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Impact of HPV vaccination: Achievements and future challenges☆

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1. Achievements

The size and scope of the impacts of HPV vaccines to date are somewhat extraordinary, given their apparent limitations and the public health challenges faced at the outset in attempting to implement mass HPV immunisation programs. These limitations and challenges included the vaccine's type specificity, need to be given prior to exposure, the three-dose schedule, target age group of early adolescence, and potential communication challenges around HPV being a sexually transmitted infection (STI). Added to this there is considerable complexity and cost in the design, conduct and interpretation of infection and disease surveillance studies following implementation of an HPV vaccine program [1]. In recognition of this, WHO does not consider that the ability to undertake post vaccination impact surveillance is a prerequisite for implementing a program [2]. However there is an undoubtedly high level of interest in being able to assess the health benefits of this anti-cancer intervention such that these is now an abundance of evidence from multiple countries, with a range of coverage and implementation strategies, that shows the vaccines are effective in real world use.

2. Impact on infection

At least fifteen countries now have data demonstrating vaccine effectiveness and/or showing falls in targeted types, and cross protective types especially for bivalent vaccine, following HPV vaccination (Table 1). Falls are largest with higher coverage and multiple cohorts vaccinated [3]. Herd protection has been demonstrated in studies that have evaluated pre and post vaccination HPV prevalence in males with female only vaccination program [4], as well as in unvaccinated women [5]. Although HPV being an STI may pose an impediment to acceptance of HPV vaccination in some communities (cancer prevention messages are a more effective strategy to achieve high coverage), it does make HPV potentially easier to control in a population that traditional vaccine preventable diseases which are spread by airborne transmission (eg measles) or faecal oral routes (eg polio). This is borne out by modelling showing that herd protection occurs even at relatively low coverage of 30% and that elimination is possible in a closed population within 70 years of vaccination if coverage in both sexes can be sustained over 80% [6].

3. Impact on high grade cervical disease

Because cervical intraepithelial neoplasia (CIN) is diagnosed by cervical screening, detecting its decline following vaccination is dependent upon stability of screening recommendations, overlapping age groups for vaccination and screening, and accurate high-quality screening data. Countries with long standing screening programs, catch up vaccination cohorts and registry infrastructure have been the first to demonstrate reductions in diagnosis of CIN in screening women due to vaccination. Clinic based studies and subnational studies have also been utilised, with evidence of declines now available from at least nine countries (Table 1).

4. Impact on genital warts

Countries using the quadrivalent HPV vaccine, which provides protection against HPV types 6 and 11, have demonstrated declines in genital wart diagnoses in targeted cohorts, and in non-targeted male cohorts (Table 1). Australian surveillance data also suggest a decline in juvenile onset recurrent respiratory papillomatosis, a disease caused by vertical transmission of HPV6/11 infection from an infected mother to her infant [7], likely due to a very low post-vaccination prevalence of maternal HPV 6/11 infection in Australia.

A reason that the observed impacts described above may be larger than anticipated, given the difficulties experienced with achieving high coverage with three doses in most countries, is if one or two doses are providing partial or complete protection. This seems increasingly plausible on the basis of immunological, post hoc trial and emerging observational data consistent with a significant protective effect of less than three doses [8].

☆ In this paper, I review the main achievements in terms of HPV vaccination impact over the last 13 years. Looking to the future, ongoing and emerging challenges in the evaluation of HPV vaccine impact are highlighted, as well as the need to ensure equitable vaccine access if we are ever to effectively reduce the global HPV disease burden.

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Table 1
HPV vaccine impact and effectiveness: list of countries with published outcome data by endpoint.

Outcome	Country	References
HPV infection	Australia	Tabrizi et al. JID 2012, Tabrizi/Brotherton et al. Lancet ID 2014, Machalek et al. JID 2018, Chow et al. Lancet ID 2015, Chow et al. Lancet ID 2017, McGregor et al. Vaccine 2018
	Colombia	Castillo et al. PVR 2019
	Denmark	Dillner et al. Vaccine 2018
	England	Mesher et al. Vaccine 2013, BMJ Open 2016, JID 2018, Sonnenberg et al. Lancet 2013, Tanton et al. PVR 2017
	France	Heard et al. JID 2017
	Italy	Carozzi et al. BMC ID 2018
	Japan	Kudo R et al., JID 2019
	Netherlands	Woestenberg et al. JID 2017, Donken R et al. JID 2018
	Norway	Feiring et al. JID 2018
	Scotland	Kavanagh et al. Br J Can 2014, Lancet ID 2017, Cameron et al. EID 2016, Sonnenberg et al. Lancet 2013, Tanton et al. PVR 2017
	Spain	Purrinos-Hermida et al. PLoS One 018
	Sweden	Dillner et al., 2018, Grun et al. Infec Dis 2016, Soderlund-Strand et al. Canc Epi Bio Prev 2014, Ährlund-Richter et al. Front Cell Infect Microbiol 2019
	Switzerland	Jeannot et al. IJEnvResPubHealth 2018, Jacot-Guillarmod BMC ID 2017
	USA	Cummings et al. Vaccine 2012, Dunne et al. JID 2015, Kahn et al., Pediatrics 2012, Clin Infect Dis 2016, Markowitz et al. JID 2013, Pediatrics 2016, Tarney et al. Obstet Gynecol 2016, Oliver et al. JID 2017, Berenson et al. Obstet Gynecol 2017, Spinner at al Pediatrics 2019, Chaturvedi et al. J Clin Oncol 2018, Hirth et al. Vaccine 2018
	Wales	Sonnenburg et al. Lancet 2013, Tanton et al. PVR 2017
Cervical abnormalities	Australia	Brotherton et al. Lancet 2011, Gertig et al. BMC Med 2013, Crowe et al. BMJ 2014, Brotherton et al. PVR 2015, Brotherton et al. CCC 2015, Brotherton et al. MJA 2016
	Canada	Mahmud et al. J Clin Oncol 2014 Ogilvie et al. IJC 2015, Righolt et al. IJC 2019
	Denmark	Baldur-Felskov et al. CCC 2014, JNCI 2014, CCC 2015, Dehlendorff et al. Vaccine 2018
	Japan	Konno R et al. Vaccine 2018, Ozawa et al., 2017 Tohoku J Exp Med, Tanaka H et al. Obstet Gynae Res 2017, Matsumoto K et al. IJC 2017
	New Zealand	Innes et al., PVR 2018
	Norway	Liaw et al. Pharmaco Drug Saf 2014
	Scotland	Pollock et al. Br J Can 2014, Palmer et al. BMJ 2019
	Sweden	Herweijer IJC 2016, Dehlendorff et al. Vaccine 2018
	USA	Bernard et al. JAMA Onc 2017, Flagg et al. AmJPubH 2016, Gargano CID 2018, Powell et al. Vaccine 2012, Niccolai et al. CEBP 2013, CID 2017, McClung et al. CEBP 2019, Hariri et al. Cancer 2015, Vaccine 2015, Hofstetter et al. JAMA Pediatr 2016, Silverberg et al. Lancet Child Adoles Health 2018
Genital warts	Australia	Donovan et al. Lancet ID 2011, Ali et al. BMJ 2013, Ali et al. MJA 2017, Chow et al. STI 2015, Smith et al. JID 2015, BMC ID 2016, Harrison et al. PLoS ONE 2014, Liu et al. STI 2014
	Belgium	Dominiak-Felden et al. PLoS ONE 2015
	Canada	Guerra et al. Vaccine 2016, Thompson et al. BMC Pub Health 2016, Steben et al. J Med Vir 2018, Willows et al. STD 2018
	Denmark	Baandrup et al. STD 2013, Blomberg et al. CID 2013, 2015, Sando et al. Acta Derm Venereol 2014, Bollerup et al. STD 2016
	England	Howell-Jones et al. JID 2013, Canvin et al. STI 2017, Checchi et al. STI 2019
	Germany	Mikolajczyk et al. STD 2013, Thone et al. BMC ID 2017
	Israel	Lurie et al. Gynecol Oncol 2017
	Italy	Cocchio et al. BMC ID 2017
	New Zealand	Oliphant et al. NZMJ 2012, NZMJ 2017
	Netherlands	Woestenberg et al. J Infect 2017
	Spain	Navarro-Illana et al. Vaccine 2017
	Sweden	Leval et al. JID 2012, JNCI 2013, Herweijer et al. Vaccine 2018
	USA	Bauer et al. Am J Pub H 2012, Flagg et al. Am J Pub H 2013, Am J Pub H 2018, Perkins et al. STD 2015, STD 2017, Zeybek et al. JLGTD 2018, Hariri et al. Am J Epi 2018

5. Future challenges

5.1. Impact on cancers

As cervical cancers arising from HPV infection typically take decades to develop, this is the same time horizon in which we should expect to confirm vaccine impact against cancer. Whilst one follow-up study of vaccine trial participants is suggestive of a lower cervical cancer risk, it has limitations in the questionable comparability of the post-hoc control group used [9]. Women under 30 are at a low absolute risk of cervical cancer so it is only in large populations with high effective coverage that a decline is likely to be statistically detectable at this time. US data suggest falling cervical cancer rates in young women, but these promising data are somewhat difficult to interpret with recent changes in screening recommendations for young women [10]. In every country where vaccinated women are now in screening age groups, management of 'vaccine failures' (i.e. women with cancer or pre-cancer diagnosed despite vaccination) will be important public health and communication challenges. Because the vaccines do not cover all HPV types, and because many already sexually active women have been vaccinated, these scenarios will be, and are, common. An additional complexity is the move to HPV based screening programs underway in many countries, which can be expected to result in a transient increase in cervical cancer diagnosis as prevalent cases are found by the more sensitive test. In Australia, for example, an increase in cancer incidence is expected to occur due to the implementation of HPV screening before falls are seen thereafter due to vaccination and HPV based screening [11]. Increasingly HPV typing of cancer cases will be vital for determining whether vaccine preventable cancers are still occurring in a population, with countries needing to establish routine typing of cervical cancers and centralised recording of results. In many countries, cancer registration itself remains challenging and global efforts to improve cancer registration are an important part of health system strengthening that can be considered a further positive impact of HPV vaccination programs.

5.2. Surveillance design

Since vaccine introduction, surveillance studies have been largely dependent upon the use of research based HPV assays of appropriate specimens, entailing additional cost and resources beyond any routine clinical care or data collection. There is continuing complexity within and between countries in assessment of vaccine impact due to changes over time in vaccine used, dose schedule, target age, introduction of

male vaccination, level of coverage achieved and accuracy of coverage measurement. Surveillance of cervical infection and related disease is likely to become significantly easier in many countries due to the move towards HPV based screening, which is increasingly considered best practice, due to its greater sensitivity and scalability (including the use of self-collected specimens) than either cytology based screening or VIA, in both developed and developing settings. Increasing adoption globally is seeing prices start to decline and increasing availability of standard HPV assays in routine use for screening. There is a likely a very high utility of HPV based assays calibrated for screening for vaccine surveillance monitoring [12].

5.3. Accelerating impact: vaccine scale up

Currently most girls in the target age globally are unvaccinated and a current shortage of supply is limiting scale up [13]. Whilst mass cohort catch-up is routinely recommended where feasible, due to evidence of the acceleration in vaccine impact that can be achieved [2], at present there is not enough vaccine supply to support such a strategy in all places that would wish to implement it. Countries wishing to introduce the vaccine through GAVI are having to wait due to supply constraints. Whilst GAVI prices assist the world's poorest countries, middle income countries remain in a difficult situation in relation to vaccine cost. Although nonavalent HPV vaccine is available, it is likely to remain out of reach to most countries due to cost for the foreseeable future. Evidence supporting the viability of one dose vaccination strategies is urgently needed, even as a temporary measure until further supply is secured.

A challenge that should be acknowledged globally is the need to support the most ethical use of HPV vaccines when there are not enough doses available to vaccinate all who could benefit from them. In an ideal world where the vaccine is cheap, the supply unconstrained, and vaccination highly feasible (one dose, ideally given orally, and the anti-vaccination movement is under control), universal vaccination of both females and males to older ages could result in mass interruption of HPV transmission and rapidly reduce cancer burden. However with limited supply, and effective screening for those already exposed to HPV, consideration should be given to prioritising the vaccination of young girls in high cervical cancer burden countries who may never receive screening, rather than vaccinating older women and men in higher resource settings. Equally, in all countries, policy priority must be given to those groups at highest risk of cervical cancer, who are most often the marginalised, those of lower socioeconomic status, Indigenous and vulnerable populations, to ensure equity of access, and culturally appropriate provision of services. We must strive for equal impact of HPV vaccines on cervical cancer for all women and, where necessary, unequal, greater impact where the burden is greatest and the vaccine is needed most.

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Conflicts of interest

In the last 5 years, Associate Professor Brotherton has received unrestricted partial funding for investigator initiated epidemiological HPV research studies from Seqirus/ Merck, but has never received any personal financial benefits. She is an investigator on the Compass trial, conducted and funded by VCS Foundation. VCS Foundation have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Roche Tissue Diagnostics, AZ USA.

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