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HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010–2019

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A B S T R A C T

WHO/UNICEF estimates for HPV vaccination coverage from 2010 to 2019 are analyzed against the backdrop of the 90% coverage target for HPV vaccination by 2030 set in the recently approved global strategy for cervical cancer elimination as a public health problem.

As of June 2020, 107 (55%) of the 194 WHO Member States have introduced HPV vaccination. The Americas and Europe are by far the WHO regions with the most introductions, 85% and 77% of their countries having already introduced respectively. A record number of introductions was observed in 2019, most of which in low- and middle- income countries (LMIC) where access has been limited. Programs had an average performance coverage of around 67% for the first dose and 53% for the final dose of HPV. LMICs performed on average better than high- income countries for the first dose, but worse for the last dose due to higher dropout. Only 5 (6%) countries achieved coverages with the final dose of more than 90%, 22 countries (21%) achieved coverages of 75% or higher while 35 (40%) had a final dose coverage of 50% or less. When expressed as world population coverage (i.e., weighted by population size), global coverage of the final HPV dose for 2019 is estimated at 15%.

There is a long way to go to meet the 2030 elimination target of 90%. In the post-COVID era attention should be paid to maintain the pace of introductions, specially ensuring the most populous countries introduce, and further improving program performance globally.

1. Introduction

Cervical cancer, caused by infections from the human papillomavirus (HPV), is a major public health problem, especially in low- and middle-income countries (LMIC). Vaccines against HPV have been available since 2006 and recommended by World Health Organization (WHO) since 2009 (World Health Organization, 2009; World Health Organization, 2014; World Health Organization, 2017; World Health Organization, 2019a). They have been progressively introduced in many national immunization schedules, but several studies and international agencies have reported that both vaccine introduction and coverages achieved are still sub-optimal (Drolet et al., 2019; Gallagher et al., 2018; LaMontagne et al., 2017; World Health Organization, 2018a). In 2016, it was estimated that HPV immunization programs targeted only 12% of young adolescent females worldwide, and only 6% of girls aged 10–20 had been vaccinated by end 2014 (Bruni et al., 2016).

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Given the highly effective and cost-effective prevention strategies available and the growing inequalities worldwide, in May 2018 the WHO Director-General made a global call for action towards the elimination of cervical cancer as a public health problem (hereafter referred to as elimination), aiming to reduce the annual incidence below 4 cases per 100,000 globally (World Health Organization, 2018b; World Health Organization, 2018c). The WHO Cervical Cancer Elimination strategy includes coverage targets for scale-up by 2030 of HPV vaccination to 90% of all adolescent girls, twice-lifetime cervical screening to 70%, and treatment of pre-invasive lesions and invasive cancer to 90% (World Health Organization, 2019b). This target is aligned with the Immunization Agenda 2030 and the Sustainable Development Goals (SDGs) agenda (SDGs 3.4 and 3.b.1) (World Health Organization, 2020a; United Nations, 2015). The global strategy may be the accelerator needed to complete the introduction worldwide and improve HPV vaccine coverage globally.

This paper aims to describe the current status (by mid 2020) of HPV vaccine introduction and main characteristics of vaccination programs, alongside the results from the second edition of historical series of WHO/UNICEF coverage estimates for HPV vaccination released in July 2020 with 2010 to 2019 data (World Health Organization, 2020b). This work intends to provide more insight on where we stand on the path towards elimination. HPV vaccination coverage is one of the key indicators of the Cervical Cancer elimination strategy, as it tracks the performance of vaccination programs and proxies the potential impact on future HPV-related disease burden (Dillner et al., 2010). The long-term impact of the elimination campaign will depend primarily on the extension and success of the HPV vaccination programs (Brisson et al., 2020).

2. Methods

2.1. Data sources

This work presents the WHO/UNICEF Estimates of National HPV Immunization Coverage from 2010 to 2019 (World Health Organization, 2020b). These estimates are derived from the administrative and survey data reported annually to WHO through the WHO/UNICEF Joint Reporting Form (JRF) (World Health Organization, 2020c). WHO/UNICEF estimation methods of HPV vaccine coverage are explained in more detail in Supplementary material - section 1 and Supplementary Figs. 1–4. This methodology differs from that used for other vaccines and was reviewed and approved by the Immunization and Vaccine related Implementation Research Advisory Committee (IVIR-AC) in March 2019 (World Health Organization, 2019c).

WHO/UNICEF produce two main coverage indicators for HPV vaccination: the HPV vaccination Program performance coverage which describes the vaccination coverage according to the national schedule and the program's eligibility criteria for each calendar year (program's target population up to 14 years of age), and the HPV vaccination coverage by age 15 that represents the proportion of population turning 15 in the reporting year that have been vaccinated against HPV at any time between ages 9 to 14, at any time up to the calendar year in question. See Supplementary material - section 1 for more information on their use and limitations. Data are always reported at the national level and may not necessarily show differences at the sub-national level.

Both indicators are calculated for the first dose (HPV1) and the full recommended schedule (HPVc) and by sex. For the vaccines currently on the market, the vaccination schedule depends on the age. The general recommendation is a 2-dose schedule minimum 6 months apart for individuals under 15 years of age at the time of the first dose, and a 3-dose schedule (0, 1–2, 6 months) for individuals 15 years of age or older, immunocompromised or with HIV infection (World Health Organization, 2017; World Health Organization, 2019a). In some countries, alternative schedules with extended time intervals between doses are also applied (World Health Organization, 2019a).

2.2. Statistical analyses

Global and regional coverages for each calendar year were calculated as the population weighted average of country-specific estimates using the HPV vaccine program performance coverage indicator (see Supplementary material - section 1) and official United Nations (UN) population estimates and projections that are prepared by the Population Division of the Department of Economic and Social Affairs of the UN Secretariat (United Nations, Department of Economic and Social Affairs, Population Division, 2019). Weighted average coverage estimates include all 194 WHO Member States. A WHO Member State is considered to have an HPV vaccination program as per the WHO definition of introduced, when the country reports in the JRF to have officially included HPV vaccination in their national immunization schedule either at national or subnational level. Members states considered not have introduced or without coverage data had a 0% coverage assigned. 95% bootstrap confidence intervals were estimated using the percentile method (3000 replications). A sensitivity analysis was conducted to assess the impact of these 0% coverage values, imputing alternative values of 50% and extreme 100% for countries with a program and no coverage data. No significant impact was observed on global coverage. (Supplementary Fig. 5). In addition, we calculated an unweighted average coverage among countries with valid performance coverage estimates.

Estimates are presented under different regional groupings: by income level using the 2019 World Bank's classification (World Bank, 2019), the UN Sustainable Development Goals (SDGs) geographical regions (United Nations, Department of Economic and Social Affairs, Statistics Division, 2016), the six WHO regions, with a regional office each (World Health Organization, 2020d), and by Gavi-eligibility (Gavi, the Vaccine Alliance, 2018). Throughout this article, we used the following acronyms for country income level groupings: High Income Countries (HIC), Low- and Middle-Income Countries (LMIC).

To assess if there were differences on the performance between the first years of the program and the following years, box-plot graphs were created and tested with the Wilcoxon signed-rank test for paired data for means and Imam test of scale for paired samples for the homogeneity of variance. Only 53 programs introduced before 2018 and with data for at least the first two years and subsequent years were included. Coverage datapoints estimated by extrapolation or interpolation, subnational estimates or 99% truncated estimates were excluded. For the first-two-years period, if estimates were available for both years, the second year was prioritized. For countries that introduced before 2010, as WHO does not produce earlier estimates, the first-year estimate was considered that of 2010. As the coverage for the following years, the mean of all available coverages from the third year onwards was used. The results were stratified by income level and a 50% threshold of the first-two-years coverage. A sensitivity analysis was performed excluding small countries (N=19), but no differences were found.

3. Results

As of June 2020, 107 (55%) of the 194 WHO Member States are considered to have introduced HPV vaccination nationwide or partially as per WHO definition. As shown in Fig. 1, the extent of the introduction is not equally distributed geographically. The Americas and Europe are by far the WHO regions with the most introductions, 85% and 77% of their countries having already introduced, respectively. The annual rate of new introductions peaked in 2019 with 16 countries, compared with previous years when the average was relatively steady at approximately 7–8 introductions per yar (Fig. 2). It took less than a decade for 80% of HICs to introduce the HPV vaccine. LMICs not only started introducing later, they introduce at lower pace, and they are also more than twice as many LMICs than HICs, so they still lag far behind with only 41% of LMICs have introduced by the end of 2019 (Fig. 2). Importantly, the trend has shifted, and of the new introductions in 2019, 87% were in

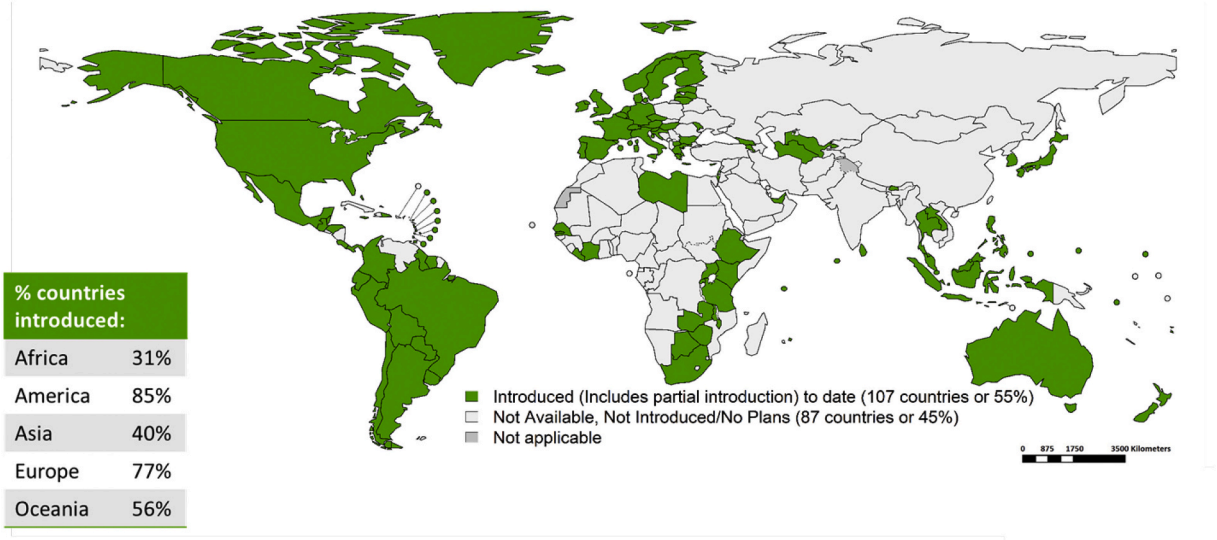

Fig. 1. WHO member states with HPV vaccination in their national immunization program, as of June 2020.
It does not include territories, state of free-association, or semi-autonomous regions. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

LMICs: 6 in sub-Saharan Africa (The Gambia, Liberia, Côte d'Ivoire, Kenya, Malawi and Zambia), 5 in Latin America and the Caribbean (Costa Rica, Dominica, Grenada, Saint Kitts and Nevis, and Saint Lucia) and 3 in Asia and the Pacific (Uzbekistan, Maldives, and Solomon Islands). To date 19 LMICs received Gavi support, that represents 35% of LMICs.

By 2019, almost one third of the programs (33 out of 107) were "gender neutral" (GN) in the sense that both girls and boys receive the vaccine. In 2019, four programs started as GN (Dominica, Niue, Saint Kitts and Nevis, and Saint Lucia) and 10 more expanded vaccination to males (Belgium, Belize, Chile, Denmark, Germany, Guyana, Ireland, Luxembourg, United Kingdom, and Uruguay). GN programs are from HICs (79%) or upper-middle-income countries (21%) (Figs. 2 and 3).

Most programs (47%) included age 12 years as the main age target, single or in combination with other ages. Usually, LMICs targeted younger girls (9–10 years) than HICs (11–13 years). As it is shown in Supplementary Fig. 6, at least 35 million girls aged 9–14 were targeted in 2019 either under a single or a multiple cohort strategy, comprising 10 million from HICs and 25 million from LMICs. 59% of programs delivered HPV vaccines through schools, either as the main strategy or in combination with facility-based delivery. While in HICs programs were similarly distributed between school-based and facility-based (39% and 48% respectively), in lower-middle- and low-income countries almost all programs were school-based or mixed (90%). Most countries used a two-dose HPV vaccination schedule with a 6-month interval, although a growing number of countries (seven) already report using a 12-month interval between the first and second dose (Chile, The Gambia, Indonesia, Malawi, Solomon Islands, Zambia and Zimbabwe). Only three countries (Bahamas, Japan and Singapore) still recommend the three-dose schedule for ages below 15 years. In 2019, 76% of programs used a single cohort approach (either age-based or school-grade based, 60% and 40% respectively). Fig. 3 presents an overview of single vs. multiple cohort changes over time. At least 18 programs have changed from a multiple-cohort strategy to a single-cohort one, while nine have done the other way around. Most countries (87%) have changed the eligibility criteria at least once (between single and multi-cohort or between age and school grade approach), 61% of them during the first two years of the Program.

Globally, we estimated that in 2019 about 15% of girls and 4% of boys were vaccinated with the full course of vaccine and 20% and 5% received at least one dose respectively. Looking at SDG regions, Australia and New Zealand, and Latin America achieved the highest HPVc coverages (77% and 61% respectively), followed by Europe and North America (35%). In contrast, as shown in Table 1, Northern Africa, Oceania (excluding Australia and New Zealand), and Asia all had very low coverage rates. Despite that only a third of Sub-Saharan African countries have included HPV vaccination in the national schedule, this region already achieved nearly 20% coverage due to overall good program performance (Table 1). Although more than half of countries (55%) globally have introduced the HPV vaccine, due to different population sizes, 70% of girls globally still live in countries that have not yet introduced. This is explained by the fact that 7 of the 10 top most populous countries have not yet introduced - or only at sub-national level, including China, India, Nigeria, Pakistan, Indonesia, Bangladesh, and Russia. This dramatically affects global coverage estimates which reached only 15% in 2019 (Fig. 4 and Table 1). It is important to bear in mind that of the 30% of the world's population of girls aged 9 to 15 years, the ones who live in countries with a HPV vaccine program, just over half (53% average performance coverage) received the final dose of HPV. Fig. 4 shows a gradual upward trend of global coverages based on both coverage indicators, but this increase is linked more to the growing number of countries introducing the vaccine than to improvement in program performance.

Fig. 5 presents country-specific HPV vaccination program coverage estimates for 99 countries in 2019 (83 countries both for HPV1 and HPVc, 12 for HPV1 only and 4 for HPVc only, 8 countries did not report data and estimates could not be produced). HPV vaccine program performance coverage averaged 67% for the first dose and 53% for the final dose. LMICs performed better than HICs with a higher median coverage for HPV1 coverage (80% versus 72%, respectively), but the mean dropout rates in LMICs were higher (18% vs 11%). School-based delivery strategies and single-cohort approaches on average performed better (HPVc Program coverage 56% and 58% respectively) than facility-based programs (38%). Most of countries with only an HPV1 estimate were countries that introduced in the second semester of 2019 and HPVc was not yet administered. Out of the 87 countries with an available HPVc estimate, only five (6%) countries achieved coverage with the final dose over 90%, which is the target coverage by 2030 for the global cervical cancer elimination strategy. Only 22 countries (21%) achieved coverage over 75% while 35 (40%) had a HPVc coverage of

Fig. 2. Cumulative number of countries that have introduced HPV vaccination by sex, year and income level.
Romania, Lesotho, Kazakhstan stopped their programs in 2011, 2012, and 2015, respectively. In Japan although the vaccine remains in the national immunization program and is free for 12–16-year-old girls, all proactive recommendations for it are suspended since 2013. Peru also temporarily stopped the program between 2012 and 2013.

50% or less, and 14 (16%) even below 20% coverage. As comparison, only 3% of countries globally report with the third dose of Diphtheria, Tetanus and Pertussis containing vaccine (DTP3) levels below 50%.

DTP3 coverage among one-year olds is a well-established measure to assess the strength of the immunization Program and health systems and has been used until recently as eligibility criteria for introducing HPV vaccines in Gavi-supported countries (Gavi, the Vaccine Alliance, 2020; Kallenberg et al., 2016). Supplementary Fig. 7 shows the complete lack of correlation among DTP3 and HPV1 performance estimate. This is a rather relevant result and indicates that DTP3 coverage is not a good predictor of how well an immunization program will perform to achieve HPV vaccine coverage.

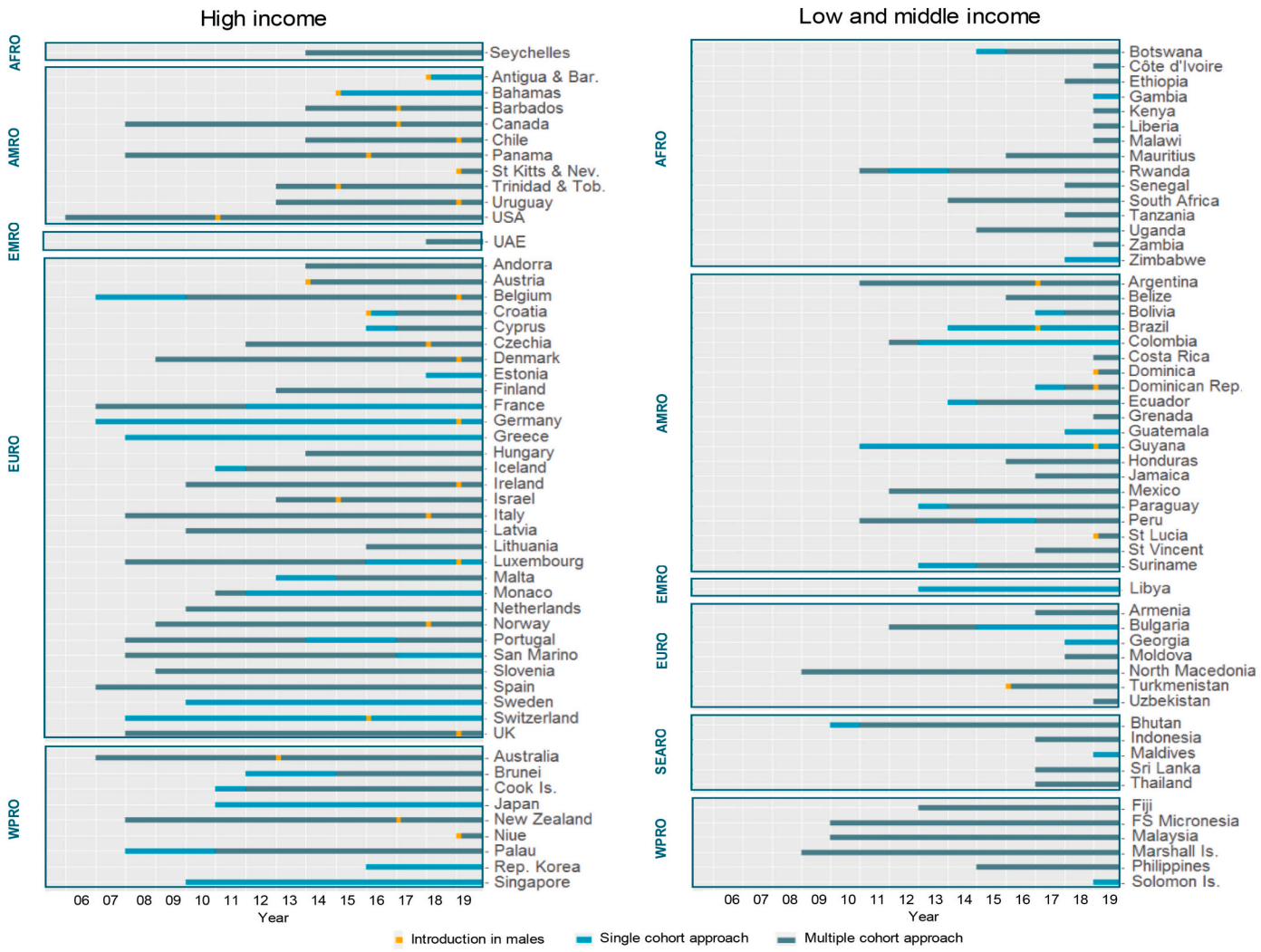

Fig. 3. Changes over time in national HPV programs (eligibility criteria).
Catch-up strategies are not included. Single cohort vaccination: only one age or birth cohort is targeted. Multi-age cohort vaccination (MAC): more than one age or birth cohort is targeted.

To compare the coverage between boys and girls in GN programs, male to female ratios were produced. These M/F ratios were close to or below 1 in most of the countries (Fig. 6) indicating good acceptation of male vaccination in most of the countries offering gender-neutral vaccination.

Fig. 7 compares, for a selection of 53 countries, the program performance during the first two years of the program with the following years using coverage results for the first dose. No significant qualitative nor statistical differences were found between the two periods (60% vs 65% mean coverage of HPV1). Results were similar for different country income levels, although HICs bordered on statistical significance (p-value=0.053, but only reflects an improvement of 7 percentage points from the initial mean) (Fig. 7A). Further stratification by initial coverage explained these slight gains. When initial coverages were lower than 50%, underperforming countries gained on average 15 percentage points during the following years, although most remained below 50% (Fig. 7B). These findings seem to indicate that, unlike in childhood vaccination where the coverage of new vaccines tends to catch up from considerably lower levels with the DTP3 coverage reference value after some years, the performance during first two years of the HPV vaccination program seems to be a strong predictor of the level of vaccine coverage in the subsequent years as experienced so far, showing a rather limited improvement.

4. Discussion

This work provides the first full overview of the WHO/UNICEF HPV vaccine coverage estimates and its methodology, which differs from that used for other childhood immunizations as per the WUENIC estimates (Burton, 2009). As of June 2020, 107 (55%) of the 194 WHO Member States reported introduction of HPV vaccination nationwide or partially into their national immunization schedules. The 2019 estimates show that program performance was sub-optimal in many countries, including high-income countries with the most resources, as is evident from the global average with last dose coverage of 53% in countries introduced the vaccine. When expressed as coverage of the global population of eligible girls (i.e. weighted by population size), global final dose HPV coverage is estimated at 15%. This low number is explained by the fact that many of the most populous countries have not yet introduced and that many of those that have introduced have low performance. Regional and income level variations of HPV vaccinate introduction confirm and perpetuate known disparities in cervical cancer prevention worldwide: the highest burden countries not only have limited secondary prevention but are less likely to provide access to vaccination. Fortunately, this trend seems to be reversing and 2019 has been an especially strong year for HPV vaccination introductions with 14 new LMICs now providing the vaccine, catalyzed by three important global

Table 1
Global and regional female HPV vaccine coverage estimates in 2019, based on program performance coverage indicator.

	First dose (HPV1)			Final dose (HPVc)		
	N countries with data	Coverage (weighted by population size)		N countries with data	Coverage (weighted by population size)	
		%	(95% CI)		%	(95% CI)
Global						
Females	95	20%	(10–36%)	87	15%	(7–26%)
*Males**	*22*	*5%**	*(0.8–13%)*	*16*	*4%**	*(0.4–9%)*
Income level						
High income	43	50%	(35–63%)	44	40%	(28–53%)
Low and middle income	52	16%	(8–31%)	43	12%	(5–24%)
Upper middle income	32	27%	(9–63%)	30	23%	(7–54%)
Lower middle income	13	4%	(1–14%)	9	1%	(0.2–4%)
Low income	7	32%	(7–56%)	4	23%	(2–45%)
Gavi eligible- countries (2018)	14	12%	(4%–32%)	6	7%	(1%–21%)
Non Gavi-eligible countries (2018)	81	28%	(14%–50%)	81	23%	(11%–41%)
SDG regions						
Sub-Saharan Africa	16	31%	(12–54%)	10	20%	(5–39%)
Northern Africa and Western Asia	5	1%	(0.2–5%)	5	1%	(0.1–4%)
Central and southern Asia	5	3%	(0.1–23%)	3	1%	(0–10%)
Eastern and south-eastern Asia	8	6%	(0.8–28%)	8	4%	(0.2–23%)
Latin America and the Caribbean	28	73%	(50–83%)	25	61%	(35–75%)
Oceania (excl. AUS/NZL)	6	11%	(0.8–74%)	5	4%	(0.2–39%)
Australia and New Zealand	2	86%	(71–89%)	2	77%	(67–79%)
Europe and northern America	25	46%	(25–59%)	29	35%	(21–49%)
WHO region						
AFRO	16	31%	(12–53%)	10	19%	(5–38%)
PAHO	30	70%	(55–81%)	27	55%	(38–72%)
EMRO	1	0.2%	(0–0.7%)	1	0.2%	(0–0.7%)
EURO	29	33%	(17–52%)	32	24%	(12–41%)
SEARO	5	3%	(0.1–26%)	4	2%	(0.1–23%)
WPRO	14	6%	(1–39%)	13	4%	(0–34%)

Country-specific HPV vaccination program coverage estimates were available for 99 countries in 2019 (83 countries both for HPV1 and HPVc, 12 for HPV1 only and 4 for HPVc only). *Global male vaccination coverage included as a comparison. Due to limited data, all other estimates are for females only

policy decisions: 1) a change in the WHO position paper in 2015 encouraging multi-age cohort vaccination programs in the initial year of introduction; 2) the 2015 decision by Gavi to allow countries who previously graduated from Gavi support prior to 2013 to apply for HPV vaccine supply in either 2015 or 2016; and 3) the 2016 decision by Gavi to remove the 2-year limited demonstration program requirement prior to national introduction. Since 2017, 28 countries have been approved by Gavi to introduce HPV vaccine into their national immunization programs. Nineteen of these introduced, mostly from Africa. Gavi-supported countries outperform higher income countries, even though most do not reach the 90% goal. Despite the impressive progress achieved over the last five years, there is a long way to go to meet the 2030 elimination targets, both in terms of new introductions and in improving coverage of existing programs.

The 2030 target is considered ambitious, but it is in line with the 90–95% coverage targets set for childhood vaccines such as DTP and measles (World Health Organization, 2020a; World Health Organization, 2013). Brisson et al. (Brisson et al., 2020) in their model analysis found that HPV vaccination coverage of 90% of girls could lead to the elimination of cervical cancer as public health problem in most LMICs within a century, but that in high incidence countries (ASR>25 per 100,000) vaccination alone may not be sufficient to bring the incidence below 4 per 100,000 and would require screening of adult women with high sensitivity test at least twice lifetime. In a recent series of papers, Lehtinen and colleagues (Lehtinen et al., 2019; Vänskä et al., 2020) argue that it would be possible to go beyond cervical cancer reduction and to even eliminate HPV vaccine types from circulation in a scenario of moderately high coverages (over 75%) with gender-neutral vaccination. For girls only vaccination, they report that much higher coverage, above 90% or even 95%, and sustained for a much longer period of time will be needed to achieve eradication of the most persistent and carcinogenic types such as HPV-16. Yet, in 2019 most countries have HPV vaccination coverage of last dose HPV below 75%.

One of the main challenges ahead is to improve underperforming programs. Despite the particularities and differences between countries, our results suggest that: 1) coverage reached in the first few years is usually the one that is maintained so far; 2) programs performed much better in delivering HPV1 than HPVc, with more than half of the countries achieving an HPV1 coverage of above 75%; 3) There were no significant differences in performance between GN and Girls-only programs; 4) Catch-up strategies may increase coverage by an average of 8–10% points, 5) Although managed by the same immunization program, HPV vaccination has significant differences compared to the childhood vaccines such as the target age group, delivery platforms, community outreach communication strategy, that make HPV program apart from the rest of childhood vaccines.

In low-resource settings, adolescents use health services to a much lesser extent, and therefore service delivery in schools is more common in LMICs (Ladner et al., 2014; Howard et al., 2016). Rwanda is an example where high HPV vaccine coverage rates (94% by 2019) have been achieved through a school-based strategy with a campaign style approach to vaccine delivery (Binagwaho et al., 2012). However, many LMICS do not have funded school health programs, making HPV vaccination in schools often expensive and hard to sustain. In addition, LMICs need to use considerable resources to reach out of school girls. We observe that a growing number of LMICs use a combination of several vaccine delivery methods including schools, health-centers and the use of campaign approaches, in combination with for example child health days even though schools may continue to be the place where most doses are provided (Wigle et al., 2016). Analysis of the 2019 data show that LMICs have been outperforming HICs with first-dose coverage. However, this should be interpreted with caution by the fact that most of the LMICs are recent introductions and that many of them have used campaign style delivery. It remains a question whether this approach is

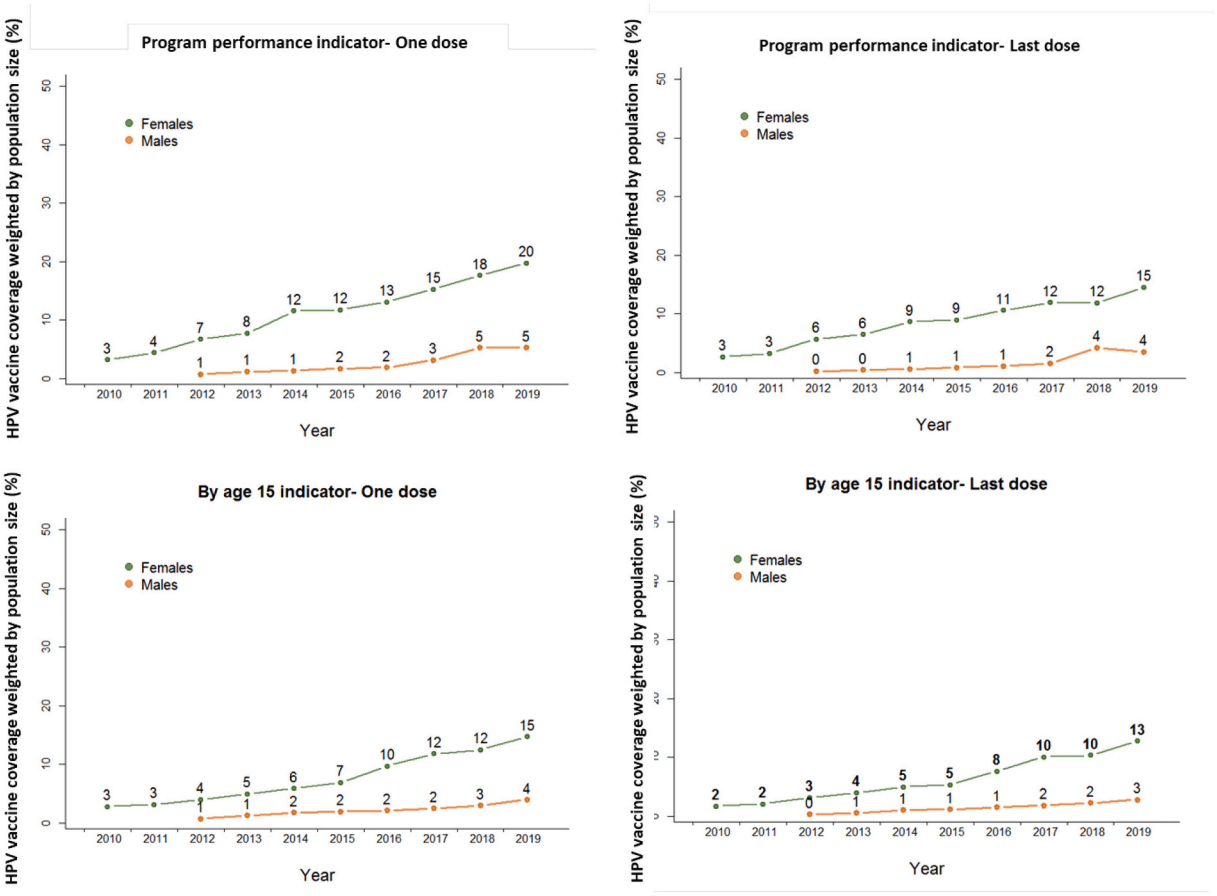

Fig. 4. Global estimates of HPV vaccination coverage by age 15 years over time 2010–2019.

sustainable and whether adaptations of the strategy will affect future results. Striking differences between programs, as observed in Fig. 5, indicate the need for further studies on determinants of performance.

According to available data from a variety of sources up to 40 additional countries have plans or are projected to introduce HPV vaccine in the national schedule by end of 2023. These plans are being affected by the recent, worldwide shortage of HPV vaccine, which is predicted to last until 2023, at the earliest until the current vaccine manufacturers ramp up their production and additional manufacturers enter the market (World Health Organization, 2019d). These shortages led WHO's Strategic Advisory Group of Experts (SAGE) to adapt its recommendations towards postponing multi age cohort at introduction and male vaccination programs as well as to extend the dosage intervals in case of need (World Health Organization, 2019c). It is unfortunate to observe that multi age catch up and introductions in LMICs have and will likely continue to be affected of the next years by the global vaccine shortage, while a record number of upper-middle and high-income countries have added male vaccination to their program in the last 2–3 years. In those countries that offer HPV vaccination to males, it is overall well accepted and the analysis of the uptake of HPV by males compared to females (Fig. 6) shows male HPV coverage often rapidly converges with coverage among females. However, it is important to note that trends in coverage do not seem to show that including boys improves coverage for girls.

The 2020 COVID-19 pandemic is affecting HPV programs in a variety of ways. School closures and interruption of routine vaccination programs have halted HPV delivery in the majority of countries and are having an impact on other antigen coverages, as well (World Health Organization, 2020e). In August 2020, around 70 countries had reportedly interrupted their immunization programs due to the global pandemic (World Health Organization, 2020e; Organización Panamericana de la Salud, 2020) . Several of the planned HPV introductions in 2020 are expected to be delayed. While the flexibility of the HPV vaccine schedule (age and interval) may help to mitigate the negative impact of these interruptions in the short term due to the possibility to catch up any missed cohorts and doses later in 2020 or in 2021, the longer term effects of the predicted economic downturn on the plans to introduce in the nearly 70% of global cohort of girls could be far reaching.

Defining meaningful and comparable coverage indicators for HPV vaccination is complex due to the wide age range targeted (adolescent girls) and the heterogeneity both inter- and intra-countries. The WHO/UNICEF HPV coverage estimate methodology (see Supplementary material - section 1) uses two complementary indicators: program performance and coverage by age 15. The first indicator is more informative for HPV programs because it monitors the yearly performance of the program reaching the population defined as eligible for vaccine (by age or grade) that year and can signal vaccination challenges and progress in a timely manner. It is also a country-specific indicator (specific target), which makes the comparison with other countries difficult as the definition of the numerators and denominators differ. By contrast, the indicator of coverage by age 15 assesses the population protection level at 15 years of age regardless of the target age and year of vaccination. It therefore allows for better comparison of vaccine coverage trends over time, can point to missed cohorts due to changes in recommended age or program disturbance and facilitate comparisons across countries. The main disadvantage is the time lag. This indicator also presents certain calculation challenges because a cohort methodology is required to transform reported numerators into birth-cohort coverages using the population age and the calendar year of the estimation. It is thereby highly dependent on the consistency and quality of reporting from the

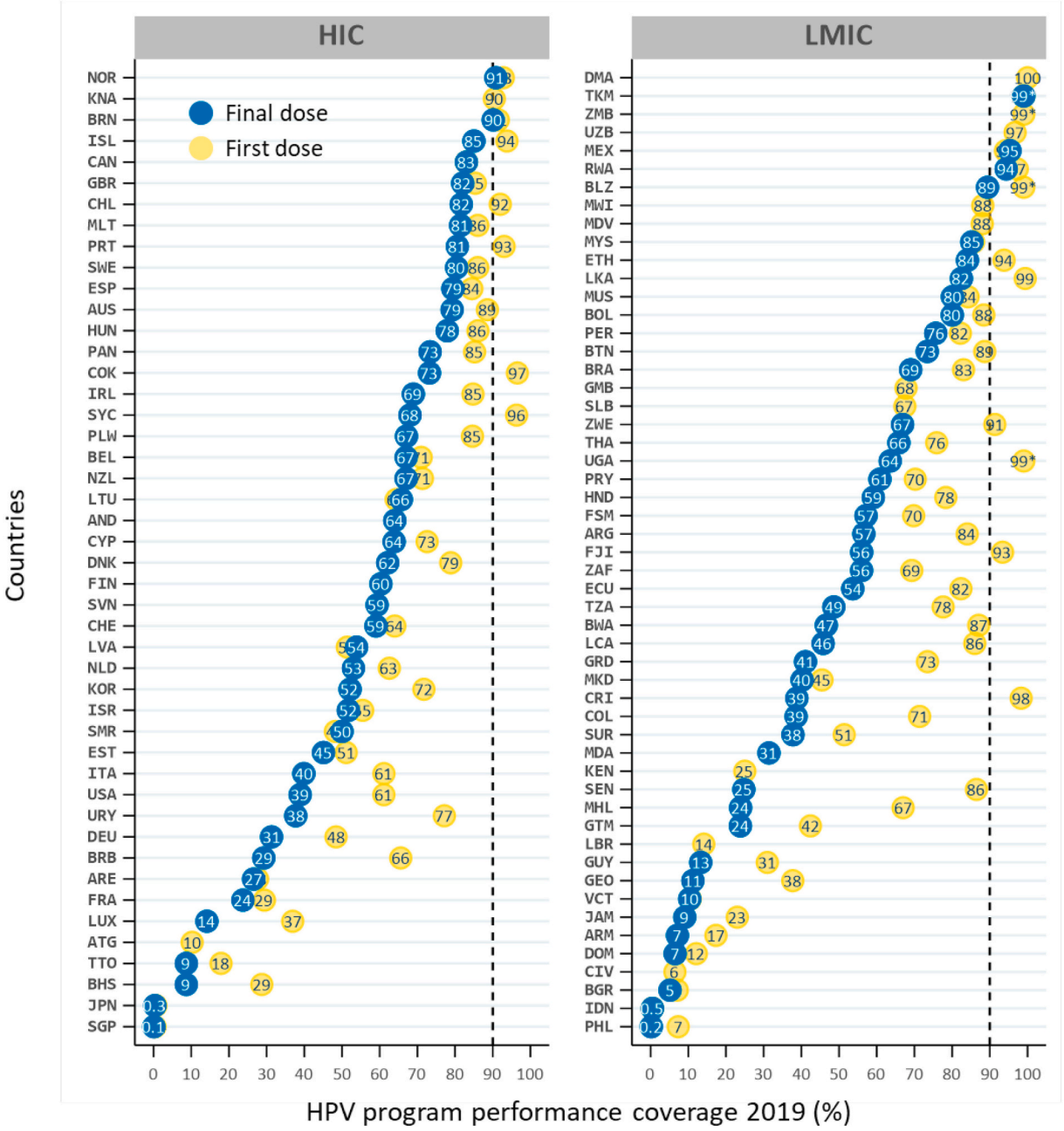

Fig. 5. Country-specific HPV vaccination program coverages estimates for girls by income level in 2019.
*Coverage over 100%. Truncated to 99%. May indicate problems with the accuracy of data.
Coverages reflect different ages at vaccination within the 9–14 year of age range recommended by WHO depending on the target population of each program.
Countries are named using their iso3 coding https://unstats.un.org/unsd/tradekb/knowledgebase/country-code;https://www.iso.org/iso-3166-country-codes.html

previous 5 years. To overcome some of these limitations and improve accuracy in coverage estimation for HPV vaccination, increase use of birth cohort approach for registration and reporting of HPV vaccination data is highly recommended (Sayinzoga et al., 2020).

The quality of denominator data for HPV vaccination target ages presents a specific problem. Whereas programs with the help of national statics bureaus have decades of experience establishing the birth cohort that serves as denominator for childhood vaccines, much less attention has gone into the precision of identifying the size of 9 or 12-year-old cohorts. Census data in many countries are outdated and projection quality and factors like internal migration (often to attend school), conflict, as well as emigration may affect the quality. Additionally, countries using school grades as eligibility criteria often use data from other sources such as the ministry of education which may have its own challenges. Partly to overcome these country level challenges and to establish a comparable historical coverage series, the WHO/UNICEF methodology has opted to use the UN Population Division population estimates for denominators for each country. In future, for countries with recent census and good age specific population, country denominators reported through the JRF may be used instead where possible.

While expensive to implement, periodic high quality population-based EPI vaccination coverage surveys using the revised WHO methodology for immunization surveys (World Health Organization, 2018d) could provide estimates of HPV national coverage which could then be compared with estimates from either country administration data and

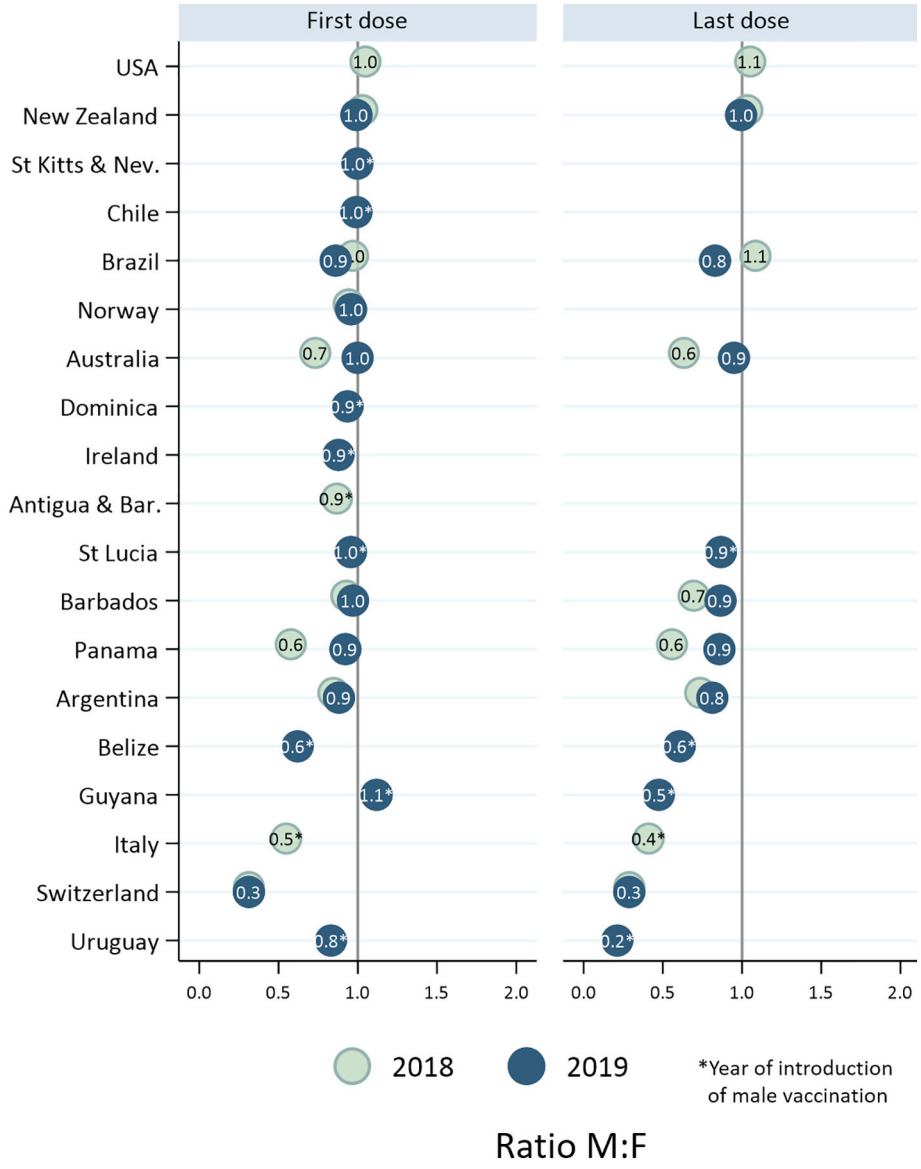

Fig. 6. Intra-country ratio of male to female (M:F) HPV vaccine program coverage.

inform WHO UNICEF HPV estimates. There are already plans to include a module for HPV coverage in existing multi indicator household surveys. Additionally, a few countries have embarked on conduct of a multi-district HPV vaccination coverage survey, with criteria-based selection of districts that broadly represent the programmatic and population characteristics of the country's HPV vaccination program. This approach was recently used in Zimbabwe to validate national estimates of HPV vaccination among the multi-age cohort of 10 to 14 year old girls (LaMontagne et al., 2020). Electronic immunization registries may improve data quality and be able to reduce the implementation cost of such a national survey by providing an easier to access sampling frame from which to make the estimate (Pan American Health Organization, 2017). Further linking with electronic medical records may facilitate the assessment of the impact of vaccination and the linkage with cervical cancer screening practices.

Collecting and reporting the data on HPV vaccination by age, dose and -in some cases - sex has proven quite challenging particularly in the early years of the program. In the absence of international guidance on HPV reporting, various practices existed that led difficulties to systematize the WHO/UNICEF historical data sets. It is crucial to build and strengthen capacity at the local level on the value and the importance of data utilization and continuously motivate to improve the quality of data (Pan American Health Organization, 2019). The last two years improving the quality of data in collaboration with the country programs has been a priority, including the recovery of unreported data from previous years. While the annual update of vaccine coverage will always include review of the historical dataset – for example by applying the new 2019 UN population data for denominator calculation as was done for the 2019 update - HPV vaccine coverage estimates have also been updated based on revision and further completion of historical data by the national programs. In the 2019 update, considerably less missing data points remained in the WHO/UNICEF historical data set than in 2018. Even so, data quality issues or missing data prevented the calculation of performance indicator in nearly one third of estimates in 2010, whereas by 2019 this percentage has been reduced to 11%. In addition, interpolation and extrapolation techniques were used to compute a further 7% of the estimates. While initially 2019 reporting was more incomplete due to COVID-19 interruptions, the final quality of the data reporting on HPV improved in 2019 compared to earlier years. The convergence found in the sensitivity analysis on the historical dataset indicates that the way missing data were treated was acceptable, especially for the performance indicator. However, to further increase

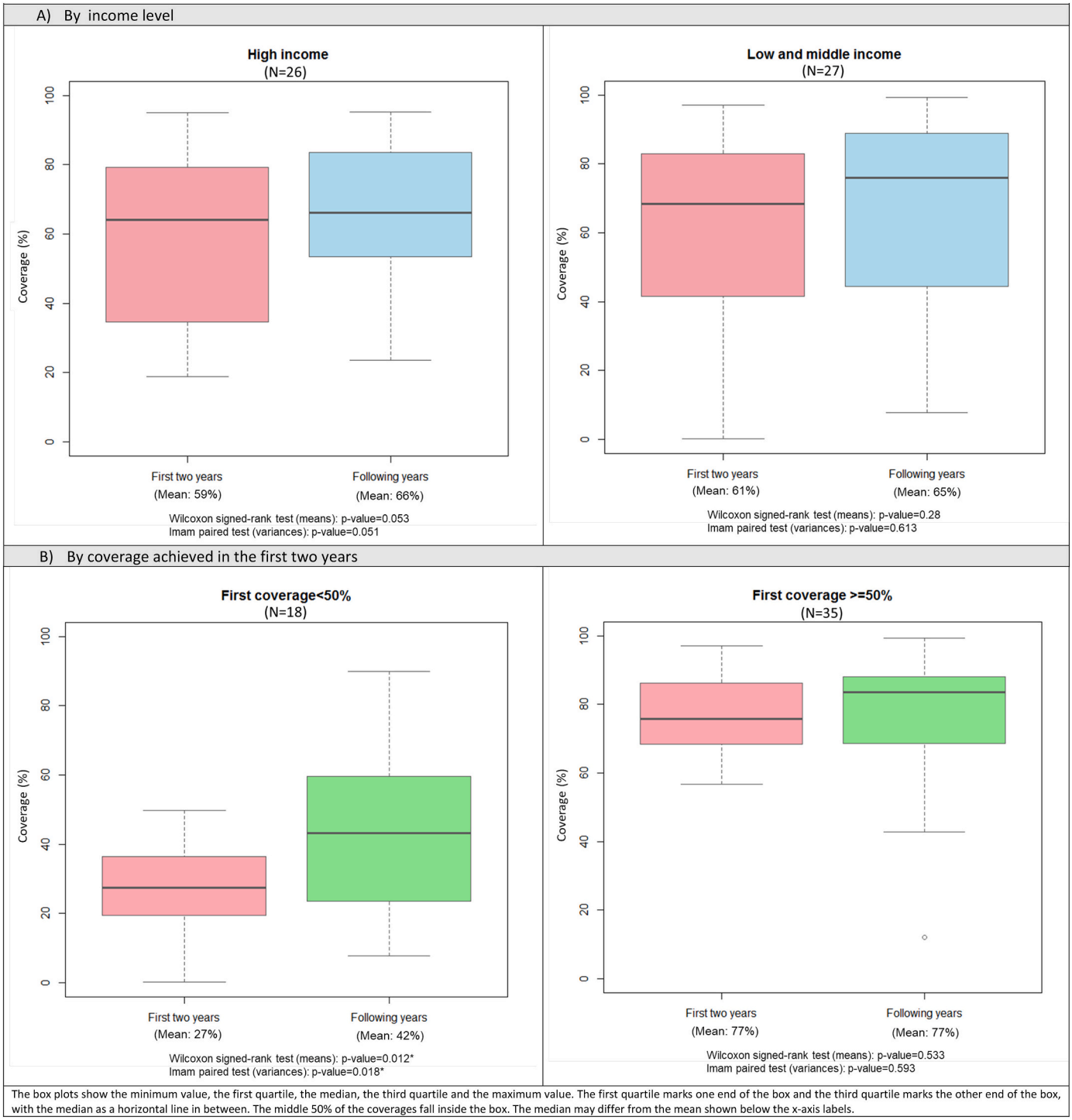

Fig. 7. Box plots and comparison of means for HPV1 coverage program performance between the first two years of implementation and the following years. The box plots show the minimum value, the first quartile, the median, the third quartile and the maximum value. The first quartile marks one end of the box and the third quartile marks the other end of the box, with the median as a horizontal line in between. The middle 50% of the coverages fall inside the box. The median may differ from the mean shown below the x-axis labels.

completeness and quality of reporting and the use of well-functioning vaccination registries will be necessary.

Another limitation is the lack of uncertainty estimates associated with the country-specific estimates. As the estimates are not based on a probability sample, no measurement error is computed, and it is not possible to calculate a confidence interval or other ways to assess the quality of the estimate. Several projects are underway to approximate either confidence intervals or a reliability index.

4.1. Conclusion

In conclusion, the pace of HPV introductions has not diminished in spite of growing supply constraints in over the last few years. A record number of introductions was observed in 2019 most of which in LMICs where access has been limited. The average performance of HPV programs is far below the performance the same countries reach with their childhood vaccines. Still there is a long way to go to meet the 2030

elimination targets, both in terms of new introductions and in improving coverage of existing programs, but in every geography we have examples of programs that met the 90% target. The use of electronic immunization registries, surveys and overall data quality improvement measures will further increase the accuracy of HPV vaccination coverage estimates.

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Disclaimer

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2020.106399.

References

Binagwaho, A., Wagner, C.M., Gatera, M., Karema, C., Nutt, C.T., Ngabo, F., 2012. Achieving high coverage in Rwanda's national human papillomavirus vaccination programme. Bull. World Health Organ. 90, 623–628. https://doi.org/10.2471/BLT.11.097253.

Brisson, M., Kim, J.J., Canfell, K., Drolet, M., Gingras, G., Burger, E.A., et al., 2020. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet. https://doi.org/10.1016/S0140-6736(20)30068-4.

Bruni, L., Diaz, M., Barrionuevo-Rosas, L., Herrero, R., Bray, F., Bosch, F.X., et al., 2016. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob. Health 4, e453–e463. https://doi.org/10.1016/S2214-109X(16)30099-7.

Burton, A., 2009. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bull. World Health Organ. 87, 535–541. https://doi.org/10.2471/BLT.08.053819.

Dillner, J., Arbyn, M., Unger, E., Dillner, L., 2010. Monitoring of human papillomavirus vaccination. Clin. Exp. Immunol. https://doi.org/10.1111/j.1365-2249.2010.04268.x.

Drolet, M., Bénard, É., Pérez, N., Brisson, M., Ali, H., Boily, M.-C., et al., 2019. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. https://doi.org/10.1016/S0140-6736(19)30298-3.

Gallagher, K.E., LaMontagne, D.S., Watson-Jones, D., 2018. Status of HPV vaccine introduction and barriers to country uptake. Vaccine 36, 4761–4767. https://doi.org/10.1016/j.vaccine.2018.02.003.

Gavi, the Vaccine Alliance, 2018. Eligibility for Gavi Support https://www.gavi.org/types-support/sustainability/eligibility (accessed August 19, 2020).

Gavi, the Vaccine Alliance, 2020. Gavi Alliance Eligibility and Transition Policy. Available from: https://www.gavi.org/sites/default/files/document/gavi-eligibility-and-transition-policypdf.pdf 2018.

Howard, N., Mounier-Jack, S., Gallagher, K.E., Kabakama, S., Griffiths, U.K., Feletto, M., et al., 2016. The value of demonstration projects for new interventions: the case of human papillomavirus vaccine introduction in low and middle-income countries. Hum. Vacc. Immunother. 0 https://doi.org/10.1080/21645515.2016.1178433.

Kallenberg, J., Mok, W., Newman, R., Nguyen, A., Ryckman, T., Saxenian, H., et al., 2016. Gavi's transition policy: moving from development assistance to domestic financing of immunization programs. Health Aff Proj Hope 35, 250–258. https://doi.org/10.1377/hlthaff.2015.1079.

Ladner, J., Besson, M.-H., Rodrigues, M., Audureau, E., Saba, J., 2014. Performance of 21 HPV vaccination programs implemented in low and middle-income countries, 2009-2013. BMC Public Health 14, 670. https://doi.org/10.1186/1471-2458-14-670.

LaMontagne, D.S., Bloem, P.J.N., Brotherton, J.M.L., Gallagher, K.E., Badiane, O., Ndiaye, C., 2017. Progress in HPV vaccination in low- and lower-middle-income countries. Int. J. Gynecol. Obstet. 138, 7–14. https://doi.org/10.1002/ijgo.12186.

LaMontagne, D.S., Manangazira, P., Marembo, J., 2020. HPV vaccination coverage in three districts in Zimbabwe following national introduction of 0,12-month schedule among 10 to 14-year-old girls. In: 33rd International Papillomavirus Conference.

Lehtinen, M., Baussano, I., Paavonen, J., Vänskä, S., Dillner, J., 2019. Eradication of human papillomavirus and elimination of HPV-related diseases - scientific basis for global public health policies. Expert Rev. Vacc. 18, 153–160. https://doi.org/10.1080/14760584.2019.1568876.

Organización Panamericana de la Salud, 2020. Resumen de la situación de los programas nacionales de inmunización durante la pandemia de COVID-19, julio del 2020. In: OPS/FPL/IM/COVID-19/20-0013.

Pan American Health Organization, 2017. Electronic Immunization Registry: Practical Considerations for Planning, Development, Implementation and Evaluation. https://iris.paho.org/handle/10665.2/34865. PAHO, Washington, D.C.

Pan American Health Organization, 2019. Methodology to Calculate HPV Vaccine Coverage in the Region of the Americas. https://iris.paho.org/handle/10665.2/51664. PAHO, Washington, D.C.

Sayinzoga, F., Umulisa, M.C., Sibomana, H., Tenet, V., Baussano, I., Clifford, G.M., 2020. Human papillomavirus vaccine coverage in Rwanda: a population-level analysis by birth cohort. Vaccine 38, 4001–4005. https://doi.org/10.1016/j.vaccine.2020.04.021.

United Nations, 2015. General Assembly Resolution A/RES/70/1 Transforming our world: the 2030 Agenda for Sustainable Development (21 October 2015). Available from undocs.org/en/A/RES/70/1.

United Nations, Department of Economic and Social Affairs, Population Division, 2019. World Population Prospects 2019, Online Edition. Rev. 1. Annual Population by Single Age https://population.un.org/wpp/Download/Standard/Population/ (accessed August 19, 2020).

United Nations, Department of Economic and Social Affairs, Statistics Division, 2016. SDG Indicators. Regional groupings used in Report and Statistical Annex https://unstats.un.org/sdgs/indicators/regional-groups (accessed August 19, 2020).

Vänskä, S., Luostarinen, T., Bausssano, I., Apter, D., Eriksson, T., Natunen, K., et al., 2020. Vaccination with moderate coverage eradicates oncogenic human papillomaviruses if a gender-neutral strategy is applied. J. Infect. Dis. https://doi.org/10.1093/infdis/jiaa099.

Wigle, J., Fontenot, H.B., Zimet, G.D., 2016. Global delivery of human papillomavirus vaccines. Pediatr. Clin. N. Am. 63, 81–95. https://doi.org/10.1016/j.pcl.2015.08.004.

World Bank, 2019. World Bank Country and Lending Groups https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed August 19, 2020).

World Health Organization, 2009. Human papillomavirus vaccines. WHO position paper. Wkly Epidemiol. Rec. 84, 118–131.

World Health Organization, 2013. Global Vaccine Action Plan 2011-2020. World Health Organization, Geneva.

World Health Organization, 2014. Human papillomavirus vaccines: WHO position paper, October 2014. Wkly Epidemiol. Rec. 89, 465–491.

World Health Organization, 2017. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. Vaccine. https://doi.org/10.1016/j.vaccine.2017.05.069.

World Health Organization, 2018a. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and recommendations. Wkly Epidemiol. Rec. 49, 661–680.

World Health Organization, 2018b. WHO Director-General Calls for all Countries to Take Action to Help End the Suffering Caused by Cervical Cancer https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/ (accessed August 19, 2020).

World Health Organization, 2018c. Report EB144/28 Accelerating Cervical Cancer Elimination (30 November 2018). Available from. https://apps.who.int/gb/ebwha/pdf_files/EB144/B144_28-en.pdf.

World Health Organization, 2018d. Vaccination Coverage Cluster Surveys: Reference Manual. (WHO/IVB/18.09). World Health Organization, Geneva.

World Health Organization, 2019a. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2019: conclusions and recommendations. Wkly Epidemiol. Rec. 47, 541–560.

World Health Organization, 2019b. Report EB146/9. Accelerating the Elimination of Cervical Cancer as a Global Public Health Problem (16 December 2019). Available from. https://apps.who.int/gb/ebwha/pdf_files/EB146/B146_9-en.pdf.

World Health Organization, 2019c. Immunization and vaccine-related implementation research advisory committee (IVIR-AC) recommendations – March 2019. Wkly Epidemiol. Rec. 94, 225–232.
World Health Organization, 2019d. Global Market Study: HPV Vaccines (December 2019). Available from https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/WHO_HPV_market_study_public_summary_Dec2019.pdf.
World Health Organization, 2020a. Immunization Agenda 2030: A Global Strategy to Leave No One Behind. Available at www.who.int/immunization/immunization_agenda_2030.
World Health Organization, 2020b. Immunization, Vaccines and Biologicals. Data, Statistics and Graphics. 4.5 WHO/UNICEF Human Papillomavirus (HPV) Vaccine Coverage Estimates in Excel. Available at http://www.who.int/immunization/monitoring_surveillance/data/HPV_estimates.xlsx 2020. https://www.who.int/immunization/monitoring_surveillance/data/en/ (accessed August 19, 2020).
World Health Organization, 2020c. WHO/UNICEF Joint Reporting Process. WHO. http://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/ (accessed August 19, 2020).
World Health Organization, 2020d. WHO Regional Offices. https://www.who.int/about/who-we-are/regional-offices (accessed August 19, 2020).
World Health Organization, 2020e. Special Feature: Immunization and COVID-19. http://www.who.int/immunization/monitoring_surveillance/immunization-and-covid-19/en/ (accessed August 20, 2020).