

Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis

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Summary

Background Since 2006, many countries have implemented publicly funded human papillomavirus (HPV) immunisation programmes. However, global estimates of the extent and impact of vaccine coverage are still unavailable. We aimed to quantify worldwide cumulative coverage of publicly funded HPV immunisation programmes up to 2014, and the potential impact on future cervical cancer cases and deaths.

Methods Between Nov 1 and Dec 22, 2014, we systematically reviewed PubMed, Scopus, and official websites to identify HPV immunisation programmes worldwide, and retrieved age-specific HPV vaccination coverage rates up to October, 2014. To estimate the coverage and number of vaccinated women, retrieved coverage rates were converted into birth-cohort-specific rates, with an imputation algorithm to impute missing data, and applied to global population estimates and cervical cancer projections by country and income level.

Findings From June, 2006, to October, 2014, 64 countries nationally, four countries subnationally, and 12 overseas territories had implemented HPV immunisation programmes. An estimated 118 million women had been targeted through these programmes, but only 1% were from low-income or lower-middle-income countries. 47 million women (95% CI 39–55 million) received the full course of vaccine, representing a total population coverage of 1.4% (95% CI 1.1–1.6), and 59 million women (48–71 million) had received at least one dose, representing a total population coverage of 1.7% (1.4–2.1). In more developed regions, 33.6% (95% CI 25.9–41.7) of females aged 10–20 years received the full course of vaccine, compared with only 2.7% (1.8–3.6) of females in less developed regions. The impact of the vaccine will be higher in upper-middle-income countries (178 192 averted cases by age 75 years) than in high-income countries (165 033 averted cases), despite the lower number of vaccinated women (13.3 million vs 32.2 million).

Interpretation Many women from high-income and upper-middle-income countries have been vaccinated against HPV. However, populations with the highest incidence and mortality of disease remain largely unprotected. Rapid roll-out of the vaccine in low-income and middle-income countries might be the only feasible way to narrow present inequalities in cervical cancer burden and prevention.

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Introduction

Monitoring of human papillomavirus (HPV) vaccination coverage is fundamental to assess the performance of vaccination programmes and the potential impact of HPV vaccines on HPV-related diseases. Since their licensure in 2006, HPV vaccines have been progressively introduced in many countries, mainly targeting young adolescent girls aged 10–14 years. Comparison of coverage statistics is limited by differences in age at vaccination, programme delivery strategy, and year.¹

An HPV vaccination coverage of 70% in women has been regarded as the threshold for optimum cost-effectiveness.² A meta-analysis showed that a vaccination coverage of at least 50% delivered a 68% reduction in HPV types 16 and 18 and a 61% reduction in anogenital warts between the prevaccination and post-vaccination periods.³ Coverage will also affect the management of cervical cancer screening programmes. These programmes will need to be adjusted to the number of vaccinated females who will enter screening ages.

9 years after the introduction of vaccination, global quantification of the number of vaccinated women and HPV vaccination coverage is still unavailable. We aimed to quantify worldwide cumulative coverage of publicly funded HPV immunisation programmes up to 2014, and the potential impact on future cervical cancer cases and deaths in the vaccinated cohorts. We developed a specific methodology taking into account variations in national guidelines, target ages, financing, and delivery strategies, between and within countries at subnational level.

Methods

Data sources

We systematically reviewed the literature and official websites to identify HPV immunisation programmes worldwide from June, 2006, to October, 2014.^{1,4–9} Identification of data sources was done in two steps (appendix p 5). First, scrutiny of official websites of countries with an HPV immunisation programme (eg, health departments, national epidemiological centres) was

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See Online for appendix

Research in context

Evidence before this study

Since 2006, many countries have introduced human papillomavirus (HPV) vaccines through national immunisation programmes. Vaccination coverage is a key indicator to assess programme performance and to monitor the potential impact of HPV vaccines on HPV-related diseases. Many countries produce HPV immunisation statistics from administrative data or representative surveys. However, these data are disseminated throughout miscellaneous sources and are non-standardised. Comparison of coverage statistics is limited by differences in age at vaccination, programme delivery strategy, and year. Country-specific coverage rates could range from less than 5% to more than 80%. 9 years after vaccine introduction, global estimates of vaccination coverage using appropriate methodology are still unavailable and the number of vaccinated women in the world is unknown.

Added value of this study

We present the first estimates of global HPV vaccination coverage up to October, 2014. We have developed a specific method to address comparability limitations and appropriately combine coverage statistics. Methods comprise the compilation of the most comprehensive database to date on publicly funded national HPV immunisation programmes, including conversion of all retrieved coverages from multiple sources into birth-cohort-specific coverages, design of an imputation algorithm to treat missing data, and use of global

population estimates and projections. These procedures allow continuous monitoring and production of vaccination coverage trends, together with the use of cancer statistics to approximate the expected reduction on cervical cancer in vaccinated cohorts.

Implications of all the available evidence

By October, 2014, 64 countries nationally, four countries subnationally, and 12 overseas territories have introduced the HPV vaccine into their national immunisation programmes, mostly in high-income and upper-middle-income settings. Globally, we estimate that 47 million women received a full course of HPV vaccine between 2006 and 2014, and 59 million women received at least one dose, representing 39.7% and 50.1% of the targeted female cohorts, respectively. Behind these statistics there are huge differences not only in global distribution by development level, but also in the performance of HPV immunisation programmes. Individually, many countries with a national HPV vaccination programme achieve high coverage rates, mostly in the younger cohorts, but older cohorts and large countries with poorer performances contribute to lowering of the overall coverage estimates. The most vulnerable populations, which would benefit most from vaccination, still remain unprotected. Access to HPV vaccination in low-income and lower-middle-income countries is almost non-existent, despite these countries carrying most of the burden of cervical cancer cases worldwide.

followed by a global review with internet search engines between Nov 1 and Dec 22, 2014. Search terms included specific country names and “HPV”, “vaccine”, “immunization calendar” or “cervical cancer” for immunisation programmes, and “HPV”, “coverage”, “uptake”, “vaccine” for data on coverage. Second, we systematically searched PubMed and Scopus from Jan 1, 2006, to Oct 31, 2014, using MESH terms related to “HPV”, “vaccine”, and “coverage”. References cited in retrieved articles were also assessed and included if appropriate. Publication languages other than English, Spanish, or French were assessed using online language translation services. Eligibility criteria comprised a detailed description of the characteristics of the HPV immunisation programmes or the availability of age-specific HPV coverage data with the date of the estimation. Coverage data included official estimates or survey data. Surveys had to include a detailed description of the methodology and be representative of the targeted population. Data were extracted by two independent investigators (LB and LB-R), with discrepancies resolved by forced consensus.

Procedures

For HPV immunisation programmes, we retrieved information about year of introduction, target ages, the vaccination schedule, and other features of specific

programmes (appendix pp 17–29). We subdivided each immunisation programme into two possible implementation strategies: primary and catch-up. Both strategies could use either an organised or an opportunistic approach (appendix p 26). For each immunisation programme and strategy, we derived the birth cohorts that had been targeted by the end of 2014. We considered subnational variations in Belgium, Canada, Italy, Spain, Switzerland, and the UK.

For HPV vaccination coverage rates, we obtained data for one-dose, two-dose, and three-dose HPV vaccine coverage by country and birth cohort (appendix pp 30–35). If data were not originally reported by birth cohort, we converted retrieved coverage rates into birth-cohort-specific rates from the population age and the year of the estimation. We made an effort to obtain vaccination coverage by single year of age. When coverage rate was only available for a specific age group, that rate was assigned to all relevant birth cohorts. When there were discrepancies among multiple sources, official estimates prevailed or, in the absence of official estimates, we selected the most representative sample.

Female population data by birth cohort and country were obtained annually for the years 2010–2100 from the UN Population Division, or from the US Census Bureau when unavailable from the UN.^{10,11} For

subnational regions, we applied the regional population weight to the national estimate. Estimates of cervical cancer incidence and mortality rates by 5 year age groups and country were obtained from GLOBOCAN 2012, produced by the International Agency for Research on Cancer (IARC).¹²

Statistical analysis

We grouped countries with the UN classification system, which categorises the world into five macro-geographical (continental) regions and 22 geographical subregions.¹³ We also classified countries by income level with the World Bank's classification.¹⁴ We calculated full-course coverage as the proportion of individuals in the targeted birth cohorts who received the complete three-dose HPV vaccine (or a minimum of two doses within at least 6 months if that was the recommended schedule in the immunisation programme). We calculated one-dose coverage as the proportion of individuals in the targeted birth cohorts who received at least one dose of HPV vaccine.

Appendix pp 6, 36, and 37 present the different stages in the methodology to calculate global figures and their assumptions. We identified 1922 birth cohorts from 75 countries covered by an HPV immunisation programme anytime between 2006 and 2014. Coverage

data were available for only 645 birth cohorts from 39 countries. We used an iterative procedure to impute values for missing data (appendix pp 1, 2). This procedure comprised an eight-step process that assigned the previous or subsequent birth cohort coverage estimate to the missing coverage (appendix pp 8–10, 38). In countries with no coverage reported, we imputed a cross-country weighted average by implementation strategy, age at vaccination, geographical region, and income level. In birth cohorts in which only full-course or one-dose coverage was reported, we derived the missing dose-specific coverage from those available with a regression model based on 444 birth cohorts with complete information (appendix pp 1, 2, 7). Appendix pp 1 and 2 also present a comprehensive evaluation of the validity of the missing data treatment methods. To provide an estimation of the uncertainty of the parameters, we computed 95% CIs with the percentile method in a bootstrap process with 3000 replications using Stata (version 13).¹⁵

We calculated the expected number of new cervical cancer cases or deaths up to age 74 years by multiplying the contemporary age-specific incidence and mortality rates¹² by the corresponding expected annual population for 2013, 2014, and onwards, until the year of the 75th birthday by birth cohort, age, and country.¹⁰ We

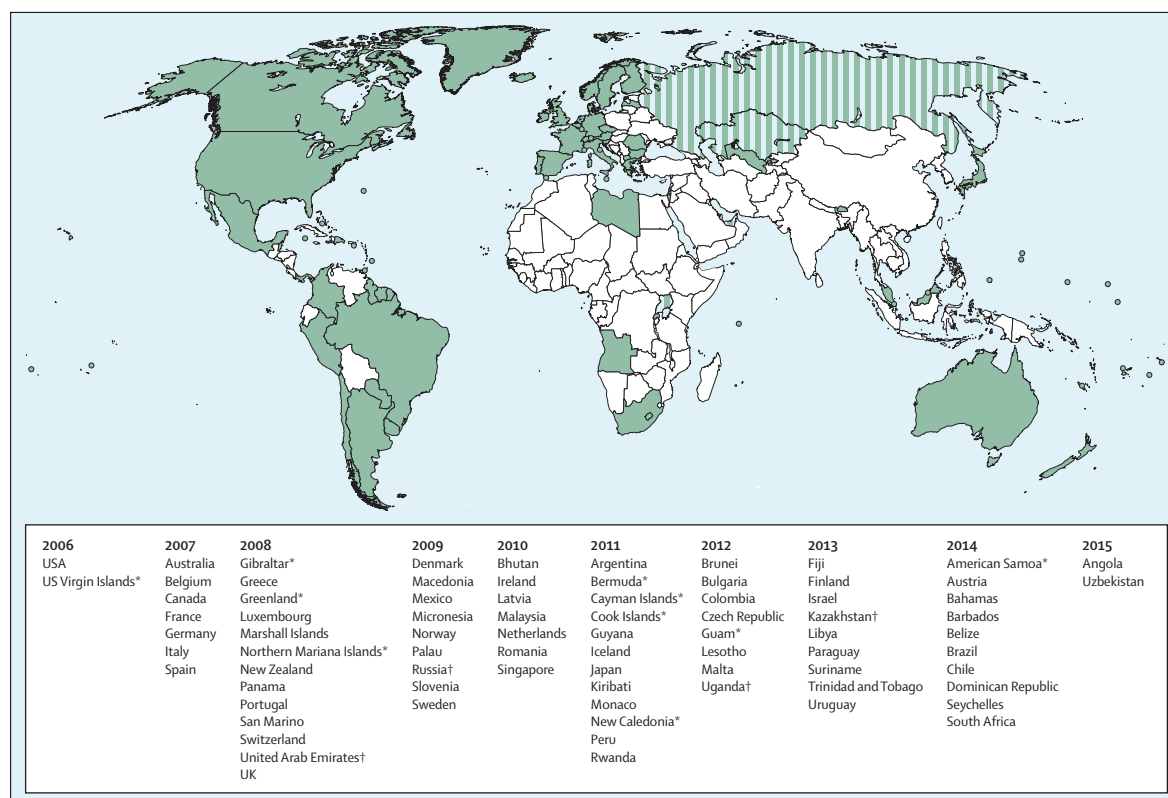


Figure 1: Countries that have introduced a publicly funded national human papillomavirus vaccination programme since 2006, by year

Striped sections indicate implementation in a part of the country. French Polynesia, Liechtenstein, and Niue have reported vaccine programmes, but no information was available about year of introduction. *Special territory. †Partial implementation.

computed the cumulative number of cases prevented by multiplying individual HPV vaccination coverages by the number of expected cancer cases for each birth cohort and year up to age 74 years (appendix pp 3, 4). For both full-course and one-dose HPV vaccination, we assumed 70% vaccine effectiveness (100% efficacy against HPV types 16 and 18, which are the cause of 70% of cervical cancer cases worldwide).¹⁶ Appendix pp 36 and 37 summarise all the methods and general assumptions of each step in the process.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From June, 2006, to October, 2014, 64 countries nationally, four countries subnationally, and 12 overseas territories had implemented HPV immunisation programmes (figure 1). The most frequently targeted age was 12 years (non-exclusively) in 57 (71.8%) programmes, followed by 11 years in 37 (47.4%) programmes, 13 years in 29 (37.2%) programmes, 9 years in 15 (19.2%) programmes, and 14 years in 14 (17.9%) programmes (appendix pp 17–29). Of 62 programmes with information, 42 (67.7%) programmes delivered the vaccine through schools, but most allowed vaccination at primary health-care centres or other health-care facilities to complement the programme (appendix pp 17–29). In 2014, at least 20 countries introduced a two-dose schedule for girls younger than 15 years following new WHO recommendations.¹⁷ Before this time, Canada, Mexico, and Switzerland had previous established alternative schedules to the three-dose standard (appendix pp 17–29).

We estimated that 118 million women worldwide had been targeted by an HPV immunisation programme at some point between 2006 and 2014: 62 million as a primary target, 12.5 million by organised catch-up, and 43 million by opportunistic catch-up (appendix p 15). These numbers represent 3.5% of females globally, 8.7% of those aged 15–26 years, and 11.9% of those aged 10–14 years. Females born between 1994 and 2004 (aged 10–20 years old in 2014) were the most common vaccine target cohorts in the primary programmes (appendix p 15).

Appendix p 16 shows the gradual introduction of HPV vaccination according to the annual number of cervical cancer cases and socioeconomic development level. 82% of targeted women (97 million) were from more developed regions and 18% (21 million) were from less developed regions with a later introduction (appendix p 16). Only seven (18%) of 38 less developed countries implemented HPV immunisation programmes before 2010. These countries targeted fewer birth cohorts on average than did

more developed regions (mean 6.7 [SD 5.6] vs 10.7 [6.0] cohorts; $p=0.0031$).

An estimated 47 million (95% CI 39–55 million) women worldwide were vaccinated against HPV (full course) through immunisation programmes by 2015 (table). This number represents 1.4% (95% CI 1.1–1.6) of the female population and 6.1% (4.9–7.4) of females aged 10–20 years (table). Globally, coverage among the 118 million targeted females (aged 9–45 years) was 39.7% (95% CI 33.0–46.8) increasing to 54.9% (45.1–65.4) among primary targets and organised catch-ups (table). An additional 12 million women were estimated to have received one dose of HPV vaccine, accounting for a total of 59 million (95% CI 48–71 million) women worldwide having received at least one dose of HPV vaccine, 1.7% (95% CI 1.4–2.1) of the female population, 7.5% (5.9–9.2) of females aged 10–20 years, and 50.1% (40.7–60.0) of targeted females (table).

Most targeted and subsequently vaccinated women were from high-income countries (68%) or upper-middle-income countries (28%, and mainly from Latin America; figures 2, 3). In high-income countries, by 2014, 32% of females aged 10–20 years had received the full course of HPV vaccine and 41% had received at least one dose (table). By contrast, 19% of Latin American females aged 10–20 years had received the full course of vaccine and 22% had received at least one dose (table). Only 1.4 million vaccinated women were from low-income and lower-middle-income countries, representing global coverage of 2.7% among 10–20-year-old females in less developed regions, compared with 33.6% in more developed regions (table). Although few cohorts had been vaccinated in low-income and lower-middle-income countries, estimated coverage among targeted cohorts was high (89%; table).

Figure 4 and appendix pp 43–46 show HPV vaccine coverage rates by geographical region, age, and strategy. Northern Europe and Australia and New Zealand presented the highest age-specific coverage rates, reaching 69% of females currently aged 15–19 years. In Central America, South America, and southern Africa, almost all vaccinated females were in the younger age group (aged 10–14 years). Oceania had the highest coverage estimates globally, accounting for 17% of all females in Australia and New Zealand and 10% in Micronesia (figure 4, appendix).

We calculated that about 379 000 cases (95% CI 368 000–391 000) of cervical cancer and 156 000 deaths (151 000–161 500) by age 75 years could be averted in the 47 million fully vaccinated women (figure 5), assuming lifelong protection. For a 10% increase or decrease in vaccine effectiveness, the number of new cases would vary by 54 145 worldwide. These estimates increased to about 444 600 cases (95% CI 431 000–458 500) and 184 000 deaths (177 000–191 000) when we considered

	Number of vaccinated females (millions)	Coverage among the total female population		Coverage among the targeted population (all ages)		
		All ages	Aged 10–20 years	All	Primary target and organised catch-up	Opportunistic catch-up*
Full-course vaccination						
Worldwide	46.9 (39.0–55.3)	1.4% (1.1–1.6)	6.1% (4.9–7.4)	39.7% (33.0–46.8)	54.9% (45.1–65.4)	13.3% (6.8–21.0)
Less developed regions	15.0 (10.4–20.3)	0.5% (0.4–0.7)	2.7% (1.8–3.6)	71.3% (49.6–96.6)	73.7% (50.9–100.0)	21.2% (12.9–29.6)
More developed regions	31.9 (25.7–38.7)	5.4% (4.4–6.5)	33.6% (25.9–41.7)	32.9% (26.5–39.8)	48.0% (38.2–58.5)	13.1% (6.7–21.5)
Full-course vaccination by income						
High income	32.2 (26.2–38.9)	5.4% (4.4–6.5)	32.1% (25.0–39.9)	33.6% (27.3–40.6)	48.5% (38.6–59.3)	13.8% (7.3–22.4)
Upper middle income	13.3 (8.9–18.6)	1.1% (0.7–1.6)	7.2% (4.8–10.1)	64.6% (43.0–90.1)	70.8% (47.0–98.9)	3.5% (2.2–4.7)
Lower middle income	0.3 (0.2–0.5)	0.0% (0.0–0.0)	0.1% (0.1–0.2)	69.6% (42.1–100.0)	69.6% (42.1–100.0)	..
Low income	1.0 (0.7–1.4)	0.3% (0.2–0.4)	1.0% (0.7–1.4)	95.2% (60.3–100.0)	95.2% (60.3–100.0)	..
Full-course vaccination by geographical region						
Africa	1.6 (0.9–2.6)	0.3% (0.2–0.5)	1.2% (0.7–2.0)	88.0% (46.5–100.0)	88.0% (46.5–100.0)	..
Asia	4.2 (2.4–6.3)	0.2% (0.1–0.3)	1.1% (0.6–1.7)	57.2% (32.6–85.5)	62.5% (34.0–95.4)	21.4% (14.3–28.9)
Europe	14.0 (12.0–16.1)	4.3% (3.7–5.0)	31.1% (26.1–36.5)	39.2% (33.7–45.2)	52.8% (44.5–61.7)	11.7% (8.5–15.3)
Latin America and Caribbean	11.6 (7.1–16.6)	3.8% (2.3–5.4)	19.0% (11.6–27.3)	71.0% (43.6–100.0)	71.0% (43.6–100.0)	3.8% (2.1–5.8)
Northern America	13.1 (8.0–18.9)	7.3% (4.5–10.5)	35.6% (18.5–56.6)	24.6% (15.1–35.5)	39.3% (20.5–62.5)	13.7% (5.3–25.1)
Oceania	2.4 (1.6–3.3)	12.7% (8.6–17.3)	35.9% (18.8–56.0)	62.2% (42.1–84.6)	62.2% (42.1–84.6)	..
One-dose vaccination						
Worldwide	59.2 (48.1–70.9)	1.7% (1.4–2.1)	7.5% (5.9–9.2)	50.1% (40.7–60.0)	67.3% (53.9–81.7)	20.2% (10.5–31.6)
Less developed regions	17.0 (11.2–23.8)	0.6% (0.4–0.8)	3.0% (2.0–4.3)	80.6% (53.1–100.0)	83.2% (54.4–100.0)	25.5% (15.6–35.6)
More developed regions	42.3 (33.2–52.2)	7.1% (5.6–8.8)	43.3% (32.0–55.3)	43.5% (34.1–53.7)	61.5% (47.0–76.8)	20.1% (10.4–32.8)
One-dose vaccination by income						
High income	42.6 (33.6–52.3)	7.1% (5.6–8.8)	41.3% (30.9–52.9)	44.4% (35.0–54.5)	62.1% (47.8–77.5)	20.9% (11.2–33.8)
Upper middle income	15.3 (9.7–22.0)	1.3% (0.8–1.9)	8.3% (5.2–12.0)	74.4% (46.9–100.0)	81.4% (51.1–100.0)	5.2% (3.2–7.1)
Lower middle income	0.4 (0.2–0.6)	0.0% (0.0–0.0)	0.1% (0.1–0.2)	76.5% (46.5–100.0)	76.5% (46.5–100.0)	..
Low income	0.9 (0.5–1.4)	0.2% (0.1–0.3)	0.9% (0.5–1.4)	86.1% (43.9–100.0)	86.1% (43.9–100.0)	..
One-dose vaccination by geographical region						
Africa	1.6 (0.8–2.7)	0.3% (0.1–0.5)	1.2% (0.6–2.0)	85.2% (40.9–100.0)	85.2% (40.9–100.0)	..
Asia	4.6 (2.7–6.9)	0.2% (0.1–0.3)	1.2% (0.7–1.8)	62.8% (36.1–93.7)	68.3% (37.3–100.0)	25.6% (17.3–34.4)
Europe	16.7 (14.3–19.3)	5.2% (4.4–6.0)	36.4% (30.3–42.9)	46.9% (40.1–54.3)	62.3% (52.1–73.0)	15.8% (11.5–20.7)
Latin America and Caribbean	13.5 (7.8–19.9)	4.4% (2.5–6.4)	22.1% (12.7–32.6)	82.4% (47.8–100.0)	82.5% (47.8–100.0)	13.3% (7.2–20.1)
Northern America	20.0 (12.3–29.0)	11.2% (6.9–16.2)	53.4% (27.1–85.6)	37.6% (23.2–54.6)	59.0% (29.9–94.5)	21.7% (8.9–38.7)
Oceania	2.8 (1.9–3.9)	15.0% (10.1–20.4)	41.1% (21.5–64.0)	73.2% (49.4–99.6)	73.2% (49.4–99.6)	..

Data in parentheses are 95% CIs. *Not implemented in some countries in a group.

Table: Estimated number of vaccinated females and human papillomavirus vaccine coverage by October, 2014

one-dose vaccination data. The number of cancer cases prevented showed the same distribution when assessed by income (figure 5). Despite a lower number of vaccinated women in upper-middle-income countries than in high-income countries, the higher incidence of cervical cancer translates into a higher expected impact, with 178 192 cases prevented by age 75 years in 13 million fully vaccinated females (figure 5).

To assess the potential effect of our imputation system, we did a comprehensive sensitivity analysis of our missing data treatment (appendix pp 1, 2). First, we ran 50 simulations in each of which we drew a random sample of 100 birth cohorts to impute (appendix p 11). Results showed a correlation index of 0.81 (range 0.63–0.95) between imputed and original data. Second, we did a new

literature search between Nov 15 and Nov 20, 2015, and updated a set of 61 birth cohorts with new original data, showing a response correlation of 0.79 (95% CI 0.66–0.88; appendix p 12). Finally, we did a sensitivity analysis considering different coverage scenarios ranging from 0% to 100% for countries without data (appendix pp 13, 14, 40). The global estimate of 47 million vaccinated women ranged from 39 million to 51 million in the most extreme scenarios. The impact of these imputations was more prominent in upper-middle-income countries, where the number of vaccinated women ranged from 51% lower to 19% higher than in high-income countries. However, in high-income countries, which contributed the largest number of vaccinated women (70%), the impact was almost negligible.

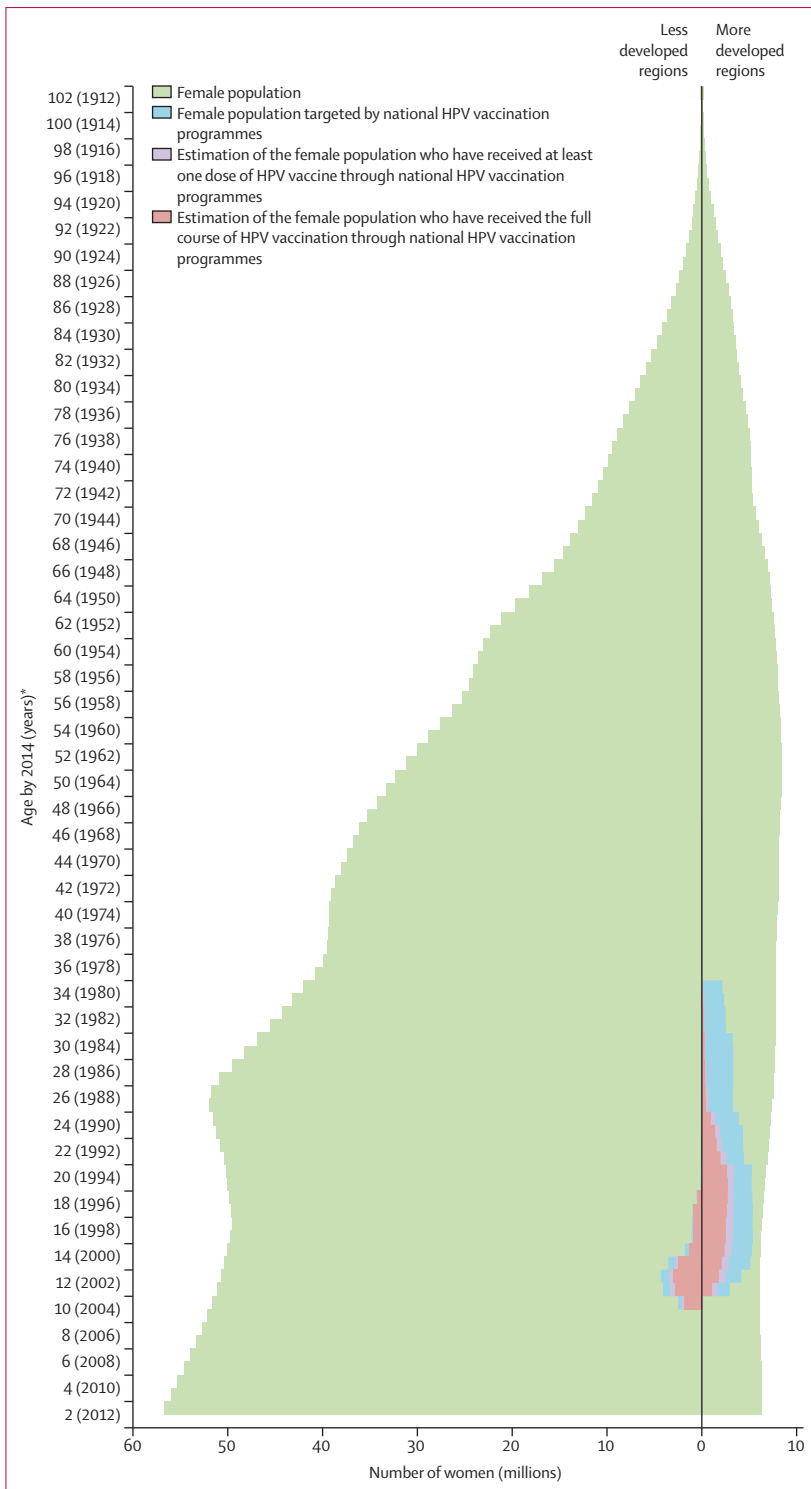


Figure 2: Female population pyramid by development level and age distribution of women targeted by national HPV vaccination programmes
 We grouped countries with the UN classification system.¹³ More developed regions comprise Europe, northern America, Australia and New Zealand, and Japan. Less developed regions comprise all regions of Africa, Asia (except Japan), Latin America and the Caribbean, plus Melanesia, Micronesia, and Polynesia. HPV=human papillomavirus.
 *Birth cohorts of women are shown in parentheses.

Discussion

Since the licensure and progressive introduction of HPV vaccines in 2006, this is, to our knowledge, the first attempt to estimate current HPV vaccination coverage globally and the corresponding reduction in cervical cancer incidence and mortality among currently vaccinated women. We provide a comprehensive description of HPV immunisation programmes worldwide. We base all our analyses on the use of birth cohorts, an approach that circumvents the comparability limitations posed by the heterogeneous data available for HPV vaccines. This method can be used to monitor trends in HPV vaccination coverage. Our results show high disparities in vaccine implementation and numbers of vaccinated women according to income level of countries.

Despite accounting for only 14% of annual cervical cancer cases, on the basis of our estimations, high-income countries accounted for almost 70% of vaccinated women worldwide by the end of 2014. Due to the high initial prices of the vaccines, only high-income countries could afford them. Furthermore, these same countries had already largely invested in cervical cancer screening programmes that were successful in lowering and stabilising cervical cancer rates.¹⁸ Redoubling efforts, most (69%) high-income countries have progressively introduced HPV vaccination in these years, mostly to pre-adolescent females, but some extended the coverage to older cohorts using catch-up strategies. High-quality cervical cancer screening and HPV vaccination—the most comprehensive prevention strategies against cervical cancer—are currently deployed in combination in high-income countries. However, high-income countries show the lowest levels of vaccination coverage among targeted primary groups, achieving globally less than 50% coverage, mostly due to the strong influence of underperforming countries such as the USA, France, or Germany in the final estimates.

Other countries that have introduced HPV vaccination in the past few years are Latin American (48% of 33 Latin American countries). Most of these countries are upper-middle-income countries with high incidence rates of cervical cancer despite long-term screening programmes. Screening has not had the expected impact, even with the high coverage rates of cervical cytology achieved, because women do not universally access proper follow-up and treatment.¹⁹ Many of these countries are now introducing HPV vaccination focusing on one or two cohorts of females. HPV vaccine introduction outside high-income and Latin American countries is scant: only some middle-income countries (Pacific countries, South Africa, Libya, Seychelles, Malaysia, some Kazakhstan regions, Macedonia, and Bulgaria) and three GAVI-eligible countries (Bhutan, Lesotho, and Rwanda) have started HPV immunisation programmes. Romania initiated a publicly funded school-based programme targeting 10–11 year olds that

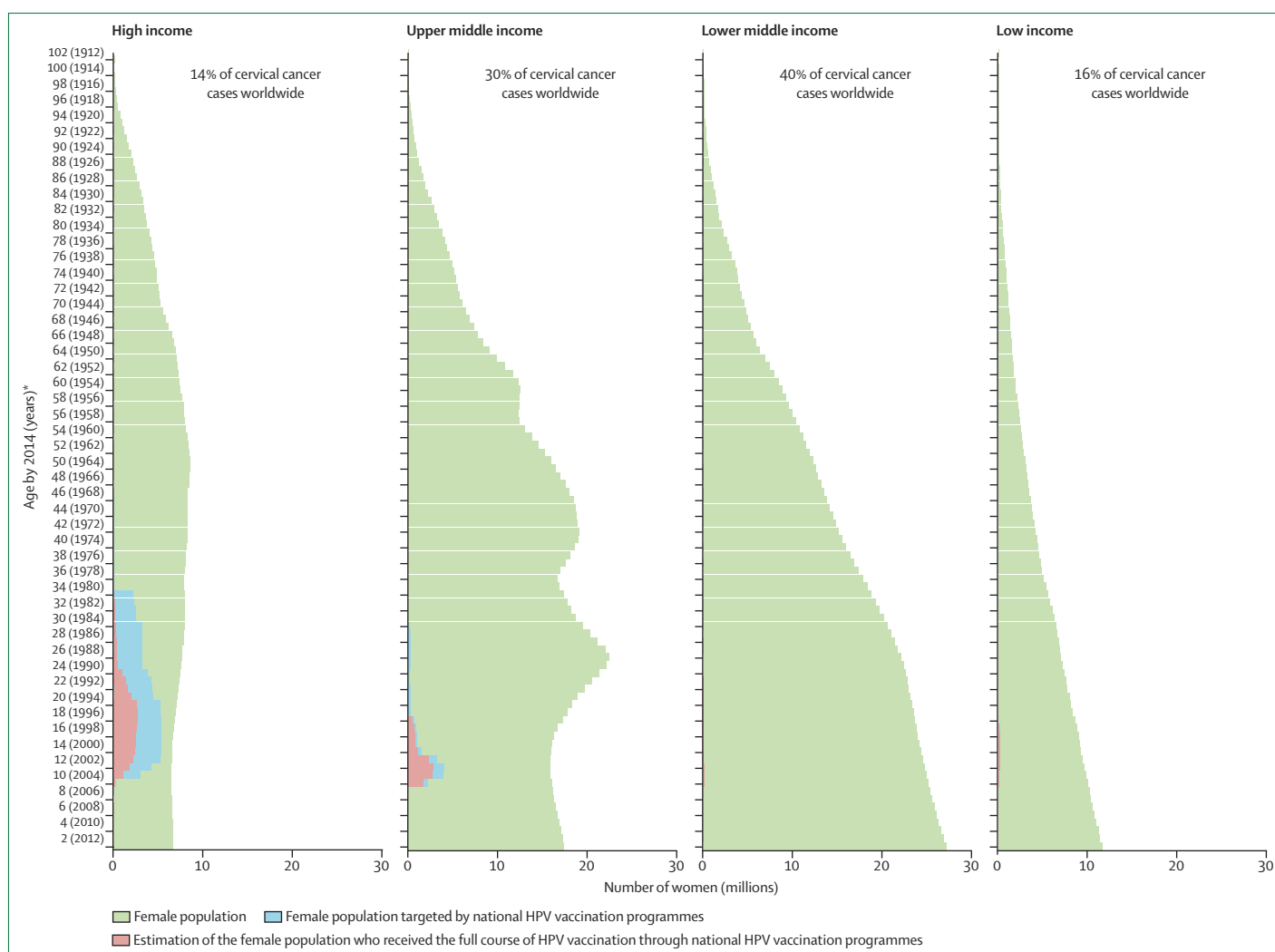


Figure 3: Female population pyramid of women targeted by national HPV vaccination programmes by income

Income classification follows World Bank classification of the world's economies based on estimates of gross national income (GNI) per head for the previous year.¹⁴ As of July 1, 2014, low-income economies are defined as those with a GNI per head, calculated with the World Bank Atlas method, of US\$1045 or less in 2013; middle-income economies are those with a GNI per head of more than \$1045 but less than \$12 746; high-income economies are those with a GNI per head of \$12 746 or more. Lower-middle-income and upper-middle-income economies are separated at a GNI per head of \$4125. Low-income and middle-income economies are sometimes referred to as developing economies. Proportion of cervical cancer cases calculated from GLOBOCAN 2012, produced by the International Agency for Research on Cancer.¹² HPV=human papillomavirus. *Birth cohorts of women are shown in parentheses.

reached only 2% coverage in the first year, and, after several attempts to improve the uptake, it was finally suspended.⁷

Countries that have not yet introduced the vaccine are those that can gain the most in terms of health benefits.²⁰ Our analysis of the expected averted cervical cancer cases in these vaccinated cohorts shows that, in upper-middle-income countries, vaccination of 13·3 million women is expected to reduce more cervical cancer cases than would vaccination of 32·2 million women in high-income countries. Efforts should pursue vaccine introduction in all these low-income and middle-income countries, where screening has been neither successful nor implemented and vaccination remains the only feasible preventive option. For less developed countries, many

women have been vaccinated through demonstration projects, such as the Gardasil Access Program, which has shipped 1·3 million doses to 21 countries—enough to vaccinate more than 445 900 eligible women.^{21,22} PATH undertook four demonstration projects between 2008 and 2011, targeting 52 755 women from Peru, Uganda, Vietnam, and India.²³ GAVI, the Vaccine Alliance, is supporting more than 20 demonstration projects in developing countries for the 2013–15 period (mostly in sub-Saharan Africa) where about 400 000 women will benefit from vaccination.²⁴ GAVI demonstration projects will provide an opportunity for low-income and lower-middle-income countries and could represent a gateway for national introduction. However, only low-income countries and 40% of lower-middle-income countries fall

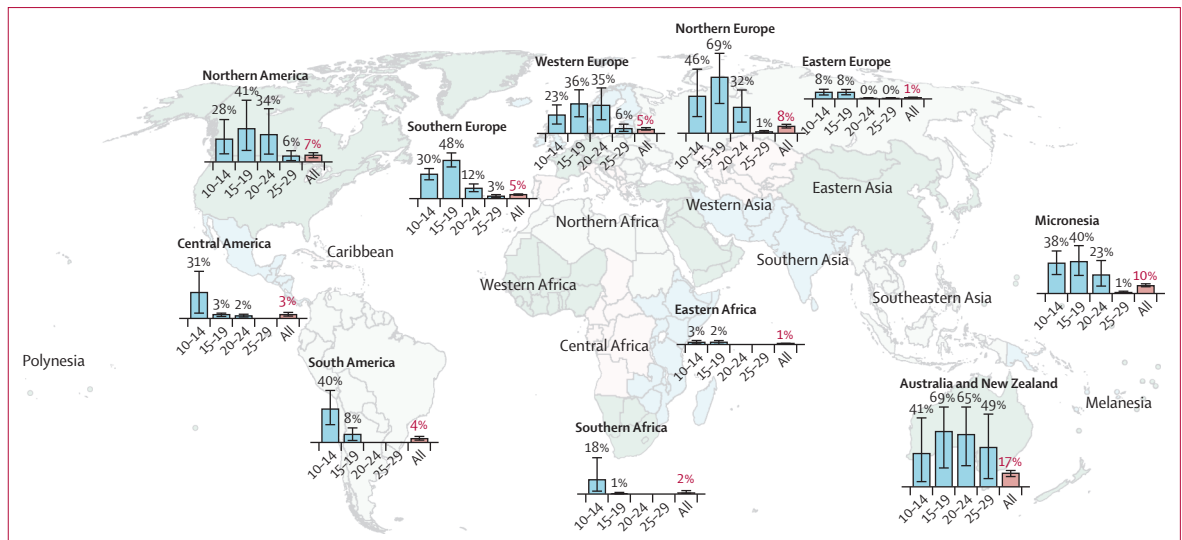


Figure 4: Estimated full-course coverage of human papillomavirus vaccine by 2014, by age group and geographical region

Error bars represent 95% CIs. Regions without bar charts had no or very low estimated coverage. More detailed data are provided in the appendix (pp 43–46).

Countries included in the analysis are geographically classified as follows: northern Africa (Libya); eastern Africa (Rwanda, Seychelles, Uganda); southern Africa (Lesotho, South Africa); Caribbean (Barbados, Cayman Islands, Dominican Republic, Trinidad and Tobago, US Virgin Islands); Central America (Mexico, Panama); South America (Argentina, Brazil, Chile, Colombia, Guyana, Paraguay, Peru, Suriname, Uruguay); northern America (Bermuda, Canada, Greenland, USA); central Asia (Kazakhstan); eastern Asia (Japan); southern Asia (Bhutan); southeastern Asia (Brunei, Malaysia, Singapore); western Asia (Israel, United Arab Emirates); eastern Europe (Bulgaria, Czech Republic, Romania, Russia); northern Europe (Denmark, Finland, Iceland, Ireland, Latvia, Norway, Sweden, UK); southern Europe (Gibraltar, Greece, Italy, Malta, Portugal, San Marino, Slovenia, Spain, Macedonia); western Europe (Austria, Belgium, France, Germany, Luxembourg, Monaco, Netherlands, Switzerland); Australia and New Zealand (Australia, New Zealand); Melanesia (Fiji, New Caledonia); Micronesia (Guam, Kiribati, Marshall Islands, Micronesia, Northern Mariana Islands, Palau); Polynesia (American Samoa, Cook Islands).

into GAVI eligibility criteria. Without further support, GAVI non-eligible countries could face many obstacles in the introduction of vaccination due to affordability issues and competing health needs.

We recorded large heterogeneity in programme design and performance. Coverage levels varied between countries and subnationally within countries. School-based programmes have been reported to achieve the highest coverage.²⁵ Social norms and values related to sexual activity, and trust in vaccination programmes and health-care providers, are other key factors associated with the uptake.^{25,26} In the USA, HPV vaccination did not reach the same levels of uptake as other adolescent immunisations, such as meningococcal ACWY and varicella.²⁷ By contrast, Australia is a model of success that has already demonstrated first benefits of vaccination, with coverage levels reaching 70% in targeted young adolescent females and more than 50% in older catch-up cohorts.²⁸ Little information is available about coverage outside HPV immunisation programmes. Sweden reported one-dose coverage rates ranging from 3.5% to 9.4% among females born between 1986 and 1989 outside HPV immunisation programmes, compared with 82.3% of those born in 2001 and included in immunisation programmes.²⁹

On average, countries from developing regions reached higher vaccination coverage levels than did those in developed regions. In some developing countries, estimated national coverage levels were based on previous

demonstration projects, which reached high coverage rates and might be outperforming relative to on-the-ground implementation.^{21,23,30,31} Of 21 HPV demonstration projects from 14 countries, 60% were managed by the Ministry of Health, and the overall uptake rate was 88.7%.²¹ Targeted females from less developed regions were younger and mainly reached by primary programmes (68%), whereas targeted females from more developed regions were older and 44% were reached by means of opportunistic strategies. Northern America and eastern and western Europe were the regions with coverage levels less than 50% among the primary target groups.

From a methodological point of view, one of the main challenges in aggregation and compiling of country data into global coverage estimates is the variability in the age of vaccination among cohorts.³² Birth cohorts have the advantage that they can be calculated from the date of the coverage estimation and the reported age of vaccinated individuals; they also provide clearly identifiable denominators (population statistics). However, use of population denominators instead of the actual number of targeted and vaccinated women might be subject to overestimation or underestimation. By 2014, vaccine manufacturers reported distributing more than 175 million doses worldwide.³³ These figures are consistent with our estimates, even despite our approximation including neither distributed doses that are not finally administered nor the number of women vaccinated outside HPV immunisation programmes.

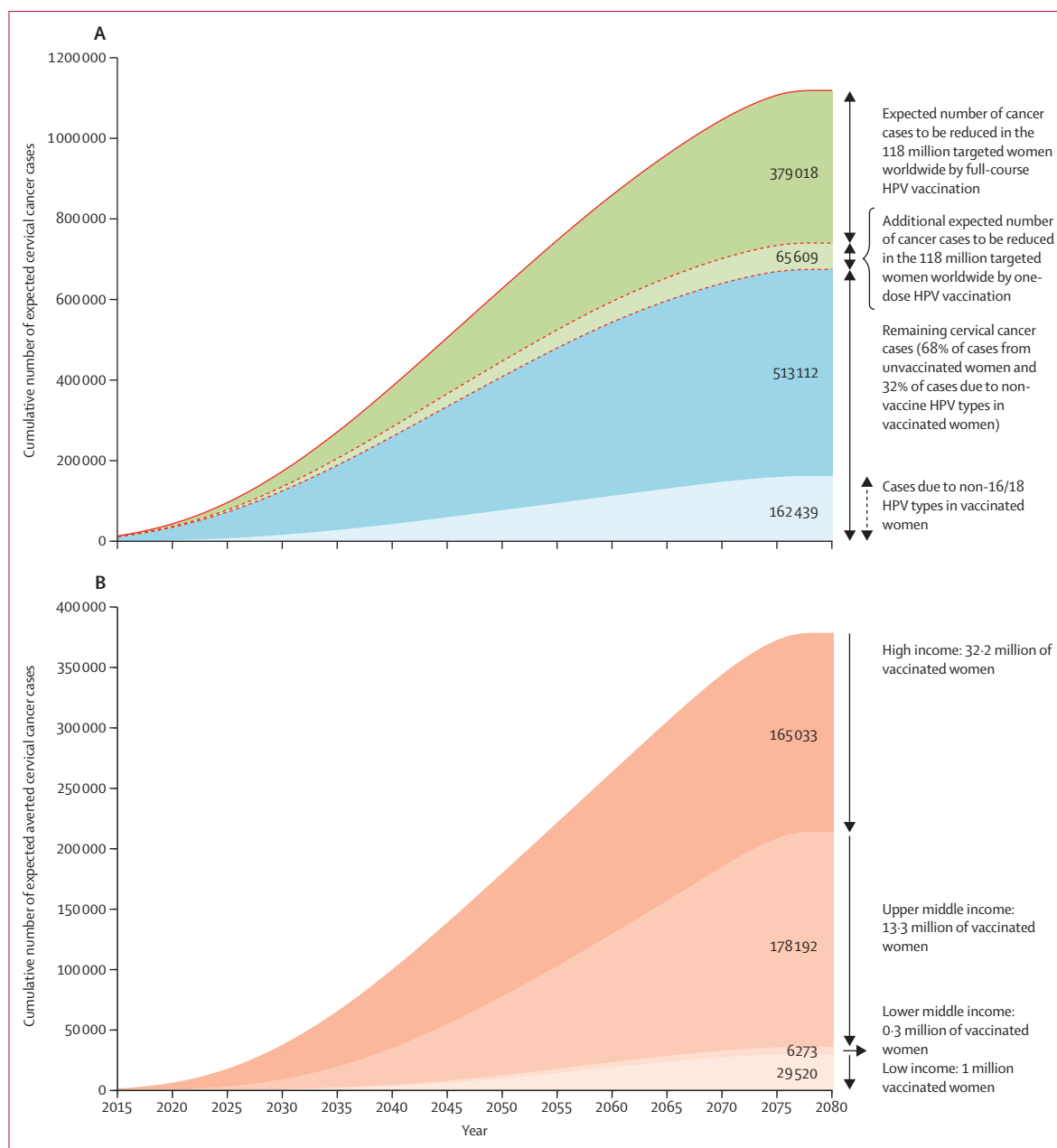


Figure 5: Cervical cancer cases before age 75 years in the cohort of women targeted by HPV vaccination programmes by the end of 2014

(A) Estimated incident cervical cancer averted before age 75 years in the 118 million women ever targeted by HPV vaccination programmes. Solid line shows the cumulative number of expected cervical cancer cases up to age 74 years in targeted cohorts that would not have been vaccinated. Dashed line shows the cumulative number of expected cervical cancer cases up to age 74 years in targeted cohorts considering current HPV vaccination coverage. (B) Estimated incident cervical cancer averted before age 75 years in the 47 million fully vaccinated women by income level. Figure shows the cumulative number of expected cervical cancer cases up to age 75 years in vaccinated women assuming 70% vaccine effectiveness.

Immunisation coverage estimates basically derive from official estimates from administrative data systems or from representative surveys. Both data sources are subject to some biases.^{34,35} Vaccination data are politically sensitive and thus might be prone to data manipulation, especially when funding is based on performance.³⁶ Moreover, publication bias in government data should be considered, by which positive coverage might be highly disseminated

and negative results less available. Surveys and non-official sources could identify those cases.³⁷ Our coverage estimates were usually extracted from only one source. When additional sources were available, few discrepancies were found and official estimates were commonly selected. In 60% of cases, sources were governmental (statistics, press notes, reports, or official epidemiological bulletins), and 30% of cases were scientific publications.

However, our most important challenge and limitation was missing data. We could not retrieve any information about coverage levels for 32 countries and had to impute them with the average rate of the remaining countries with the same year, age at vaccination, geographical region, and income level. Importantly, the contribution to global estimates of these 32 countries was relatively low, representing only 2% of targeted women. These countries were more likely to have recently started vaccination and therefore had few targeted birth cohorts, and 60% were territories or countries with small populations. More than half of the global and high-income country estimates were based on the original data retrieved. However, use of imputed data increased in the rest of the regions, increasing also the uncertainty of our estimates. On the basis of the results of our comprehensive sensitivity analysis of missing data treatment, we can conclude that the performance of our sophisticated imputation system was more than acceptable, particularly in high-income countries and globally.

Despite the high number of women successfully vaccinated worldwide between 2006 and 2014 worldwide, many populations have still not yet had the opportunity to be vaccinated. Notably, current HPV immunisation programmes target only 12% of young adolescent females worldwide, while the remaining females will miss the opportunity for vaccination without rapid roll-out of the HPV vaccine. Many countries in Africa and Asia, representing most of the population worldwide, have highly vulnerable populations at very high risk of developing cervical cancer and other HPV-related diseases. HPV vaccination might be the only feasible prevention strategy in those settings, with the great potential to narrow inequalities. The support of GAVI is becoming a crucial driving force in expansion of access in the coming years. However, upper-middle-income countries and half of lower-middle-income countries fall outside GAVI eligibility criteria. Affordability and programmatic issues of HPV vaccine introduction are major obstacles in most of these settings that require full attention and probably international support. The reduction of doses required could be a crucial issue. The magnitude of cervical cancer cases that could be averted by HPV vaccination emphasises the need to implement HPV immunisation programmes, which might become the only realistic opportunity to reduce present inequalities in cancer risk.

Contributors

LB developed the study design, planned the analyses, collected the data, did the literature search, did the statistical analyses, prepared the tables and figures, contributed to the interpretation of data, and wrote the manuscript. MD contributed to statistical analyses, data interpretation, figure preparation, and writing and revising of the Article. LB-R contributed to data collection, the literature search, data interpretation, and revising of the Article. RH, FB, FXB, and SdS contributed to data interpretation, and writing and revising of the Article. XC contributed to study design, planning of the analyses, and writing and revising of the Article. All authors approved the final submitted version.

Declaration of interests

LB, MD, LB-R, RH, and FB declare no competing interests. FXB has received scientific advisory board fees, speaker's fees, or travel grants from GlaxoSmithKline, Merck, Sanofi Pasteur MSD, Gentecel, and Roche; and unrestricted institutional research grants from GlaxoSmithKline, Merck, Qiagen, and Roche. SdS has received occasional travel grants to conferences, symposia, and meetings from GlaxoSmithKline, Sanofi Pasteur MSD, or Qiagen; and unrestricted institutional research grants from GlaxoSmithKline, Merck, Qiagen, and Roche. XC has received occasional travel grants to conferences, symposia, and meetings from Merck and Sanofi Pasteur MSD; has received speaker's fees from Sanofi Pasteur MSD and Vianex; has received unrestricted institutional research grants from GlaxoSmithKline, Merck, and Sanofi Pasteur MSD; and has participated in human papillomavirus vaccine trials sponsored by GlaxoSmithKline, Merck, and Gentecel.

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