated service delivery, there was more evidence to support a beneficial impact on cervical screening participation than on HPV vaccination coverage; although this conclusion is tentative, given the small number and sizes of the studies we found. The demonstrated value of integration typology 1 hinges on its ability to utilize the school student to female caregiver pathway as an opportunity to distribute cervical screening self-collection kits. This access enhancement could be important in resource-constrained settings where women may not be able to

take time off work, postal services lack reach, or the costs of travel are prohibitive [26]. In the two studies that directly compared strategies for this, their results suggested face-to-face communication with health workers gave higher rates of sample return. However, the findings across all included studies of this typology suggest that both school-based or facility-based HPV vaccination programs could be leveraged to benefit cervical cancer screening, where self-obtained specimens are an option. Further research is needed to determine aspects of feasibility, such as costs or staff time and training, in settings with limited resources. Future studies should also assess positive or negative effect on HPV vaccination uptake; this was not measured by any of the studies we reviewed under this typology.

The integration of HPV vaccination and cervical screening into established primary health care settings (typology 2) was reported to offer efficiencies in service delivery. However, careful planning and additional resources are required to ensure that the combination of tasks do not overburden the staff, clinic operations or health system [6]; noting two reports from Cameroon in our review that stressed the importance of considering staff workloads [16,19]. The value of typology 3 [17] where girls and women were recruited together but services provided separately, lay in increasing access to cervical cancer screening for women who may not have frequent contact with the health system. There is a major limitation in Typology 1 in that the households, parents and caregivers of girls receiving HPV vaccination may not comprise women of appropriate age for screening in national programs. This limitation needs close attention and may in fact make this type of integration insufficiently cost-effective to be worth pursuing. It may be that cervical cancer screening and treatment services may benefit more from integration into other services that address the needs of adult women in LMICs, such as those for HIV infection; noting that these forms of integration are beyond the scope of the methods used for this paper.

Integrated outreach clinics were found to be an effective complement to school-based HPV vaccination programs for hard-to-reach girls and women; including girls who are not attending school and women who lack access to cervical cancer screening [6], noting that such disadvantage may exist for both generations in the same community. Three studies [14,18,19] used outreach to enable access, while also reporting the considerable resources involved in this strategy. There is a tradeoff between resource-intensive outreach programs, which engage with rural and hard-to-reach communities, and ensuring that fixed clinics are well staffed and resourced to serve the community in which they are situated. This trade-off is not unique to HPV vaccination or cervical cancer screening, but a challenge experienced in all resource-constrained settings. The WHO's Reaching Every District Strategy promotes the benefits of allocating extra resources to outreach to ensure equitable coverage [27] and this aspiration to "leave no one behind" is embedded in the Immunization Agenda 2030 [28].

It is important to ensure that the integration of services is not used as a solution to under-resourced health systems, but rather a technique of optimizing the contacts that individuals have with the existing health system and providing more client-centered care. This applies to immunization programs more broadly, as discussed in WHO's Working Together Strategy [6]. The experiences documented here do show this as achievable in certain contexts.

4.2. Integrated health communications

Two key techniques, take-home leaflets and health professional-led information sessions, were used to disseminate information about cervical cancer screening to women at HPV vaccination opportunities [20–23]. The limited outcome measures we reviewed do suggest that integrating health education and infor-

mation about cervical cancer with HPV vaccination is valuable. There is greater engagement with women through the in-person information sessions, however this technique is more resource intensive for both health workers and women. This review also supports the potential for vaccination staff to provide other forms of information on cervical cancer prevention to girls and families. It is important to note that integrated health communications is only valuable if the services being promoted are accessible and available in a form acceptable to women and girls [29]. Thus, integrated health communications is not a technique that can be used in isolation but rather needs to be paired with the provision of both HPV vaccination and cervical cancer screening within communities.

Ancillary education accompanying outreach and clinic-based approaches (typology 2 and 3) were also found to be effective mechanisms to support intergenerational conversations between female caregivers and girls [21]. Greater engagement between ‘mother figures’ and ‘daughter figures’ was seen to offer particular value in settings experiencing higher levels of stigma surrounding reproductive health [30]. There may be value in developing and testing broader health communication efforts such as a “Mother-Daughter Day” that aim to reduce barriers in inter-generational communication on important sensitive health issues.

4.3. Future research priorities

A style of integrated health communication which was expected in our *a priori* framework was the use of cervical screening services as an opportunity to disseminate information to parents about HPV vaccination: however, this form of integration was not featured in any of the included papers (although it did take place in one [19] as a complement to service delivery). It may be that such additions do occur in routine programs, but have not been included in studies explicitly aiming to improve the process of integration. There is room for more structured exploration, perhaps using implementation research techniques, into how cervical cancer screening could be used as an opportunity to benefit HPV vaccination in LMICs. A further need is for well-designed studies of integrated service delivery that include standard measures of vaccination or screening uptake with careful comparators, and better measures of feasibility including staff time and program costs.

Most importantly, there is a need to test novel models of health education and communication throughout the cervical cancer prevention pathway, ensuring that integrated health communications are implemented at primary and secondary levels of prevention and also at the tertiary level. These should explore the potential of explicit inter-generational communication approaches to promote access to sexual and reproductive health care across all age groups. Further research should also aim to gain a better understanding of how integration of HPV vaccination and cervical screening serves to overcome the range of barriers, age, gender, socio-cultural and economic, which currently exist at the national and program levels.

To further promote this, we propose that cervical cancer screening and treatment programs include as an evaluation indicator the degree to which they also work to promote knowledge and uptake of HPV vaccination.

5. Conclusion

As noted in the Introduction, slow progress in HPV vaccination imperils achievement of the global strategy for elimination of cervical cancer as a public health problem [5]. Better integration of services is just one among many elements of new thinking that are required. This review has demonstrated a range of techniques that have been used to integrate HPV vaccination and cervical can-

cer screening in LMICs. This has allowed elucidation of four typologies of such integration, along with exploration of how effective these typologies are in practice. Some examples of integrated service delivery were found, although at small scale and more often in health facilities and community outreach than schools. Benefits were seen when extending cervical cancer screening (including of self-collection of screening samples) and the promotion of cancer screening through HPV vaccination services. Integrated education on both vaccination and cervical cancer screening has clear benefits, including promotion of inter-generational exchanges. There is more work to be done in LMICs to fully test the limits and outcomes of integration across the spectrum of primary, secondary and tertiary prevention, as promoted in the global strategy to eliminate cervical cancer as a public health problem.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Charlotte Wirtz: Conceptualization, Methodology, Investigation, Project administration, Formal analysis, Writing – original draft, Writing – review & editing. **Yasmin Mohamed:** Conceptualization, Methodology, Investigation, Project administration, Formal analysis, Writing – original draft, Writing – review & editing. **Danielle Engel:** Conceptualization, Formal analysis, Writing – review & editing. **Anissa Sidibe:** Conceptualization, Formal analysis, Writing – review & editing. **Megan Holloway:** Formal analysis, Writing – review & editing. **Paul Bloem:** Conceptualization, Formal analysis, Writing – review & editing. **Somesh Kumar:** Formal analysis, Writing – review & editing. **Julia Brotherton:** Formal analysis, Writing – review & editing. **Veronica Reis:** Formal analysis, Writing – review & editing. **Christopher Morgan:** Conceptualization, Methodology, Investigation, Project administration, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2021.11.013>.

References

- [1] World Health Organization. Human papillomavirus (HPV) and cervical cancer [fact sheet] 2021. [https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-\(hpv\)-and-cervical-cancer](https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer) [accessed 19th February 2021].
- [2] Carter JR, Ding Z, Rose BR. HPV infection and cervical disease: a review. *Aust N Z J Obstet Gynaecol* 2011;51(2):103–8. <https://doi.org/10.1111/j.1479-828X.2010.01269.x>. Epub 2011 Jan 28.
- [3] Castellsague X. Natural history and epidemiology of HPV infection and cervical cancer. *Gynecol Oncol* 2008;110(3 Suppl 2):S4–7. <https://doi.org/10.1016/j.ygyno.2008.07.045>.
- [4] World Health Assembly adopts global strategy to accelerate cervical cancer elimination [press release]. WHO, 19 August 2020. <https://www.who.int/news/item/19-08-2020-world-health-assembly-adopts-global-strategy-to-accelerate-cervical-cancer-elimination> [accessed 19th February 2021].
- [5] World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
- [6] World Health Organization. Working together: an integration resource guide for immunization services throughout the life course. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

- [7] Gallagher KE, Howard N, Kabakama S, Mounier-Jack S, Griffiths UK, Feletto M, et al. Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. *PLoS ONE* 2017;12(6):e0177773. <https://doi.org/10.1371/journal.pone.0177773>.
- [8] Hindin MJ, Bloem P, Ferguson J. Effective nonvaccine interventions to be considered alongside human papilloma virus vaccine delivery. *J Adolesc Health* 2015;56(1):10–8. <https://doi.org/10.1016/j.jadohealth.2014.08.004>.
- [9] LaMontagne DS, Barge S, Le NT, Mugisha E, Penny ME, Gandhi S, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. *Bull World Health Organ* 2011;89(11):821–830B. <https://doi.org/10.2471/BLT.11.089862>.
- [10] Watson-Jones D, Lees S, Mwanga J, Neke N, Chagalucha J, Broutet N, et al. Feasibility and acceptability of delivering adolescent health interventions alongside HPV vaccination in Tanzania. *Health Policy Plann* 2016;31(6):691–9. <https://doi.org/10.1093/heapol/czv119>.
- [11] Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version 1. 2006;1:b92.
- [12] Snijlsteit SB, Oliver S, Vojtkova M. Narrative approaches to systematic review and synthesis of evidence for international development policy and practice. *J Development Effectiveness* 2012;4(3):409–29. <https://doi.org/10.1080/19439342.2012.710641>.
- [13] Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed methods appraisal tool (MMAT), version 2018. Registration of copyright. 2018; 1148552.
- [14] Ogumbo JG, Manga S, Nulah K, Foglabenchi LH, Perlman S, Wamai RG, et al. Achieving high uptake of human papillomavirus vaccine in Cameroon: Lessons learned in overcoming challenges. *Vaccine* 2014;32(35):4399–403. <https://doi.org/10.1016/j.vaccine.2014.06.064>.
- [15] Wamai RG, Ayissi CA, Oduwo GO, Perlman S, Welty E, Manga S, et al. Assessing the effectiveness of a community-based sensitization strategy in creating awareness about HPV, cervical cancer and HPV vaccine among parents in North West Cameroon. *J Community Health* 2012;37(5):917–26. <https://doi.org/10.1007/s10900-012-9540-5>.
- [16] Welty. HPV Vaccination Campaign, Cameroon Cameroon Baptist Convention Health Board Cameroon Baptist Convention Health Board; 2010 3/6/10.
- [17] Abuelo CE, Levinson KL, Salmeron J, Sologuren CV, Fernandez MJV, Belinson JL. The Peru Cervical Cancer Screening Study (PERCAPS): The design and implementation of a mother/daughter screen, treat, and vaccinate program in the Peruvian Jungle. *J Community Health* 2014;39(3):409–15. <https://doi.org/10.1007/s10900-013-9786-6>.
- [18] Levinson KL, Abuelo C, Chyung E, Salmeron J, Belinson SE, Sologuren CV, et al. The Peru cervical cancer prevention study (PERCAPS): community-based participatory research in Manchay, Peru. *Int J Gynecologic Cancer* 2013;23(1):141–7. <https://doi.org/10.1097/IGC.0b013e318275b007>.
- [19] Llave C. Mother-Daughter Initiative (MDI) in Cervical Cancer Prevention. Baltimore: Jhpiego (Johns Hopkins University affiliate); 2010.
- [20] Botha MH, van der Merwe FH, Snyman LC, Dreyer G. The Vaccine and Cervical Cancer Screen (VACCS) project: Acceptance of human papillomavirus vaccination in a school-based programme in two provinces of South Africa. *S Afr Med J* 2015;105(1):40–3. <https://doi.org/10.7196/samj.8419>.
- [21] Dreyer G, Van der Merwe FH, Botha MH, Snyman LC, Constant D, Visser C, et al. School-based human papillomavirus vaccination: An opportunity to increase knowledge about cervical cancer and improve uptake of screening. *S Afr Med J* 2015;105(11):912. <https://doi.org/10.7196/SAMJ.2015.v105i11.9814>.
- [22] Moodley I, Mubaiwa V, Tathiah N, Denny L. High uptake of Gardasil vaccine among 9–12-year-old schoolgirls participating in an HPV vaccination demonstration project in KwaZulu-Natal Province. *South African Med J* 2013;103(5):2013. <https://doi.org/10.7196/samj.6414>.
- [23] Snyman LC, Dreyer G, Botha MH, van der Merwe FH, Becker PJ. The Vaccine and Cervical Cancer Screen project 2 (VACCS 2): Linking cervical cancer screening to a two-dose HPV vaccination schedule in the South-West District of Tshwane, Gauteng, South Africa. *South African Med J* 2015;105(3):191–4. <https://doi.org/10.7196/samj.8888>.
- [24] Snyman LC, Dreyer G, Botha MH, van der Merwe FH, Becker PJ. The vaccine and cervical cancer screen (VACCS) project: linking cervical cancer screening to HPV vaccination in the South-West District of Tshwane, Gauteng, South Africa. *South African Med J* 2015;105(2):115–20. <https://doi.org/10.7196/samj.8418>.
- [25] Botha MH, Richter KL. Cervical cancer prevention in South Africa: HPV vaccination and screening both essential to achieve and maintain a reduction in incidence. *South African Med J* 2015;105:33–5. <https://doi.org/10.7196/samj.9233>.
- [26] Juntasopeepun P, Thana K. Parental acceptance of HPV vaccines in Chiang Mai, Thailand. *Int J Gynecol Obstetrics* 2018;142(3):343–8. <https://doi.org/10.1002/ijgo.2018.142.issue-310.1002/ijgo.12539>.
- [27] World Health Organization. The Reaching Every District Strategy 6th March 2018. https://www.who.int/immunization/programmes_systems/service_delivery/red/en/ [accessed 19th February 2021].
- [28] World Health Organization. Immunization Agenda 2030: A Global Strategy to Leave No One Behind. 25th November 2020 <https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030> [accessed 19th February 2021].
- [29] Black E, Hyslop F, Richmond R. Barriers and facilitators to uptake of cervical cancer screening among women in Uganda: a systematic review. *BMC Women's Health* 2019;19(1):1–12. <https://doi.org/10.1186/s12905-019-0809-z>.
- [30] Salam RA, Faqqah A, Sajjad N, Lassi ZS, Das JK, Kaufman M, et al. Improving adolescent sexual and reproductive health: A systematic review of potential interventions. *J Adolesc Health* 2016;59(4):S11–28. <https://doi.org/10.1016/j.jadohealth.2016.05.022>.